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# Carcinogenesis: Failure of Resolution of Inflammation?

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**Abstract**

Inflammation in the tumor microenvironment is a hallmark of cancer and is recognized as a key characteristic of carcinogens. However, the failure of resolution of inflammation in cancer is only recently being understood. Products of arachidonic acid and related fatty acid metabolism called eicosanoids, including prostaglandins, leukotrienes, lipoxins, and epoxyeicosanoids, critically regulate inflammation, as well as its resolution. The resolution of inflammation is now appreciated to be an active biochemical process regulated by endogenous specialized pro-resolving lipid autacoid mediators which combat infections and stimulate tissue repair/regeneration. Environmental and chemical human carcinogens, including aflatoxins, asbestos, nitrosamines, alcohol, and tobacco, induce tumor-promoting inflammation and can disrupt the resolution of inflammation contributing to a devastating global cancer burden. While mechanisms of carcinogenesis have focused on genotoxic activity to induce mutations, nongenotoxic mechanisms such as inflammation and oxidative stress promote genotoxicity, proliferation, and mutations. Moreover, carcinogens initiate oxidative stress to synergize with inflammation and DNA damage to fuel a vicious feedback loop of cell death, tissue damage, and carcinogenesis. In contrast, stimulation of resolution of inflammation may prevent carcinogenesis by clearance of cellular debris via macrophage phagocytosis and inhibition of an eicosanoid/cytokine storm of pro-inflammatory mediators. Controlling the host inflammatory response and its resolution in carcinogen-induced cancers will be critical to reducing carcinogen-induced morbidity and mortality. Here we review the recent evidence that stimulation of resolution of inflammation including pro-resolution lipid mediators and soluble epoxide hydrolase inhibitors may be a new chemopreventive approach to prevent carcinogen-induced cancer that should be evaluated in humans.

**Keywords** - eicosanoid, carcinogen, inflammation, resolution, resolvin, soluble epoxide hydrolase

**Abbreviations**

- 12-*O*-tetradecanoylphorbol-13-acetate **TPA**
- 4-nitroquinaline 1-oxide **4-NQO**
- 7,12-dimethylbenz[a]anthracene **DMBA**
- Aflatoxin $B_1$ **$AFB_1$**
- Azoxymethane **AOM**
- benzo[a]pyrene **BaP**
- Dextran sodium sulfate **DSS**
- Diethylstilbestrol **DES**
- Hepatocellular carcinoma **HCC**
- Inducible nitric oxide synthase **iNOS**
- Lipopolysaccharide **LPS**
- Liquid chromatography-tandem mass spectrometry **LC-MS/MS**
- N-butyl-N-(4-hydroxybutyl)-nitrosamine **BBN**
- N-nitrosobis(2-oxopropyl)amine **BoP**
- N-nitrosodiethylamine **NDEA** / Diethylnitrosamine **DEN**
- N-nitrosodimethylamine **NDMA** / Dimethylnitrosamine **DMN**
- N-nitrosomethylbenzylamine **NMBA**
- Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone **NNK**
- Nuclear factor erythroid-2 related factor 2 **Nrf2**
- Perfluorinated carboxylic acids **PCFAs**
- Perfluorooctanoic acid **PFOA/C8**
- Phorbol 12-myrisate 13-acetate **PMA**
- Polycyclic aromatic hydrocarbons **PAHs**
- Soluble epoxide hydrolase **sEH**
- Specialized pro-resolving mediators **SPMs**

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## 1. Introduction

Carcinogens induce inflammation, an established hallmark of cancer (Greten & Grivennikov, 2019; Hanahan & Weinberg, 2011; Mantovani, Allavena, Sica, & Balkwill, 2008). With potential exposure to greater than 15 million environmental chemicals worldwide, controlling inflammation and its resolution will be a critical component of the successful prevention and treatment of cancer (Gilligan et al., 2019; Panigrahy et al., 2019; Sulciner, Serhan, et al., 2018). Uncontrolled local and systemic hyperinflammation is an underlying driving force of diseases including cardiovascular disease (e.g. atherosclerosis and myocardial infarction), abdominal aortic aneurysm, heart arrhythmias, arthritis, central nervous system disorders, periodontal disease, inflammatory bowel disease, gallstones, sepsis, infection, stroke/epilepsy, infection, acute respiratory distress syndrome (ARDS), fibrosis (e.g. liver, kidney and lung), portal hypertension, fatty liver, neurodegenerative diseases (e.g. Alzheimer's disease), traumatic brain injury, asthma, obesity, diabetes, pain, severe coronavirus disease (e.g. COVID-19), and autoimmune diseases (Chelko et al., 2019; Chiang et al., 2012; Espinoza et al., 2016; Imig & Hammock, 2009; Libby, 2002; Mehta et al., 2020; Serhan, 2014; Spite et al., 2009). Over the past century, the study of anti-inflammatory mechanisms has focused on the suppression of pro-inflammatory mediators, such as cytokines, eicosanoids, and enzymes (D. Wang & Dubois, 2010). In recent years, a new direction has emerged to "turn off" inflammation with the discovery of a new superfamily of endogenous specialized pro-resolving lipid-autacoid mediators (SPMs), such as resolvins, which have potent novel inflammation clearing ('pro-resolution') activity without being immunosuppressive (Serhan, 2014; Serhan et al., 2002; Serhan et al., 2009). Unlike the majority of anti-inflammatory agents including the nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib and ibuprofen that work by directly suppressing cyclooxygenase (COX-2) enzyme activity, SPMs are endogenous inhibitors of inflammation, which function as "brake signals" to turn off inflammation (Serhan, 2014). These

pro-resolution lipid autacoids act through clearance of cellular debris by immune cells such as macrophage resulting in reduced localized pro-inflammatory cytokines in a process termed “resolution” (Serhan, 2014). Failure of resolution via reduced SPMs (e.g. resolvins) is a key biological mechanism of pathogenesis and a unifying component of many underlying chronic inflammatory human diseases such as obesity, infection, asthma, wound healing, Alzheimer’s Disease, Parkinson’s disease, aging, sepsis, Pseudomonas aeruginosa infections, periodontitis, cardiovascular diseases, obesity, inflammatory bowel disease, neuroinflammation, respiratory diseases, multiple sclerosis, arthritis, cystic fibrosis, scleroderma, ocular disorders (e.g. age-related macular degeneration), atherosclerosis, rheumatic diseases, leukemia, sickle cell anemia, and chronic liver disease (e.g. cirrhosis) (Arita et al., 2005; Arnardottir et al., 2016; Chiang et al., 2012; Claria et al., 1998; Flitter et al., 2017; Fredman et al., 2016; Haworth, Cernadas, Yang, Serhan, & Levy, 2008; Karp et al., 2004; Kasuga et al., 2008; Kowal-Bielecka, Kowal, Distler, & Gay, 2007; Levy et al., 2005; C. Li et al., 2020; Lukiw et al., 2005; Matte et al., 2019; Merched, Ko, Gotlinger, Serhan, & Chan, 2008; Neuhofer et al., 2013; Planaguma et al., 2008; Serhan, 2014; Serhan & Levy, 2018; Stenke, Edenius, Samuelsson, & Lindgren, 1991; Yacoubian & Serhan, 2007).

Inflammation was first described according to the four cardinal signs: calor (heat), pallor/dolor (pain), rubor (redness), and tumor (swelling), which reflect the pro-tumorigenic activity of cytokines, immune cells, and blood vessels (e.g. angiogenesis) in the tumor microenvironment (Serhan, 2017; Sulciner, Serhan, et al., 2018). In healthy individuals, the acute inflammatory response(s) is self-limited and can be classically divided into initiation and resolution phases (Serhan, 2014). Neutrophils (polymorphonuclear leukocytes) are one of the first immune cell types to enter the wounded area and remove microbes as well as cellular debris (Serhan & Levy, 2018). Cancer is viewed as a wound that does not heal, thus attracting similar cell types and mechanisms as wound healing and tissue regeneration (Dvorak, 1986). A

paradigm shift is emerging in our understanding of the pathogenesis of pathological inflammation which not only results from the persistent activation of inflammatory signals, but also the failure of engaging pro-resolving mechanisms including clearance of cell death "debris" and counter-regulation of pro-inflammatory cytokines (Serhan, 2014; Serhan & Levy, 2018). Experimental and human studies suggest that cancer progression results from the "failure to clear debris" after chemotherapy, radiation, or surgery (Chaurio et al., 2013; da Silva-Jr, Chammas, Lepique, & Jancar, 2017; Ford et al., 2015; Gartung et al., 2019; Gilligan et al., 2019; Gunjal et al., 2015; Q. Huang et al., 2011; Panigrahy et al., 2019; Revesz, 1956; Sulciner, Serhan, et al., 2018; Y. Ye et al., 2018). Thus, failure to engage resolution of inflammation mechanisms including clearance of debris may lead to carcinogenesis. Differentiating between suppression and resolution of inflammation is critical to mechanistic studies in inflammation-driven diseases including cancer (Fishbein et al., 2020; Gilligan et al., 2019; Kuang, Hua, Zhou, & Yang, 2016; Panigrahy et al., 2019; Serhan, 2014; Shan et al., 2020; Sulciner, Serhan, et al., 2018; Y. Ye et al., 2018).

A key concept in resolution of inflammation is that the immune system can be beneficial in fighting cancer, in accordance with the increasing interest in immune-mediated approaches in targeting cancer (Serhan, 2011; P. Sharma & Allison, 2015). In 1790 the Scottish surgeon John Hunter remarked "Inflammation in itself is not to be considered as a disease" (Turk, 1994). In 1893 William Coley successfully treated sarcomas with bacterial mixtures, leading to tumor regression (Coley, 1910). It has been known from the 11$^{th}$ Century "The Canon of Medicine," a historical encyclopedia of medical books, that inflammation is not entirely bad and can be good – "pus bonum ert laudable" (good and laudable pus) (Serhan, 2011). "Laudable pus" was believed to be a sign of a healthy, healing wound (Freiberg, 2017), and the Serhan laboratory discovered pro-resolution lipid mediators that are biosynthesized in the resolving inflammatory

exudates to identify the “stop” signals which turn inflammation off (Serhan, 2014; Serhan, Hamberg, & Samuelsson, 1984; Serhan et al., 2002; Serhan et al., 2009). In Taber’s Cyclopedic Medical Dictionary “resolution” is defined as “cessation of inflammation without suppuration; the return to normal” (Serhan, 2011). Although it was previously believed that the resolution of inflammation was a passive process, it is now widely appreciated to be an active reprogramming of the immune environment regulated by pro-resolution lipid mediators (Serhan, 2014; Serhan et al., 2002; Serhan & Levy, 2018; Serhan et al., 2009). While blocking inflammation can be beneficial in cancer (Coussens, Zitvogel, & Palucka, 2013; Greten & Grivennikov, 2019; Mantovani, 2009), stimulating the resolution of inflammation via pro-resolution mediators is an entirely distinct and unique approach from neutralizing pro-inflammatory factors via the clearance of pro-tumorigenic cellular debris (Serhan, 2014; Serhan & Levy, 2018). Pro-resolution mechanisms are multi-pronged including counter-regulating a series of pro-inflammatory mediators including cytokines, chemokines, and eicosanoids (“eicosanoid and cytokine storm”) by stimulating the clearance of cellular debris (Sulciner, Serhan, et al., 2018).



**Inflammation and Cancer**

The relationship between inflammation and cancer harkens back over 150 years ago to 1863 when Rudolf Virchow suggested that chronic inflammation from tissue injury stimulates the proliferation of cells leading to cancer (Balkwill & Mantovani, 2001). Virchow’s hypothesis that cancer is initiated at sites of “lymphoreticular infiltrate” is highly relevant to many cancer patients as pancreatitis, hepatitis, colitis, esophagitis, cholangitis, *Helicobacter pylori* and other chronic inflammatory diseases are established risk factors for cancer in these tissues (Beasley, 1988; Greene, Huang, Serhan, & Panigrahy, 2011; Guerra et al., 2011; Guerra et al., 2007; Rutter et

al., 2004). Virchow studied the four signs of inflammation (redness, swelling, heat and pain) and hypothesized a link between microinflammation and subsequent tumor progression (Heidland, Klassen, Rutkowski, & Bahner, 2006). Experimental studies have indeed confirmed that inflammation can stimulate or induce tumor initiation, growth, and metastasis (Bogen, 2019; Chang et al., 2019; Coussens & Werb, 2002; Fishbein et al., 2020; Gartung et al., 2019; Gilligan et al., 2019; Guerra et al., 2007; Mantovani et al., 2008; Panigrahy et al., 2019; Sulciner, Serhan, et al., 2018; D. Wang & Dubois, 2010). Cancers arise frequently at sites of chronic inflammation and injury as the observation that secondary tumors occur at the points of injury (e.g. tumor growth next to surgical placement of glass rods) was noted in 1914 (F. S. Jones & Rous, 1914). The wound inflammatory response stimulates the growth of pre-neoplastic cells and cancer progression (Antonio et al., 2015). Experimental evidence demonstrates that cancer therapies including chemotherapy, radiation, and surgery can stimulate tumor growth via a pro-tumorigenic host response including a eicosanoid/cytokine storm of pro-inflammatory and pro-angiogenic mediators (Camphausen et al., 2001; Chang et al., 2019; Filippou & Karagiannis, 2020; Fishbein et al., 2020; Gartung et al., 2019; Karagiannis et al., 2017; Shaked, 2019; Sulciner, Serhan, et al., 2018; Volk-Draper et al., 2014). Wounding including surgery or biopsy can stimulate cancer growth via inflammation and angiogenesis (Alieva et al., 2017; Forget, Simonet, & De Kock, 2013; Hobson et al., 2013; Krall et al., 2018; J. W. Lee et al., 2009; Panigrahy et al., 2019).

Chronic inflammation and infection contributes to about 25% of all human cancers, including various tumor types such as hepatocellular, bladder and prostate cancer (De Marzo et al., 2007; Greene et al., 2011; Sulciner, Gartung, Gilligan, Serhan, & Panigrahy, 2018). For example, inflammation initiates cancer growth within 5 to 8 months in a genetically engineered model of pancreatic cancer (Guerra et al., 2007). The importance of inflammation in cancer was further demonstrated in a randomized double-blind trial in patients with atherosclerosis. Patients

who received canakinumab, an IL-1β inhibitor used to treat systemic inflammatory diseases, developed significantly reduced incidence of lung cancer and cancer-related mortality (Ridker et al., 2017). Chronic inflammation also increases the risk of various malignancies such as those of the gastrointestinal tract including colorectal (CRC), gastric, gallbladder, and esophageal cancers (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006; Espinoza et al., 2016; D. Wang & Dubois, 2010). Increased infiltration of innate immune cells to the tumor, such as macrophages and neutrophils, correlates with increased angiogenesis and poor prognosis (Pollard, 2004). In contrast, lymphocytic/monocytic inflammatory infiltrates can be associated with tumor inhibition and a beneficial prognosis (L. Zhang et al., 2003). The inflammatory cells in the tumor may be genetically stable, and thus less susceptible to development of drug resistance making them an ideal target for new cancer therapies.

The traditional view that cancer is a cell-autonomous disease driven by genetic changes with selection for fast-growing and increasingly malignant cell clones has been supplanted with the understanding that cancer requires support from the host tissue microenvironment, including immune cells such monocytes/macrophages, neutrophils, and lymphocytes as well as endothelial cells, pericytes, fibroblasts and cancer stem cells (Folkman, 2007; Joyce, 2005). An early event in tumor progression is the recruitment of monocytes to the tumor site, where they differentiate into macrophages (Balkwill & Mantovani, 2001). Tumor infiltrating immune cells such as macrophages play a key role in tumor growth, angiogenesis, and inflammation (Pollard, 2004) and exhibit critical crosstalk in tumor cell-stromal cell communication via pro-inflammatory and pro-resolution mediators (Gilligan et al., 2019; Panigrahy et al., 2019; Sulciner, Serhan, et al., 2018).

Cancer therapies either directly (e.g. chemotherapy and radiation) or indirectly (targeted therapies such as immunotherapy and anti-angiogenic therapy) result in apoptotic tumor cell death ("tumor cell debris"). However, apoptotic cell death ("debris") is a double-edged sword and can paradoxically stimulate tumor growth and metastasis via pro-inflammatory mechanisms including a macrophage-secreted "cytokine and eicosanoid storm" of pro-angiogenic mediators (Chang et al., 2019; Fishbein et al., 2020; Gartung et al., 2019; Revesz, 1956; Sulciner, Serhan, et al., 2018). Therapy-induced inflammation and immune infiltration in cancer from chemotherapy, radiation, and immunotherapies can be beneficial by triggering anti-tumor immunity or stimulate tumor growth via immunosuppression (Greten & Grivennikov, 2019). Over the past century anti-inflammatory therapies in cancer have focused on suppressing pro-inflammatory "go" signals such as cytokines, angiogenic factors and eicosanoids (Gilroy, Lawrence, Perretti, & Rossi, 2004; Serhan, 2014). Targeting inflammation and angiogenesis allows for the development of interventional strategies that can complement the traditional cell-autonomous cancer approaches which target the mutational capacity of tumors. Traditional anti-inflammatory agents such as steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), coxibs, and selective cytokine blockade exhibit potent anti-tumor activity in various pre-cancer models (D. Wang & Dubois, 2010). Cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome (CYP) P450 enzymes and their inhibitors are widely used to treat inflammation and cancer. The prostaglandin receptors (e.g. EP1, EP2, EP3, and EP4) are overexpressed in cancers and are a target to treat various types of cancer, e.g. breast and colorectal cancer (Majumder, Nandi, Omar, Ugwuagbo, & Lala, 2018; D. Wang & Dubois, 2010). Moreover, anti-inflammatories such as aspirin have exhibited potent chemopreventive activity in patients (Gilligan et al., 2019). However, in clinical trials anti-inflammatory agents have resulted only in transient anti-tumor activity, multiple toxicities, and immunosuppression severely limiting their use in cancer patients and healthy individuals with inflammatory disorders at risk for cancer (e.g. inflammatory bowel disease) (Milagre et al., 2015; Panigrahy et al., 2019; Sandhu et al., 2013; Serhan, 2014). Side

effects and toxicities from their immunosuppressive activity include impaired wound healing, fungal infections, osteoporosis, stomach bleeding, increased thrombosis, cardiovascular (e.g. heart attacks) and kidney toxicity (Serhan, 2014; D. Wang & Dubois, 2010). Moreover, anti-cytokine biologics designed to block pro-inflammatory factors may abrogate host defense against infections and increase risk of other cancers. In dramatic contrast, pro-resolution lipid mediators such as resolvins, lipoxins, protectins, and maresins are non-immunosuppressive, anti-thrombotic, anti-angiogenic, anti-fibrotic, stimulate the clearance of debris, stimulate tissue repair/regeneration, enhance postischemic revascularization, promote wound healing and exhibit potent biological activity at nanogram concentrations without overt toxicity reported to date (Cherpokova et al., 2019; de la Rosa et al., 2018; Gilligan et al., 2019; Hellmann et al., 2018; Jin et al., 2009; Norling et al., 2011; Panigrahy et al., 2019; Qu et al., 2012; Serhan & Levy, 2018; Sulciner, Serhan, et al., 2018; M. J. Zhang et al., 2016).

**Carcinogens and inflammation**

A carcinogen is defined as a chemical substance, or a mixture of chemical substances, after inhalation, ingestion, dermal application or injection which induces cancer, increases its incidence, or shortens the time to tumor occurrence (i.e. latency) at any dosage level by any route in any species of animals as compared to controls (Luch, 2005). Examples include tobacco, natural and synthetic chemicals, and environmental toxins (National Toxicology, 2011). Although it is challenging to estimate the number of cancer deaths caused by carcinogen exposure, an astonishing 70-95% of cancer cases can be traced to identified risk factors including diet (30–35%), tobacco (25–30%), infections (15–20%), obesity (10–20%), alcohol (4–6%), and others, including pollutants and radiation (10–15%) (Anand et al., 2008; Madia, Worth, Whelan, & Corvi, 2019). Substances that induce tumors in animals are considered as presumed

or suspected human carcinogens until convincing evidence to the contrary is presented (Maronpot, Flake, & Huff, 2004). To establish a chemical as an human carcinogen requires experimental animal studies, human epidemiological cancer studies, clinical studies, and/or samples from human tissues exposed to the carcinogen to demonstrate a causal relationship (Suarez-Torres, Alzate, & Orjuela-Ramirez, 2020). Many substances which have limited evidence from human studies but have sufficient evidence from animal carcinogenicity studies may also be carcinogens.

Since the 1970s the International Agency for Research on Cancer (IARC) has screened over 1000 agents which exhibited a cancer risk to humans (Krewski, Rice, et al., 2019). Over 100 carcinogenic agents can be divided into six general categories: (I) pharmaceuticals; (II) biological agents; (III) arsenic, metals, fibers and dusts; (IV) radiation; (V) personal habits and indoor combustions; and (VI) chemical agents and related occupations (Krewski, Rice, et al., 2019). Carcinogens including nitrosamines and aflatoxins can initiate or stimulate tumor growth and metastasis via multiple mechanisms including inflammation (Shi, Godschalk, & van Schooten, 2017; M. T. Smith et al., 2016). Inflammation is a driving force for genotoxicity including impaired particle clearance leading to macrophage activation and persistent inflammation (Borm, Tran, & Donaldson, 2011). Human carcinogens recently were categorized by 10 key characteristics of carcinogens including: (1) to be electrophilic or metabolically activated, (2) genotoxic, (3) alter DNA repair, (4) lead to epigenetic alterations or genomic instability, (5) generate oxidative stress, (6) chronic inflammation, (7) immunosuppression, (8) activate receptor mediated signaling, (9) cause cell immortalization and (10) alter cell proliferation, cell death, and angiogenesis (Figure 1) (M. T. Smith et al., 2016; M. T. Smith et al., 2020). These key characteristics of carcinogens provide a mechanistic basis to evaluate the activity of carcinogens (Guyton, Rieswijk, Wang, Chiu, & Smith, 2018; Guyton, Rusyn, et al., 2018; M. T. Smith et al., 2016). Many carcinogens exhibit several of the 10 key characteristics,

with an average of four characteristics per agent (Krewski, Bird, et al., 2019). These characteristics of carcinogens help to create the necessary tumor microenvironment for tumor initiation and progression via mechanisms distinct from the hallmarks of cancer (Guyton, Rieswijk, et al., 2018; M. T. Smith et al., 2016; M. T. Smith et al., 2020). These key characteristics may also lead to the development of human-based assays and biomarkers for assessing cancer risk (Fielden et al., 2018). At low concentrations, a chemical mixture has synergistic pro-tumorigenic activity on benign and malignant cells at a significantly lower concentration than as single chemicals (Dairkee, Luciani-Torres, Moore, Jaffee, & Goodson, 2018). Carcinogens may not directly be genotoxic but cause DNA damage by stimulating inflammation. Chronic inflammation triggers oxidative stress via the release of pro-inflammatory cytokines and stimulation of cell proliferation, leading to DNA damage (Krewski, Bird, et al., 2019). Heavy metals such as arsenic, aluminum, nickel, cadmium, chromium, cobalt, palladium, and titanium induce severe damage triggering pro-inflammatory cytokines and oxidative stress (Jomova & Valko, 2011; Magrone, Russo, & Jirillo, 2019). Carcinogens such as per- and polyfluoroalkyl substances (PFAS) cause cancer in animals and increase risk of cancer in humans via several key characteristics including oxidative stress, immunosuppression, and receptor-mediated activity (Temkin, Hocevar, Andrews, Naidenko, & Kamendulis, 2020). Primary genotoxicity can result from carcinogen-induced particles (e.g. from polycyclic aromatic hydrocarbons) while oxidative stress-induced DNA damage can induce secondary genotoxicity (Schins & Knaapen, 2007).

This important classification of key characteristics focused on the mechanisms of action of the cancer-causing activity of carcinogens provides a robust platform for novel chemopreventive treatment approaches to carcinogen-induced cancers. The carcinogenic potential of a compound is its ability to induce neoplasia via genotoxicity, cytotoxicity,

proliferation, and inflammation depending on dose and duration of exposure (Doe et al., 2019). Importantly, inflammation can induces genetic changes which can cause cancer (Kay, Thadhani, Samson, & Engelward, 2019; Kiraly, Gong, Olipitz, Muthupalani, & Engelward, 2015). Cancer may be initiated with a mutation post-exposure to a DNA-damaging carcinogen, followed by pro-tumorigenic mechanisms such as inflammation which fuel the fire (Aggarwal et al., 2006; Cooks, Harris, & Oren, 2014). Oxidative stress including reactive oxygen and nitrogen species (RONS) critically mediate cancer progression by carcinogens and pathogens (Kay et al., 2019; Meira et al., 2008). While oxidative stress can induce DNA damage and inflammation, repair of DNA lesions formed by RONS during chronic inflammation can protect from carcinogen-induced cancers (Meira et al., 2008). DNA damage also indirectly promotes inflammation through cytotoxicity (Kay et al., 2019). Excessive DNA damage during proliferation may not be cleared by DNA repair pathways, resulting in cell death including apoptosis, necroptosis, necrosis, or senescence. Thus, DNA damage is considered essential to carcinogenesis.

Initiators of carcinogenesis include radiation, certain chemotherapeutics and chemicals such as aflatoxin, urethane, tryptophan metabolites, and nitrosamines, can cause an irreversible genetic modification in a normal cell leading to cancer (Chung & Gadupudi, 2011; Molho-Pessach & Lotem, 2007; Xie et al., 2012). Initiators can bind to and alter the DNA to generate adducts. The initiation stage is an event in which carcinogens usually induce mutations or other modifications in critical genes, which can produce cancer stem cells (J. He, Liu, & Lubman, 2012; Tirino et al., 2013). A compound that acts as both an initiator and a promoter is referred to as a 'complete carcinogen' because tumor development can occur without the application of another compound (Rastogi, Dogra, Khanna, & Das, 2006). In studies of mouse skin carcinogenesis, a linear relationship has been observed between the dose of initiator and the quantity of tumors that can be produced (Gills et al., 2006). Thus, the more exposure to the

carcinogen, the higher the risk of developing tumors (D. S. Kang et al., 2018). Cancer risk and slope factor are calculated in a linear dose-response (D. S. Kang et al., 2018). All known human carcinogens that have been studied for carcinogenesis in experimental animals have generated positive results in one or more animal species (Tomatis, Aitio, Wilbourn, & Shuker, 1989; Wilbourn et al., 1986). For several carcinogens, such as aflatoxins and vinyl chloride, carcinogenesis in experimental models of cancer was established before epidemiological studies confirmed their carcinogenesis in humans (Vainio et al., 1995).

The mechanism of action of carcinogens traditionally has been simplified as genotoxic and/or nongenotoxic. A genotoxic carcinogen is defined as a chemical that causes cancer by directly altering the genetic material of target cells, while non-genotoxic carcinogens are chemicals that can induce cancer by mechanisms not related to direct genetic damage. Many genotoxic carcinogens cause cancer in carcinogenic bioassays in animals (W. J. Lee et al., 2014). Concerning cancer risk assessment, genotoxic carcinogens exert carcinogenic potential regardless of the animal species. Thus, chemicals that are carcinogenic via genotoxicity to rodents are also presumed to be carcinogenic to humans unless proven otherwise. Because genotoxic carcinogens are mutagenic and may act through interaction with DNA to produce irreversible genetic changes in target organ cells, they may exhibit no dose threshold for their carcinogenic potential (Preussmann, 1980; Tomatis et al., 1997). A genotoxic chemical can induce mutations (e.g. induction of DNA modifications). Carcinogens may induce a specific gene mutation frequently observed in a particular cancer increasing the risk of cancer (Moore et al., 2008). While carcinogen-induced DNA damage can cause cancer, some studies suggest that DNA adducts alone or mutations alone may not be sufficient to cause cancer (Bogen, 2019; Johnson et al., 2014). Non cell-autonomous mechanisms such as inflammation and angiogenesis may also be critical to tumor initiation and progression (Folkman, 2007). Importantly, proliferation of cells alone does not cause cancer as tumors can also develop in

tissues subjected to infection, wounding, and inflammation (Coussens & Werb, 2002; Krall et al., 2018; Panigrahy et al., 2019).

Carcinogens (e.g. aflatoxins, nitrosamines, asbestos, dioxins, tobacco, and alcohol) can initiate and stimulate cancer progression through various mechanism including inflammation, oxidative stress, DNA damage, cytotoxicity, acute or chronic injury, and subsequent regenerative proliferation via cell death (e.g. apoptosis) (Bogen, 2019; Klaunig, Hocevar, & Kamendulis, 2012; X. Yao & Zhong, 2005). Environmental and occupational exposure to carcinogenic metals (e.g. arsenic, chromium, and vanadium) causes cancer via cell apoptosis, inflammation, DNA damage, and lipid peroxidation (F. Chen, Vallyathan, Castranova, & Shi, 2001). There are over 8,000 compounds identified as carcinogens to date. Carcinogens can stimulate cancer via the production of critical pro-inflammatory, pro-angiogenic and pro-tumorigenic cytokines/transcription factors including TNF-α, IL-6, and NF-κB, as well as proto-oncogenes (e.g., c-Myc) (D. Chen, Yan, & Ye, 1998; George, Tsuchishima, & Tsutsumi, 2019). Moreover, carcinogens may impair the host protective immune response via immunotoxicity, including increased apoptosis of leukocytes and reactive oxygen species (Iwaniuk, Jablonska, Jablonski, Ratajczak-Wrona, & Garley, 2015; Jablonski, Jablonska, & Chojnowski, 2001; Jablonski, Jablonska, & Leonik, 2011; Nowak, Ratajczak-Wrona, Garley, & Jablonska, 2018; Ratajczak-Wrona et al., 2014). Impaired resolution of inflammation can lead to many human diseases including cancer (Gartung et al., 2019; Panigrahy et al., 2019; Serhan & Levy, 2018; Sulciner, Serhan, et al., 2018). Carcinogens can disrupt inflammation resolution by impairing host-protective immune cells (e.g. neutrophil and macrophage) phagocytosis of debris (Fishbein et al., 2020; Mehrzad et al., 2011; Moon, Rhee, & Pyo, 1999). Impaired clearance of debris fuels a pro-tumorigenic feedback loop between inflammation, DNA damage and carcinogenesis which can be aggravated by the tumor cell debris generated by cytotoxic cancer therapy including chemotherapy and radiation (Chang et al., 2019; Gartung et al., 2019; Q. Huang et al.,

2011; Sulciner, Serhan, et al., 2018). Cross-talk between the cellular responses to DNA damage, RNA processing, and the extracellular vesicles mediate metastasis (Meng, Yang, & Camp, 2019). Thus, differentiating between genotoxicity and non-genotoxicity mechanisms emphasizing the critical role of the tumor microenvironment including cancer stem cells (or tumor initiating cells), circulating tumor cells, inflammation and angiogenesis are critical for tumor initiation, tumor promotion, tumor dormancy escape and tumor progression (Alitalo et al., 2013; Balkwill, Charles, & Mantovani, 2005; Fujiki, Sueoka, & Suganuma, 2013; Hanahan & Coussens, 2012; Hanahan & Folkman, 1996; Hanahan & Weinberg, 2000, 2011; Trosko, 2001).

**Human carcinogens**

More than 1,400 chemicals and chemical groups are known or likely carcinogens. Human carcinogens include a wide range of substances from alcohol, nitrosamines, aflatoxins, physical stressors (e.g. UV and ionizing radiations), and infections include viruses-, bacteria- and parasites-induced infections (e.g. HIV, hepatitis, HPV and *H. pylori*). Infections, tobacco smoking, carcinogens (e.g. aflatoxins, nitrosamines, polycyclic aromatics), alcohol, obesity, inflammatory bowel disease and other diseases with a chronic inflammatory component have been associated with various cancers (Mantovani, Marchesi, Malesci, Laghi, & Allavena, 2017). Infectious agents including *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus have been classified as carcinogenic agents in humans by International Agency for Research on Cancer (IARC). For example, almost half the world's population is infected by the pathogen *Helicobacter pylori*, categorized as a group I carcinogen, which is responsible for the highest rate of cancer deaths through the world (Chmiela, Karwowska, Gonciarz, Allushi, & Staczek, 2017). Carcinogens are grouped into aminoazo dyes, aromatic amines and amides, aromatic hydrocarbons, metals, natural compounds, olefins, and paraffines/ethers (Luch, 2005). Environmental exposures to soot, wood dust, vinyl chloride,

sulfuric acid, coal emissions, nitrosamines, and other carcinogens may occur via occupations such as carpentry, plastic production, automobile manufacturing, mining and other industries (Hidajat et al., 2019; Rogers, Vaughan, Davis, & Thomas, 1995; Song, Wu, & Guan, 2015). People can be exposed to chemical carcinogens such as trichloroeythylene in daily routines in house cleaning compounds, benzidine which used to be used often for color dyes, or asbestos found in housing insulation (Kumagai-Takei et al., 2018).

While exposure to certain carcinogens has declined with preventative education, other carcinogens cannot be completely avoided as they occur naturally or in the diet. Aflatoxins are mycotoxins produced by fungi which may contaminate a large portion of the world's food supply leading to cancer progression including hepatocellular carcinoma (HCC) (Marchese et al., 2018; Xue et al., 2019; J. Zhang, O. Orang'o, et al., 2019). Other natural carcinogens include minerals like cadmium, nickel or erionite, thorium, crystalline silica, ultraviolet light, or radon gases. Arsenic can be found in contaminated ground water. Polycyclic aromatic hydrocarbons (PAH), such as benzo[a]pyrene (BaP) or dibenz[a,h]anthracene (DBA), can also be ingested in the diet or result in exposure in work environments (Luch, 2005; Poirier, 2016).

Two of the most common human carcinogens are alcohol and tobacco, which is the leading risk factor for lung cancer with up to 80% of lung cancer deaths resulting from smoking inducing inflammation mechanisms such as increased macrophage recruitment, delayed clearance of neutrophils, and stimulation of reactive oxygen species (Walser et al., 2008). While ethanol is not genotoxic nor mutagenic, its metabolite acetaldehyde is a potent local carcinogen (Salaspuro, 2017). Tobacco smoke is also associated with many other carcinogens such as benzene, naphthalene, cadmium, and nickel compounds. Environmental risk factors for bladder cancer, for example, include tobacco smoking, occupational exposure to aromatic amines, exposure to arsenic, chronic infection with *Schistosoma* species, radiation therapy to nearby organs, and the use of alkylating agents (Freedman, Silverman, Hollenbeck, Schatzkin, &

Abnet, 2011; Grosse et al., 2013; Johansson & Cohen, 1997), and smokers are more than twice as likely to get bladder cancer than non-smokers. Moreover, the increased risk from smoking, although progressively decreasing after cessation, remains elevated by 62% and 50% even after 25 and 32 years, respectively (Brennan et al., 2000). The carcinogen alcohol can lead to 4-6% of cancers (Madia et al., 2019). Chronic consumption of alcohol stimulates inflammation due to leakage of bacteria and bacterial products, predominantly lipopolysaccharide (LPS), from the gut into the bloodstream and the liver.

Aflatoxins are a group of mycotoxins produced by *Aspergillus* fungi which are natural carcinogens and contaminate a large portion of the world's food supply including grains and other food sources in tropical and subtropical climates, wetlands, and high temperatures. Up to 5 billion people exposed to aflatoxins are at increased risk for developing hepatocellular carcinoma (HCC) as the carcinogen causes up to 28% of HCC cases globally (Y. Liu & Wu, 2010; Strosnider et al., 2006; J. D. Yang et al., 2019). Although aflatoxins have been primarily characterized as hepatocarcinogens, they are also carcinogenic in other tissues including mammary and lung (Eldridge, Gould, & Butterworth, 1992; X. J. Yang et al., 2012; Yi et al., 2017). Aflatoxins have been linked to high levels of gallbladder cancers in Bolivia and Peru, as well as esophageal squamous cell carcinomas in China (Asai et al., 2012; Xue et al., 2019). Aflatoxins require bioactivation to reactive epoxides for genotoxic activity. The carcinogenicity of aflatoxins can result from metabolic activation of $AFB_1$ to a genotoxic epoxide, with a high prevalence of point mutations in the p53 gene (Chappell, Pogribny, Guyton, & Rusyn, 2016; Tam, Foley, Devereux, Maronpot, & Massey, 1999). $AFB_1$ exposure can induce genotoxicity as reflected by sister chromatid exchange, micronuclei, chromosomal alterations, and DNA and protein adducts (Humans, 2012). Aflatoxin precursors and metabolites can generate cytotoxic and immunosuppressive nongenotoxic activity (Bianco et al., 2012). $AFB_1$ exhibits the highest

hepatotoxic potential and has synergistic carcinogenic effects with fumonisin $B_1$, another hepatocarcinogen, as well as with lipopolysaccharide (LPS), hepatitis C, and alcohol (Abbes, Ben Salah-Abbes, Jebali, Younes, & Oueslati, 2016; Barton, Ganey, & Roth, 2000; Chu et al., 2018). Aflatoxins have demonstrated genotoxic as well as nongenotoxic mechanisms of carcinogenesis including significant numbers of DNA-adducts from $AFB_1$ from HCC analysis (C. J. Chen, Zhang, Lu, & Santella, 1992; W. J. Wang, Xu, Yu, & Xu, 2017).

Triclosan (TCS) is a chemical that is commonly used in toothpaste, cosmetics, cooking materials, and other products as an antimicrobial but has recently been identified as a possible carcinogen. Up to 75% of people in the United States have likely been exposed to the chemical (Weatherly & Gosse, 2017). Importantly, this carcinogen exposure induces an inflammatory response even at very low doses by activating TLR4 signaling and altering gut microbiota predisposing to colon carcinogenesis (H. Yang et al., 2018). TCS has been found in fluids and tissues of people of all ages and has demonstrated a wide range of effects including endocrine disruption, induction of inflammation and oxidative stress, epigenetic alterations, and carcinogenicity (Yueh & Tukey, 2016).

The perfluorinated carboxylic acids (PFCAs) are a family of synthetic perfluorinated compounds that include perfluorooctanoic acid (PFOA, also known as C8), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA). PFOA has been used in the manufacture of items such as Teflon non-stick coating, Gore-Tex water-repellent gear, microwave popcorn bags, carpet, and fire-fighting foam (Nicole, 2013). Most carcinogens such as PFOA frequently exhibit several modes of action in causing cancer in animals. For example, PFOA can initiate and cause cancer through promoting oxidative stress and DNA damage (Klaunig et al., 2012; X. Yao & Zhong, 2005). PFOA can also stimulate breast and colon cancer cell invasion via matrix metalloproteinases (MMPs) (Miao et al., 2015; W. Zhang et al., 2014).

Nitrosamines including N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) play a critical role in the initiation stage of carcinogenesis (J. Y. Hong et al., 1991; Ratajczak-Wrona, Jablonska, Garley, Jablonski, & Radziwon, 2013). IARC has classified NDMA and NDEA as probable carcinogens to humans (Group 2A) (W. Wang, Yu, An, & Yang, 2016). NDMA induces cancer via a dose-response (Peto, Gray, Brantom, & Grasso, 1984). NDMA has demonstrated highly carcinogenic, mutagenic, and teratogenic activity (Dennehy & Loeppky, 2005; Fitzgerald & Robinson, 2007; O. Zhang et al., 2016). Nitrosamines have been associated with an increased risk of many cancers including gastric, esophageal, nasopharyngeal, and bladder cancers (Bartsch, Ohshima, Shuker, Pignatelli, & Calmels, 1990; Mirvish, 1995). N-nitroso compounds are used as a prototype carcinogens to induce various types of cancer in animal models, including liver, lung, bile duct and pancreatic (V. Sharma & Singh, 2014). In a large matched case–control study of pancreatic cancer, a significant positive association was found for NDEA, NDMA and pancreatic cancer (J. Zheng et al., 2018). Moreover, extensive studies have demonstrated the cytotoxicity, genotoxicity, carcinogenicity, mutagenicity, as well as reproductive and developmental toxicity of nitrosamines (W. H. Chen & Young, 2009; Yin et al., 2019; Zhao et al., 2008; Zhou, Boyd, Qin, Hrudey, & Li, 2009). Tumors in multiple organs have been induced by nitrosamine compounds in 39 species including higher primates (Bogovski & Bogovski, 1981). NDMA causes cancer both as a single dose and with long-term exposure to lower quantities (Pottegard et al., 2018). Other carcinogens such as dibenzo[*a*,*l*]pyrene (DBP) can potently transform cells, even in the absence of detected DNA adducts (Nesnow et al., 1997).

**Carcinogenesis is a multi-stage, multi-mechanism process**

Although epidemiology and studies with human tissues or cells are relevant to carcinogen exposure in humans, the mechanistic of action studies underlying carcinogenesis are focused in animal models for obvious ethical considerations. Laboratory animals are routinely utilized to mimic cancer in humans because there are more genetic, physiologic, biochemical, and metabolic similarities than differences to humans, large sample size, reproducibility, and feasibility to generate various cancers as well as study the mechanism of action of carcinogens (Maronpot et al., 2004). For example, FDMA is a powerful carcinogen which induces 100% incidence of transitional cell carcinoma of the urinary bladder in the rat and the Syrian golden hamster (Lijinsky & Taylor, 1975; Reznik-Schuller, 1981). An example of an initiation-promotion model is a DMBA-induced, phorbol 12-myrisate 13-acetate (PMA) promoted or 12-*O*-tetradecanoylphorbol-13-acetate (TPA) promoted squamous cell carcinoma (Monga et al., 2014; Muller-Decker et al., 2002). A frequent model of colon carcinogenesis is induced by azoxymethane (AOM) and promoted with dextran sodium sulfate (DSS) (Hattori et al., 2019; Yamaguchi, Takai, Hosono, & Seki, 2014; H. Yang et al., 2018). N-nitrosomethylbenzylamine (NMBA)-induced tumorigenesis in esophagus is a model of human esophageal squamous cell carcinoma used for investigations of chemical carcinogenesis (Carlton et al., 2002; Yan et al., 2015). Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancer is commonly used to study mechanisms of lung and smoking-induced carcinogenesis (Rioux & Castonguay, 1998; H. C. Zheng & Takano, 2011). 4-nitroquinaline 1-oxide (4-NQO) is utilized to induce tongue and oral cancers (Yanaida et al., 2002). N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) is used to create a mouse model of human muscle invasive bladder cancer to study histological, physiological, molecular, and mutational mechanisms of carcinogenesis (Fantini et al., 2018). Various chemically induced cancer models reflect various routes of exposure as tools to study mechanisms of carcinogens (Figure 2).

Carcinogenesis, the process of initiating and stimulating cancer, is viewed as a multi-hit/multi-step process from the transition of normal cells into cancer cells via multiple mechanisms of action. In experimental cancer models, carcinogenesis is a multi-stage, multi-mechanism process, consisting of the “initiation,” “promotion,” and “progression” (Weinstein et al., 1984). The well-established mouse skin model is an important tool to study the mechanisms of multistage carcinogenesis (Marks, Furstenberger, Neufang, & Muller-Decker, 2003; Perez-Losada & Balmain, 2003; Slaga, Budunova, Gimenez-Conti, & Aldaz, 1996; Zoumpourlis, Solakidi, Papathoma, & Papaevangeliou, 2003). Initiation can be induced by the topical application of the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA), which is potently immunosuppressive. Here, mutations are not sufficient to induce malignant transformation. In the mouse skin model the first stage involves a tumor initiator with the genetic material of stem cells leading to changes in growth control and/or differentiation. The major activity of tumor promoters is the specific expansion of the initiated stem cells in the skin (Perez-Losada & Balmain, 2003; Slaga et al., 1996). This can occur by both direct and indirect mechanisms that involve the direct growth stimulation of the initiated cells or cytotoxicity (Perez-Losada & Balmain, 2003). Promotion of tumorigenesis is generated by the topical application of phorbol esters such as TPA to the skin, leading to epithelial cell proliferation with increased expression of the ligand EGF as well as cyclin D1, c-Jun, c-Fos, and c-Myc (DiGiovanni, Rho, Xian, & Beltran, 1994). TPA-treated mice form multiple benign papillomas and conversion to malignant squamous carcinomas within 10–20 weeks. An initiated cell can be amplified to a premalignant lesion, such as a papilloma in the skin, a nodule in the breast, or a polyp in the colon eventually invading and metastasizing to distal sites (the “progression” phase) (Trosko & Carruba, 2017).

Notably, bacterial and viral infections can also be carcinogenic. *Helicobacter pylori*, hepatitis B or C, Epstein-Barr virus, and other infections are associated with increased cancer

risk and carcinogenesis (Moss & Blaser, 2005). In a mouse model benzo(a)pyrene (BaP) and lipopolysaccharide (LPS) promote lung tumorigenesis (L. Huang et al., 2019). Multiple liver infections including liver fluke and *Clonorchis sinensis* administered with NDMA cause experimental cholangiocarcinoma (E. M. Kim, Bae, Choi, & Hong, 2019; Laothong et al., 2013). Hepatitis C virus is synergistic with $AFB_1$ in hepatocarcinogenesis including an enhanced inflammatory response and lipid peroxidation (Jeannot et al., 2012; London et al., 1995). While viral or bacterial infections can induce DNA methylation indirectly via chronic inflammation, certain viruses have direct activity on the epigenetics of host cells (Hattori & Ushijima, 2016).

Anti-bacterial agents can improve outcome by reducing associated inflammation and manipulating the microbiome in colon carcinogenicity models (Hattori et al., 2019). Parasite infection results in immune responses to generate nitrosamines (NDMA) in humans (Satarug et al., 1998). Additionally, carcinogens such as aflatoxin $B_1$ may promote influenza viral replication demonstrating synergy between environmental toxins and infections in causing cancer (Y. Sun et al., 2018). The immune response to bacterial infection including stimulated eicosanoid production (e.g. prostaglandin $E_2$ ($PGE_2$) and cytokines (e.g. IL-8) shows the tight association between carcinogenesis and the immune response, particularly an inflammatory response (Biarc et al., 2004).

**Detection of carcinogens**

An important strategy to prevent carcinogen-induced cancers is the detection of environmental carcinogens. Biomonitoring is critical to evaluating exposure to chemical carcinogens and involves the measurement of chemicals or their metabolites in various human samples including blood, urine, breast milk, and hair. Carcinogens can originate from various

sources such as heavy metals, pesticides, industrial chemicals, commercial products and solvents. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis is a powerful analytical technique utilized to detect genotoxic and non-genotoxic chemicals (e.g. in the environment and food) at very low concentrations (Escriva, Font, Manyes, & Berrada, 2017). One-step competitive enzyme immunoassays have been developed for monitoring carcinogen (e.g. fumonisin B1 and ochratoxin A) contamination in food such as cereals (X. Liu et al., 2015; Shu et al., 2016). Many genotoxic carcinogens may also be detected via DNA binding assays with a new biosensor assay detecting carcinogens in contaminated food samples with a 24-base guanine rich DNA segment at ranges as low as 0.0001 ppm (Sani, Heng, Marugan, & Rajab, 2018). DNA adducts formed from genotoxic carcinogens can be identified in exposed people. Environmental carcinogens can be detected in serum, blood, and urine samples allowing for the measurement of chemicals such as tobacco and lead (Pirkle, Osterloh, Needham, & Sampson, 2005). Detection methods including electrochemical detection, mass spectrometry, fluorescence, and immunohistochemistry, have advanced to accelerator mass spectrometry, which can detect about 1 in $10^{12}$ nucleotides if labeled with a heavy isotope. Importantly, this mass spectrometry technique can be used to identify DNA as well as protein adduct formation to more accurately determine chemical carcinogen exposure in human populations (Poirier, Santella, & Weston, 2000). A metabolomics approach can predict the activity of non-genotoxic carcinogens via alterations in the levels of eicosanoids and reactive oxygen species (Ament et al., 2013).

## 2. Mechanisms of pro-tumorigenic activity by carcinogens

### Genotoxicity and mutations

Genotoxicity is measured via a series of *in vitro* and *in vivo* assays such as gene

mutations in bacteria and mammalian cells; chromosomal aberrations, micronuclei formation, unscheduled DNA synthesis or DNA damage in mammalian cells and in rodents. Environmental mutagens such as ultraviolet light or cigarette smoke can lead to a high mutation rate in certain cancer types (e.g., skin and lung) (Srivastava, Reid, Ghosh, & Kramer, 2016). Carcinogens can act as environmental stress factors and induce cancer-promoting genotoxicity by binding and mutating DNA via adduct formation. Carcinogens are metabolized by the human body to generate DNA-reactive species. Further, carcinogens can induce epigenetic changes which can lead to cellular transformation. DNA repair is critical for cancer prevention as DNA repair prevents the genetic mutations in normal cells (Kay et al., 2019). Examples of genotoxic carcinogens include NDMA or 4,4'-methylenedianiline (MDA) which bind directly to DNA generating adducts, DNA damage, and mutations (Kessler et al., 2015). Cancer risk is determined beyond only DNA mutations. Aflatoxin $B_1$ ($AFB_1$) exposure generates genetic mutations via DNA adducts and is associated with a specific mutational pattern, including a mutational signature of *TP53,* in humans with aflatoxin-induced HCC (Besaratinia, Kim, Hainaut, & Pfeifer, 2009; Chawanthayatham et al., 2017). Nitrosamines, including NDMA, are mutagenic, genotoxic, and carcinogenic, even at low doses (Wagner, Hsu, Lagunas, Mitch, & Plewa, 2012; H. Y. Wang, Qin, Dong, Lv, & Wang, 2017). Genotoxic carcinogens, such as NDMA, can induce DNA double-strand breaks in the comet assay and induce transformation of non-tumorigenic cells, such as NIH3T3 fibroblasts, to cancer causing cells (Le Hegarat et al., 2010; Liviac, Creus, & Marcos, 2011; H. Y. Wang et al., 2017; Winter et al., 2008). Genotoxicity induced by NDMA is further demonstrated in extrahepatic tissues of rats by the persistence of DNA damage in the lung, liver, kidney and nasal cavity (Brendler, Tompa, Hutter, Preussmann, & Pool-Zobel, 1992; Pool, Brendler, Liegibel, Tompa, & Schmezer, 1990; Pool-Zobel et al., 1992). Also, N-nitroso compounds such as NDMA activate *ras* oncogenes, which play a pro-tumorigenic role in the development of various cancers (e.g., colon) (Tricker & Preussmann, 1991). DNA damage induced by NDEA increases micronuclei due to DNA breakage that could not be repaired,

leading to an increase in chromosomal aberrations, and apoptotic cell death which can lead to cancer (Aiub et al., 2011; Fishbein et al., 2020). Thus, carcinogens can initiate tumor growth via genotoxic mechanisms in synergy with nongenotoxic processes including cell death, inflammation, oxidative stress, angiogenesis and tissue injury.

**Nongenotoxic mechanisms**

Non-cell-autonomous contribution to tumorigenesis from the non-transformed "host-tissue", epitomized by tumor vasculature and inflammation, are crucial for tumor expansion and progression (Bhowmick, Neilson, & Moses, 2004; Folkman, 2007; Greten & Grivennikov, 2019). The tumor stroma is comprised of a variety of cells essential for tumor growth, including "tumor associated" fibroblasts, inflammatory cells (e.g. macrophages), and the pericytes surrounding the tumor endothelium (Hanahan & Coussens, 2012). Nongenotoxic carcinogens such as 1,4-dichloribenzene (DCB), phenobarbital sodium (PB), benzene, asbestos, arsenic or piperonyl butoxide (PBO) do not interact directly with DNA but promote carcinogenesis via other key characteristics of carcinogens (M. T. Smith et al., 2016; M. T. Smith et al., 2020). Many carcinogens can exhibit both genotoxic and nongenotoxic activities. In a study of mRNA biomarkers following carcinogen exposure signatures of nongenotoxic carcinogens involved cell injury and necrosis leading to regenerative proliferation, as well as immunosuppression (Kossler et al., 2015). However, many chemicals considered to be nongenotoxic carcinogens actually possess certain genotoxic activities (Melnick, Kohn, & Portier, 1996). Importantly, chronic inflammation can lead to genetic instability and DNA damage without direct DNA adduct mechanisms of genotoxic carcinogens, which along with the ability to dysregulate DNA repair pathways potently promotes carcinogenesis (Colotta, Allavena, Sica, Garlanda, & Mantovani, 2009). Interestingly, both genotoxic, and non-genotoxic carcinogens generate oxidative stress

as an underlying cause for carcinogenesis (Deferme, Wolters, Claessen, Briede, & Kleinjans, 2015). A new highly innovative model of carcinogenesis has been proposed as the Inflammation Somatic Model (ISM) based off the 2-stage somatic mutation model suggesting genotoxic effects are not sufficient to promote carcinogenesis and that inflammation as well as oxidative stress can prime tissues for cancer growth (Bogen, 2019). Importantly, $AFB_1$-induced hepatocarcinogenesis was prevented in rats with systemic administration of an anti-inflammatory and antioxidant CDDO-Im despite significant DNA adduct burden suggesting a protective effect and a DNA damage threshold (Eaton & Schaupp, 2014; Johnson et al., 2014). Thus, carcinogens can generate a feedforward cycle of tissue damage, inflammation, oxidative stress, mutagenesis, cell death, and subsequent regeneration and carcinogenesis (Figure 3).

**Inflammation and DNA damage**

Inflammation generated from carcinogens, such as crystalline silica, can be a critical underlying mechanism promoting genotoxicity (Borm et al., 2011). Inflammation-induced cell proliferation potently stimulates carcinogen-induced mutations (Kiraly et al., 2015). These elegant studies demonstrate a key mechanism by which inflammation can act synergistically with DNA damage to induce mutations that drive cancer progression and cancer recurrence (Kiraly et al., 2015). Inflammation enhances the production of reactive chemical species that damage DNA which may stimulate mutations (Kay et al., 2019). Inflammation and cholangiocarcinoma (bile duct tumors) can be induced by NDMA combined with infections (Wongsena et al., 2018; Yothaisong et al., 2014). Infection and NDMA-induced tumor tissue exhibit significantly higher numbers of inflammatory cells (especially eosinophils), bile duct proliferation, and IL-17+ cell infiltration compared to normal livers (Wongsena et al., 2018). NDMA activates the PI3K-Akt/PKB pathway in human neutrophils which activates pro-

inflammatory transcription factors NF-κB, c-Jun, and FosB involved in nitric oxide (NO) production (through modulation of inducible nitric oxide synthase (iNOS) expression) (Ratajczak-Wrona et al., 2014). Thus, nitrosamines including NDMA stimulate inflammation via oxidative stress and an immune response (Hebels, Jennen, Kleinjans, & de Kok, 2009). The association between N-nitroso precursors and esophageal cancer may be modified by inflammation (Rogers et al., 1995). NDEA stimulates inflammatory cell infiltration (e.g. (lymphocytes, neutrophils, eosinophils, and Kupffer cells), pro-inflammatory cytokines, including the IL-1 and IL-6 signaling pathway, as well as oxidative stress and proliferation in the liver, stomach and colon including cyclooxygenase (COX-2) expression in hepatic tissues (Ding, Wu, Wei, Shu, & Peng, 2017; X. Y. Duan et al., 2014; Hebels et al., 2009; Mansour et al., 2019). Thus, inflammation plays a critical role in carcinogen-induced cancers.

Carcinogens such as NDMA also induce fibrosis leading to inflammation accompanied by the infiltration of lymphocytes, monocytes, granulocytes, and macrophages into the space of Disse (Koyama & Brenner, 2017). Activation of transcription factors including NF-κB, c-Jun, and FosB in inflammatory cells underlie NDMA-induced NO synthesis/release (Ratajczak-Wrona et al., 2013). N-nitrosamines are activated by inflammatory cells, such as macrophages (Sheweita, El-Shahat, Bazeed, Abu El-Maati, & O'Connor, 2004). NDMA increases the proliferation of macrophages and expression of Raf in tumor-bearing lungs. Thus, the increase of both Raf and PCNA in the lung parenchyma surrounding NDMA-induced lung tumors suggesting an important lung tumor–macrophage interaction (Ramakrishna et al., 2002). IL-1β is also able to contribute to fibrosis while TNF-α increases anti-apoptotic signals to avoid cell death (Amicone & Marchetti, 2018). Importantly, while carcinogens can induce inflammation, chronic inflammation can also increase carcinogen exposure and uptake within the body by weakening barrier functions (Greten & Grivennikov, 2019).

**Pro-inflammatory signaling**

Nuclear factor kappa B (NF-κB) is a transcription factor that plays a critical role in inflammation, cancer invasion, regulation of apoptosis, oxidative stress, tumor progression, and metastasis (Karin, 2009; Karin & Greten, 2005; Q. Shi et al., 2017). NF-κB is activated by Toll-like receptors (TLR) signaling microbes, tissue damage, or primary cytokines and can trigger production of multiple pro-inflammatory cytokines, prostaglandin synthesis enzymes (including COX), nitric oxide (NO) synthase, angiogenic molecules, and other pro-tumorigenic mediators. STAT3/NF-κB signaling is important in cancer-related inflammation associated with IL-6-induced chronic inflammation (Colotta et al., 2009). In addition to inflammation and oxidative stress, NF-κB plays a larger role in avoidance of apoptosis, which permits tumor cells to evade death while also allowing non-tumor cells to accumulate damaged cells, mutations, and increased compensatory proliferation (Y. M. Yang, Kim, & Seki, 2019). In a MYC transgenic model of hepatocellular carcinoma, deletion of NF-κB essential modulator (NEMO) from hepatocytes led to accelerated tumorigenesis but also switched the tumor phenotype from HCC to combined hepatocellular cholangiocarcinoma as NF-κB plays a modulatory role (J. He et al., 2019). PFOA can regulate MMPs (e.g. MMP2 and MMP9) release by regulating NF-κB phosphorylation levels (Corsini et al., 2011; Miao et al., 2015). PFOA also induces the expression of the pro-tumorigenic molecules MMP2 and MMP9 via NF-κB in breast cancer cells (W. Zhang et al., 2014). In a model of NDMA-induced esophageal carcinoma lyophilized black raspberries demonstrated anti-tumorigenic activity via the downregulation of NF-κB signaling leading to reduced oxidative stress markers and upregulation of antioxidant enzymes GPx and SOD (Q. Shi et al., 2017). Chemopreventive activity of natural compounds, including flavonoids, in nitrosamine-induced hepatocarcinogenesis can lead to anti-inflammatory and antioxidant activity with reduction of MMP and VEGF angiogenic signals via NF-κB inhibition (Bishayee et al., 2013; S. Liao et al., 2019; Sadeeshkumar et al., 2017; Sivaramakrishnan & Niranjali Devaraj, 2009;

Subramanian & Arul, 2013). In a NDEA-induced hepatocarcinogenesis model, deletion of IkB kinase Beta (IKKβ) activates NF-κB from hepatocytes demonstrating increased tumorigenesis via ROS production, JNK activation, and hepatocyte death. However, hepatocarcinogenesis was decreased with IKKβ deletion from hepatocytes and Kupffer cells via reduced compensatory proliferation of hepatocytes demonstrating not only the importance of NF-κB signaling and its reduction in tumor associated immune cells, but the importance of cellular crosstalk in carcinogen-induced cancers (Maeda, Kamata, Luo, Leffert, & Karin, 2005). Thus, NF-κB activation can mediate carcinogen-induced inflammatory cancers.

**Pro-inflammatory cytokines**

Downstream signaling of NF-κB leads to chronic inflammation via upregulation of a series of pro-inflammatory cytokines and chemokines which promote carcinogenesis. Importantly, "cytokine storms" which are well established in infection (e.g. severe coronavirus (COVID-19) (Hammock, Wang, Gilligan, & Panigrahy, 2020; Panigrahy et al., 2020), are becoming appreciated in the setting of cancer therapy as immunotherapy and chemotherapy create an inflammatory tumor microenvironment via the release of a series of cytokines by immune cells (Filippou & Karagiannis, 2020; Gartung et al., 2019). In a model of NMBA-induced esophageal tumorigenesis, deficiency of riboflavin increases pro-inflammatory cytokines, elevating levels of peripheral neutrophils and monocytes, as well as the oxidative stress marker 8-0HdG (Pan et al., 2019). In addition, NDMA increases gut permeability, which accelerates the entry of LPS into the blood stream. Activated Kupffer cells then produce several cytokines and growth factors such as TNF-α, TGF-β1, PDGF, and IL−1β (George, Tsuchishima, et al., 2019). These signaling molecules drive chronic inflammation with continued carcinogen exposure as the pro-inflammatory cytokines such as IL-1β, IL-6, IL-22, IFN-γ, and TNF-α further activate NF-κB and TGF-β generating a feedforward pro-tumorigenic inflammatory cycle (George,

Tsuchishima, et al., 2019). Further, co-exposure to $AFB_1$ and $FB_1$ increase carcinogenicity via upregulation of IL-10, IL-4, lipid peroxidation (LP), and caspase 3 (Abbes et al., 2016). Anti-carcinogenic compounds, such as cordycepin, a component of a rare caterpillar fungus, demonstrated protective effects in NDEA-induced HCC via downregulation of pro-inflammatory cytokines IL-6, IL−1β, IL-2, TNF-α and modulation of the PI3K-Akt-mTOR pathway (Keshari et al., 2017; Zeng et al., 2017). In an AOM/DSS model of colon carcinogenesis, an anti-cancer compound celastrol, reduces COX-2, TNF-α, IL-6, IL−1β and iNOS (Barker et al., 2018). Another natural product, flaxseed, was able to reduce lung tumorigenesis in an NNK carcinogen-induced model affected Akt/JNK/MAPK signaling pathways to reduce the carcinogen-induced pro-inflammatory IL-6, IL-8 and increase the anti-inflammatory IL-12α (Chikara et al., 2018). Demonstrating the importance of the pro-inflammatory cytokine TNF-α, TNF-α inhibition or deletion inhibits tumorigenesis in a NDEA-induced HCC model while reducing proliferation preventing activation of progenitor cells (Jing et al., 2018).

Other carcinogens such as asbestos have extensive changes on immune cells including expression of MMP7, CXCR5, CXCL13, and CD44 on exposed T cells and increased IL-6 initiating crosstalk between B and T cells with mesothelial and epithelial cells (Kumagai-Takei et al., 2018). Additionally, PFOA stimulates the production of critical pro-tumorigenic cytokines in multiple tissues including TNF-α, IL-1β and IL-6 in the liver or spleen, and increases proto-oncogenes (e.g. c-Myc activity in the spleen and thymus), which may be another important mechanism by which carcinogens cause cancer (Son et al., 2009; J. H. Yang, 2010). PFOA may therefore impair the host-protective immune response. Carcinogen-induced immunotoxicity also occurs in other animals such as harbor porpoises living in oceans contaminated by persistent organic pollutants, polychlorinated biphenyls, and polybrominated diphenyl ether, resulting in impaired cellular responses from atrophy of the thymus and splenic depletion (Beineke, Siebert, Stott, Muller, & Baumgartner, 2007).

**Eicosanoids**

Products of arachidonic acid metabolism called eicosanoids, including prostaglandins, leukotrienes, lipoxins, and other cyclooxygenase or lipoxygenase products are potent regulators of inflammation, angiogenesis, and tissue homeostasis (Greene et al., 2011; Imig & Hammock, 2009; D. Wang & Dubois, 2010). Arachidonic acid is cleaved from the cell membrane by phospholipase 2 ($PLA_2$) and other enzymes and when in the cytosol can be metabolized by 3 main branches: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) enzymes. Studies on the arachidonic acid pathway initially focused on its role in inflammatory and cardiovascular diseases (Imig & Hammock, 2009; Zeldin, 2001). Most recently**,** arachidonic acid-derived eicosanoids have attracted increasing attention due to the increasing evidence of their role in cancer biology (Hyde & Missailidis, 2009; Sulciner, Serhan, et al., 2018). Besides epoxyeicosatrienoic acids (EETs), CYP also generate hydroxyeicosatrienoic acids (HETEs) (Zeldin, 2001) whose role in cancer biology is not as extensively characterized as the COX and LOX-derived eicosanoids (A. M. Guo et al., 2008; Moreno, 2009).

Eicosanoid dysregulation can lead to chronic inflammation and oxidative stress or prevent pro-apoptotic signals generating the accumulation of damaged cells. The ratios of eicosanoids with opposing effects can be used to predict pathology following carcinogen exposure (Jelinska, Bialek, Gielecinska, Mojska, & Tokarz, 2017). Interestingly, NNK can interact with beta-adrenergic receptors to directly stimulate the release of arachidonic acid, which could lead to aberrant eicosanoid production (Schuller, Tithof, Williams, & Plummer, 1999). In addition to their roles in inflammation, the eicosanoid pathways also play a role in metabolism and bioactivation of carcinogens. CYP450 enzymes are also the main activators of many environmental carcinogens as they play a large role in drug and toxin metabolism.

Interestingly, COX isoenzymes generate ROS and also may be responsible for bioactivation of multiple carcinogens via metabolism of aromatic and heterocyclic amines or polycyclic hydrocarbons which may account for the carcinogen specific activity of cyclooxygenases (Wiese, Thompson, & Kadlubar, 2001). Additionally, LOX is a peroxidase also generating ROS and free radicles may play an important role in the bioactivation of NNK via oxidation as the CYP450 enzymes were found to be only partially responsible for its activation (T. J. Smith, Stoner, & Yang, 1995).

The COX pathway leads to pro-tumorigenic and pro-inflammatory activity in multiple models, including carcinogen-induced cancers. COX-2 activation can sensitive tissues to genotoxic carcinogens (Muller-Decker et al., 2002). A tobacco carcinogen upregulates COX-1 expression correlated with NF-κB activation (Rioux & Castonguay, 2000). Carcinogenesis of the skin upregulates COX-2 and prostanoid signaling but suppression of COX-2 and $PGE_2$ synthase may have anti-tumorigenic effects (DeCicco-Skinner et al., 2013; Enoki et al., 2012). COX-2 was also demonstrated to stimulate tumorigenesis in a breast cancer model as COX-2 deletion reduced inflammation-associated carcinogenesis (Markosyan et al., 2011). NF-κB activation also increases colon carcinogenesis via upregulation of COX-2 leading to aberrant eicosanoid production (B. Li et al., 2019). Interestingly, a flavonoid with anti-cancer properties regulates NDEA-induced carcinogenesis by downregulating COX-2/$PGE_2$, as well as increasing antioxidants (Siddiqi, Saidullah, & Sultana, 2018). However, the role of COX-2 may be context-dependent as COX-2 overexpression and upregulated prostaglandins can suppress tumorigenesis in skin (Bol et al., 2002). Moreover, COX-2 can also be host-protective by generating anti-inflammatory and pro-resolution lipid mediators from arachidonic acid including lipoxins and pro-resolution prostaglandins (Gilroy & Colville-Nash, 2000; Levy, Clish, Schmidt, Gronert, & Serhan, 2001).

The lipoxygenase (LOX) pathways also play important roles in carcinogen-induced cancers via inflammation. Interestingly, ethanol stimulates carcinogenesis in a 4-NQO oral carcinogenesis model via induction of the 5-LOX pathway (Y. Guo, Wang, Zhang, Sun, & Chen, 2011). Similarly, use of a 5-LOX inhibitor (garcinol) or herbal extracts (zyflamend) block $LTB_4$ to exhibit chemopreventive activity in a DMBA-induced oral carcinogenesis model (X. Chen et al., 2012; P. Yang et al., 2008). Interestingly, cumin, a common spice used in curries, contained curcumin which inhibited TPA-induced skin inflammation by inhibiting the LOX metabolites 5-HETE and 8-HETE, as well as multiple prostaglandins (M. T. Huang et al., 1991). In an AOM/DSS model of colon inflammation-associated carcinogenesis, cysteinyl leukotriene receptor 1 (CysLT1R) deletion reduced pro-inflammatory cytokines leading to decreased leukocyte and macrophage infiltration via eicosanoid regulation (Osman et al., 2017). However, 15-lipoxygenase-1 (ALOX15) generates other lipid mediators which terminate inflammation, and downregulates NF-κB signaling, IL-6, IL−1β, and TNF-α in AOM/DSS-induced colorectal cancer-associated inflammation (R. Tian et al., 2017). Zileuton, a 5-LOX inhibitor, is more potent in inhibiting DMBA oral carcinogenesis than celecoxib, a selective COX-2 inhibitor, via suppression of eicosanoids. A leukotriene $A_4$ hydrolase ($LTA_4H$) inhibitor suppresses carcinogenesis via eicosanoid regulation (Z. Sun et al., 2006). However, as each of these eicosanoid pathways play key roles in carcinogen-associated inflammation, dual eicosanoid inhibition (e.g. dual COX-2/sEH inhibition) may exhibit more potent anti-tumor activity then targeting a single eicosanoid pathway (Fishbein et al., 2020; Gartung et al., 2019; G. Zhang et al., 2014). Supplementation of vitamin E or selenium in NMBA-exposed esophagus inhibited carcinogenesis via downregulation of both COX and LOX pathways inhibiting proliferation and angiogenesis (H. Yang et al., 2011).

In the context of arachidonic acid metabolism CYP450 enzymes generate monohydroxyeicosatrienoic acids (HETEs) and epoxyeicosatrienoic acids (EETs) (Panigrahy,

Greene, Pozzi, Wang, & Zeldin, 2011; Zeldin, 2001). CYP450-derived eicosanoids including EETs and epoxydocosapentaenoic acids (EDPs) play a key role in angiogenesis, tumor growth, and metastasis (Imig & Hammock, 2009; Panigrahy et al., 2012; G. Zhang, D. Panigrahy, et al., 2013). Epoxygenated fatty acids (EpFA), eicosanoid metabolites generated by CYP450, were increased in the plasma and colon of azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colon carcinogenesis (W. Wang et al., 2019). Generally, EETs, which are further metabolized into pro-inflammatory dihydroxyeicosatrienoic acids (DHETs) by soluble epoxide hydrolase (sEH), exhibit anti-inflammatory and pro-angiogenic activity (Gartung et al., 2019; Panigrahy et al., 2012; G. Zhang et al., 2014). Analysis of patients with HCC demonstrated favorable survival prognostics with increased CYP4F2, CYP4F12, and CYP4V2 expression (Eun, Cho, Lee, Seong, & Kim, 2018). Pharmacologic inhibition or genetic ablation of CYP monooxygenases, which generate epoxygenated fatty acids including EpOME, suppressed AOM/DSS-induced colon tumorigenesis (W. Wang et al., 2019). 2,3,7,8-tetrachlorodibenzop-dioxin, an environmental carcinogen, activates the aryl hydrocarbon receptor (AHR) transcription factor for CYP enzymes leading to dysregulated eicosanoid production (Diani-Moore, Ma, Gross, & Rifkind, 2014). Importantly, following dioxin exposure these arachidonic acid metabolites were found in the heart of a chick embryo even though the heart lacks enzymes to metabolize arachidonic acid, suggesting systemic movement of eicosanoids may generate profound systemic and chronic effects (Diani-Moore et al., 2014).

**Oxidative stress**

Oxidative stress results from an imbalance between production of free radicals and reactive oxygen or nitrogen species (RONS) and their elimination by through protective mechanisms, including antioxidants (Tu, Wang, Li, Liu, & Sha, 2019). Inflammation can

stimulate tumor-promoting and tumor-initiating reactive chemical species, which can damage DNA leading to genetic instability, a hallmark of cancer, and oxidative stress. Oxidative and endoplasmic reticulum stress is often intertwined in inflammatory processes and is also induced by environmental carcinogens to promote tumor growth (Fishbein et al., 2020; Nowsheen, Aziz, Kryston, Ferguson, & Georgakilas, 2012). The importance of oxidative stress is demonstrated via nongenotoxic carcinogens, such as dicyclanic hepatocarcinogenesis and arsenic, and their ability to induce DNA damage indirectly via increased ROS production, mitochondrial damage, upregulation of stress genes, and biomarkers such as 8-hydroxy-deoxyguanosine (8-OHdG) (S. X. Liu et al., 2005; Moto et al., 2006). Inflammation, including upregulation of COX-2, recruits leukocytes including neutrophils which can trigger oxidative damage, thus anti-inflammation can also prevent oxidative insult during tumorigenesis (Murakami et al., 2000). Interestingly, neutrophils can also generate further production of N-nitroso carcinogens during intestinal inflammation promoting colon carcinogenesis (Vermeer et al., 2004). NDMA increases iNOS in neutrophils associated with carcinogenesis (Ratajczak-Wrona et al., 2014). Red meat, known to contain multiple carcinogenic compounds including nitrosamines, polycyclic aromatic hydrocarbons (PAHs), and heterocyclic aromatic amines (HAAs), increases the risk of human cancers via lipid peroxidation, inflammation, and generation of reactive oxygen species (Turesky, 2018). N-nitroso compounds and their metabolism stimulate pro-inflammatory reactive oxygen species causing cellular injury (Aiub, Pinto, & Felzenszwalb, 2003, 2004; Akshatha, Raval, Arpitha, Raval, & Ghodasara, 2018; Bansal, Bansal, Soni, & Bhatnagar, 2005b). Oxidative stress-induced cell injury plays a crucial role in NDEA-induced carcinogenesis as a single necrogenic dose of NDEA enhances levels of hepatic lipid peroxidation (LPO) and conjugated dienes as markers of oxidative stress (Bansal, Bansal, Soni, & Bhatnagar, 2005a).

The genotoxic activity of nitrosamine compounds such as NDMA can stimulate pathways of oxidative stress and inflammation leading to carcinogenesis (Hebels et al., 2009). NDMA stimulates reactive oxygen species and induces toxicity including a dramatic change in the body weight of animals (V. Sharma & Singh, 2014). The NDMA-induced genotoxic activity and DNA damage in cancer cells can be measured by DNA strand breaks and oxidative DNA damage induced by intracellular reactive oxygen species (ROS). ROS are an important mechanism for tumor promotion and oxidative stress. As a consequence of NDEA-induced oxidative and nitrosative DNA damage (Klaunig & Kamendulis, 2004; Unsal & Belge-Kurutas, 2017), inflammatory markers such as IL-1β and TNF-α are significantly elevated in liver, stomach and colon (Mansour et al., 2019). The NDMA-mediated increase in NO production may also contribute to oxidative stress, a factor in the pathophysiology of numerous immune disorders. NO is a versatile regulator of numerous bodily processes and a major signaling molecule (Ratajczak-Wrona et al., 2013), while iNOS is found in various cells, including neutrophils (Beck et al., 1999; Mantovani, Cassatella, Costantini, & Jaillon, 2011). Thus, carcinogens could regulate immune cells and inflammation in part, by affecting NO formation which may lead to modulated immune function.

Other carcinogen induced processes, such as fibrosis, contribute to the vicious cycle of inflammation and oxidative stress during carcinogenesis (Ahmad & Ahmad, 2018; George, Tsuchishima, et al., 2019). These processes lead to cellular injury and initiate inflammatory responses by releasing a variety of pro-inflammatory cytokines and growth factors that trigger activation and transformation of resting hepatic stellate cells into myofibroblast-like cells, which initiate increased synthesis of connective tissue proteins, especially collagens (George, Tsuchishima, et al., 2019). NDMA-induced liver fibrosis results in the enhanced oxidative stress leading to the generation of oxyradicals which can bind to proteins and cellular constituents (Ahmad & Ahmad, 2018). Further, oxidative stress and ROS can lead to fibrosis and abnormal

healing following injury which can lead to cellular transformation and carcinogenesis (George, Tsuchishima, et al., 2019; George, Tsutsumi, & Tsuchishima, 2019).

Many antioxidants exhibit anti-carcinogenic activity in experimental models. Antioxidants may be used for the prevention of arsenic-induced carcinogenesis, NDMA-induced hepatocellular carcinogenesis, and NDEA-induced esophageal carcinogenesis (Hei & Filipic, 2004; Shetty, Kumar, & Bharati, 2019; N. Shi et al., 2017). Tocopherols, a form of vitamin E, have been suggested to have antioxidant properties, including ability to physically trap nitrogen species leading to protection in an AOM/DSS model of colon carcinogenesis (Bansal et al., 2005b; Ju et al., 2009; Lambert et al., 2009; H. J. Lee et al., 2009). A flavonoid antioxidant, silymarin, inhibits a 4-NQO-induced tongue carcinogenesis model leading to increased apoptosis and decreased proliferation (Yanaida et al., 2002). Citral suppressed NDEA-induced HCC via inhibiting the suppression of antioxidants triggered by carcinogen exposure (P. Krishnan et al., 2020).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulatory molecule of oxidative stress and a potential therapeutic agent in carcinogen-induced cancer. Inhibition of Nrf2 stimulates oxidative stress, inflammation, circulating cytokines, and proliferation leading to intestinal carcinogenesis (Cheung et al., 2014). NDEA stimulates inflammatory and oxidative stress markers via COX-2 upregulation, yet ginger extract demonstrated protective effects via Nrf2 activation to suppress oxidation and inflammation (Mansour et al., 2019). $AFB_1$ upregulates Nrf2 signaling in response to oxidative stress, although expression of the SOD antioxidant is downregulated (W. J. Wang et al., 2017). In liver carcinogenesis Nrf2 activation as a result of AHR and CYP1B1 downregulation led to restoration of liver tissue and reduced oxidative damage (Bose et al., 2020). A novel compound, CDDO-Im, with anti-inflammatory properties also activates Nrf2 to potently inhibit $AFB_1$-induced carcinogenesis in 100% of animals (Eaton &

Schaupp, 2014; Johnson et al., 2014). A structurally similar compound in the family of synthetic pentacyclic oleanane triterpenoids, CDDO-Me is in clinical development. Further, a family of compounds with the same activity but simpler synthesis, tricyclic-*bis*-enone (TBE) compounds, is also potent in reducing oxidative stress to inhibit $AFB_1$-induced carcinogenesis (Liby et al., 2008). Thus, inhibition of oxidative stress is a potent therapeutic approach to carcinogen-induced cancers.

Clinic inflammatory scores, including neutrophil to lymphocyte ratio or platelet to leukocyte ratio, can also predict cancer patient outcome (Díaz-Beveridge et al., 2018; C. B. He & Lin, 2017; C. Liu et al., 2017; Peng et al., 2017; Y. Zheng et al., 2019). Pro-inflammatory cytokines such as IL-6 and IL-8 may be used to predict patient outcome for example in HCC patients undergoing transarterial chemoembolization (Loosen et al., 2018). In an animal model of NDEA-induced HCC, the hepatic inflammation-fibrosis-cancer axis (IFC), including upregulation of TNF-α, IL-6, TGF-β1 and JAK2/STAT3 signaling, may predict carcinogen exposure after week 14-22 (Ding et al., 2017). The neutrophil/lymphocyte ratio (NLR) could be a prognostic predictor for urologic tumors, including kidney tumors. Interleukin-1β (IL-1β) and interleukin (IL-18) are products of activated inflammasomes that play central roles in innate immunity and inflammation. C-reactive protein (CRP), a prototypical pro-inflammatory cytokine and marker, may also be reflective of tumor progression through inflammation. An elevated serum level of CRP as an inflammation biomarker may portend a poor prognosis of cancer patients, including kidney and bladder cancer (J. Dai et al., 2014; Michigan, Johnson, & Master, 2011).

**Cell death ("debris")-generated inflammation**

Cancer therapy-generated tumor cell debris can stimulate tumor growth via a storm of pro-inflammatory cytokines and eicosanoids (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018). Cellular debris (apoptotic cells) and inflammation-induced cellular damage can induce cellular proliferation to activate a "Phoenix Rising" Pathway) to promote wound healing and tissue regeneration of the damaged tissue (F. Li et al., 2010). Cytotoxicity-induced pro-inflammatory activity of carcinogens and tissue damage/injury may lead to inflammation as a cancer co-initiator and predict low or negligible risk at non-inflammatory carcinogen doses (Bogen, 2019). Inflammation activated-stem cells involved in tissue repair in damaged tissue and may lead to cancer if the normal termination of inflammation is suppressed by mutations (Bogen, 2019). Non-mutagenic cytotoxic agents such as alcohol, chloroform, and ultraviolet light induce cell death triggering cytokines which stimulate hyperplasia and tumor growth (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018; Trosko, 2001). While carcinogen-induced inflammation and oxidative stress can lead to cellular damage, cell death can play a complex role in carcinogenesis by either stimulating or inhibiting tumor growth (Bonavita, Pelly, & Zelenay, 2018; Sulciner, Serhan, et al., 2018). While cell death is beneficial to prevent accumulation of cells with accumulated DNA damage, it also generates stress signals leading to more inflammation and regenerative proliferation which can stimulate tumor growth. Carcinogens in tobacco smoke, including nicotine-derived nitrosamine ketone (NNK), trigger the IKKβ/JNK1 mediated apoptotic pathway leading to a subsequent proliferation response, while other carcinogens including aflatoxins trigger cell death via ROS production (Sakurai et al., 2008; Takahashi, Ogata, Nishigaki, Broide, & Karin, 2010; J. Zhang et al., 2015). Oxidative stress induced by carcinogens as nitric oxide induces cell death associated with COX-2 and PPARgamma signaling (Lim, Jang, & Surh, 2003). In a naphthalene-induced nasal tumor model a dual mode of action links genotoxic and cytotoxic effects (Bogen, 2019). Interestingly, in a

NDEA-induced model of HCC, prevention of hepatocyte apoptotic pathways and inflammatory pathways inhibited carcinogenesis (Wree et al., 2015). Persistent apoptosis is a determinant for hepatocellular carcinoma, and lower rates of apoptosis via lower caspase 8 are associated with less aggressive disease (Boege et al., 2017).

As damage associated molecular patterns (DAMPs) released by dead cells generate inflammation, tissue injury and signal through NF-κB, the accumulation of these dead cells may promote carcinogenesis (Y. He et al., 2019; Hernandez et al., 2018). Chemotherapy-generated apoptotic tumor cells ("tumor cell debris") stimulate macrophages to release a cytokine and eicosanoid storm promoting the chronic inflammatory environment during tumor growth (Chang et al., 2019; Gartung et al., 2019; Sulciner, Serhan, et al., 2018). Tumor cells killed from chemotherapy or radiation, release soluble factors and extracellular vesicles, which can induce an immunosuppressive tumor microenvironment to trigger regenerative processes leading to increased proliferation of remaining tumor cells (Jiang, Gu, Dai, Huang, & Tian, 2020; Keklikoglou et al., 2019). Interestingly, NDEA-induced hepatocellular carcinoma was stimulated by NADPH oxidase 1 (NOX1) induction of pro-inflammatory cytokines including TNF-α and IL-6 via DAMPs released by dying hepatocytes demonstrating the importance of immune and non-immune cell crosstalk in carcinogenesis (Liang et al., 2019). In a study of three nongenotoxic carcinogens, cadmium chloride, methyl carbamate, and lithocholic acid, genome wide methylation analysis demonstrated changes in cancer and surveillance pathways, but also in autophagy pathways a mechanism by which the body clears damaged cells (Hwang, Yeom, Eom, Lee, & Lee, 2019). Another nongenotoxic carcinogen, fumonisin B1, induces carcinogenesis via induction of apoptosis and necrosis leading to regenerative proliferation (Dragan et al., 2001). NDMA-induced cytotoxic activity and apoptosis in various organs (e.g., large bowel) can lead to inflammation (Potten, Li, O'Connor, & Winton, 1992). In a liver model, NDMA-induced DNA adducts and cell necrosis were concentrated mainly in hepatocytes,

suggesting the release of mitogenic stimuli to stimulate the proliferation of the cells (V. M. Lee, Cameron, & Archer, 1993).

Natural compounds, including rice bran, with anti-carcinogenic effects induce apoptosis and thus reduce the accumulation of mutated cells, but simultaneously inhibit inflammation and regenerative proliferation (Badr El-Din, Ali, Othman, French, & Ghoneum, 2020). Many environmental carcinogens dysregulate the cycles of cell death and proliferation by regulating pro- and anti-apoptotic proteins such as Bax, Bcl-2, caspases, and other signaling cascades. Thiamethoxam-induced hepatocarcinogenesis not only stimulated oxidative stress and inflammation in rabbits, but upregulated anti-apoptotic proteins leading to transformed cell survival (El Okle, El Euony, Khafaga, & Lebda, 2018). An initiating hepatocarcinogenic dose of NDEA stimulated the apoptotic index via increased caspase-3 and Bax expression (J. S. Kang, Wanibuchi, Morimura, Gonzalez, & Fukushima, 2007).

**Dormancy escape**

Dormancy is a stage in cancer progression where the cancer cells are not dividing but survive in a quiescent state. Dormant tumors have been identified at autopsy in normal adults who died of trauma and without prior history or clinical evidence of cancer (Folkman, 2001; Harach, Franssila, & Wasenius, 1985). The reported incidence of these dormant tumor cells has been as high as 39% for in situ breast carcinoma, 46% for in situ prostate cancer, and 36% for thyroid carcinoma (Black & Welch, 1993). Thus, it is highly likely that many humans exposed to carcinogens already exhibit dormant tumors. These dormant tumors can act as a tumor initiator and promotion of tumor dormancy escape occurs when exposed to carcinogens. The trigger of dormancy escape, as numerous animal studies have shown, is typically of non-genetic nature and can include: wounding at a site near or distant from the site of the occult tumor, surgery,

chemotherapy, radiation, biopsy, sustained inflammation, stimulated angiogenesis or the presence of non-mutagenic factors that perturb the metabolism of cells (Panigrahy et al., 2012; Panigrahy et al., 2019). Cell death can paradoxically trigger dormancy escape by the stimulation of pro-inflammatory and pro-angiogenic cytokines which suggests that cell death generated by carcinogens can stimulate tumor growth (Fishbein et al., 2020; Gartung et al., 2019; Sulciner, Serhan, et al., 2018). In experimental models, tumor dormancy escape can occur by 90 days post-tumor cell injection of dormant tumor cells by the stimulation of angiogenesis (Panigrahy et al., 2012).

**Carcinogen-induced immunosuppression**

A dysregulated immune system following carcinogen exposure can lead to chronic inflammation, but also immunosuppressive activity may further damage the host response to protect from cancer. Chronic inflammation, including signaling molecules such as $PGE_2$, can lead to immunosuppression in the tumor microenvironment (D. Wang & DuBois, 2016, 2018). For example, pro-tumorigenic activity of NNK on alveolar macrophages modulated by $PGE_2$ included immunosuppression (Therriault, Proulx, Castonguay, & Bissonnette, 2003). In a DMBA model of skin carcinogenesis, in xeroderma pigmentosa mice which are more susceptible, the carcinogen-induced not only pro-inflammatory mediators but also increased systemic immunosuppression (Miyauchi-Hashimoto, Kuwamoto, Urade, Tanaka, & Horio, 2001). In an AOM/DSS model of colon carcinogenesis myeloid derived suppressor cells and their chemotaxis via CXCR2 promoted tumorigenesis via inhibition of CD8+ activity (Katoh et al., 2013). Importantly, chronic exposure to carcinogens such as NDMA induce marked and

persistent immunosuppression of cellular and humoral responses (Desjardins, Fournier, Denizeau, & Krzystyniak, 1992).

Carcinogens, including aflatoxins and tamoxifen, disrupt inflammation resolution and the innate immune system by impairing host-protective neutrophil and macrophage phagocytosis of debris (Lukac, Kusic, Kordic, Koncar, & Bolanca, 1994; Mannerstrom, Maenpaa, Toimela, Salminen, & Tahti, 2001; Mehrzad et al., 2011; Moon et al., 1999). In addition, NDMA can negatively impact neutrophil phagocytic activity, oxygen metabolism, and functions associated with production and release of immunologically-active molecules (Jablonski, Jablonska, & Moniuszko-Jakoniuk, 2007), thus impairing inflammation resolution. NDMA is immunotoxic to immune cells, cell-mediated immunity and inflammation (e.g., mononuclear cells and neutrophils (PMN)) (Holsapple, Bick, & Duke, 1985; Jablonski et al., 2011). Reduced host resistance to infectious agents (reduced response to streptococci and influenza challenge) following NDMA administration also indicate systemic toxicity on humoral immunity (Thomas et al., 1985). NDMA also impairs the cellular immune response by altering the production and/or maturation/differentiation of bone marrow stem cells into functional macrophages (Myers, Dickens, & Schook, 1987; Myers, Pullen, & Schook, 1986; Myers, Schook, & Bick, 1987).

Cytotoxic carcinogens can trigger cell death of lymphocytes leading to an immunosuppression without the ability to control the accumulating transformed cells (Badr, El-Reda, El-Gamal, & Farid, 2020; J. Chen et al., 2016). NDMA may impair the host immune response and exhibit immunotoxicity, including increased apoptosis (death) of leukocytes and production of pro-tumorigenic reactive oxygen species (Iwaniuk et al., 2015; Jablonski et al., 2001; Jablonski et al., 2011; Nowak et al., 2018; Ratajczak-Wrona et al., 2014). PFOA also exhibits immunotoxic potential in mice (Son et al., 2009). The toxic activity of NDMA greatly influences the biological activity and lifespan of immune cells (Iwaniuk et al., 2015), including

neutrophils, by inducing a respiratory burst and subsequent release of ROS responsible for the apoptosis of these cells (Jablonski et al., 2001). NDMA can also modulate the apoptosis of human neutrophils by regulating the expression of death receptor DR5 as well as through the release of its soluble form (sDR5) (Jablonski et al., 2007). In a prospective clinical study the hepatocellular carcinoma tumor microenvironment exhibited pro-angiogenic and pro-inflammatory activity, but also a distinctly immunosuppressed environment including upregulation of PD-1, PD-L1 and FoxP3 regulatory immune cells in patients (Critelli et al., 2017; O'Rourke, Sagar, Shah, & Shetty, 2018).

Carcinogens generate further immune suppressed environments through inhibition of the adaptive immune system. One of the primary cell targets of NDMA is the B-lymphocyte, thus likely reducing the overall reactivity of both T- and B-lymphocytes as exposure suppresses the IgM antibody-forming cell response to sheep red blood cells in a dose–dependent manner (Holsapple, McNerney, Barnes, & White, 1984; Holsapple, Tucker, McNerney, & White, 1984; White & Holsapple, 1984). NDMA depressed T-lymphocyte function as measured by T-cell proliferation in response to T-cell mitogens (Holsapple et al., 1985). NDMA suppresses T-cell-dependent antibody response (Jeong & Lee, 1998). PFOA causes splenic and thymic atrophy with suppressed thymocyte proliferation (Q. Yang, Xie, Eriksson, Nelson, & DePierre, 2001). PFOA also inhibited $CD4^+$ $CD8^+$ populations, demonstrating impaired splenocyte and thymocyte maturation from $CD4^-CD8^-$ to $CD4^+CD8^+$ cells (Son et al., 2009). Normally, immune cells, such as T lymphocytes, secrete soluble factors (cytokines) that activate phagocytes to destroy the pathogens they have internalized (Q. Yang, Xie, Alexson, Nelson, & DePierre, 2002). Furthermore, phagocytes utilize antibodies generated by B lymphocytes to allow them to recognize and destroy pathogens (Hansson, 1997; Stemme et al., 1995). Carcinogens such as aflatoxins generate tumor cell death (“debris”) that can trigger tumor dormancy escape via an eicosanoid and cytokine storm of pro-inflammatory as well as pro-angiogenic mediators

(Fishbein et al., 2020). Thus, carcinogen exposure may disrupt host-protective anti-tumor host immune responses and impair the resolution of inflammation.

## 3. Therapeutic approaches

### Resolution and anti-inflammation are not equivalent

Epidemiologic evidence suggests that the nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin reduces the risk and incidence of cancer (Gilligan et al., 2019; D. Wang & Dubois, 2010). However, severe toxicity including bleeding has precluded the routine application of anti-inflammatory agents in the chemoprevention and treatment of cancer. Moreover, selective cytokine or eicosanoid blockade may not be sufficient to prevent carcinogen-induced cancers (Fishbein et al., 2020; Gartung et al., 2019). Inflammatory transcription factors such as Nrf2 can reduce the DNA damage by neutralizing reactive chemicals with antioxidants and upregulating DNA repair pathways (Kay et al., 2019). The triterpenoid oleanane, a highly potent anti-inflammatory agent, prevents hepatocellular carcinoma (HCC) in an experimental rat model while only partially reducing $AFB_1$-DNA adducts (Johnson et al., 2014). Other anti-inflammatory mechanisms designed to reduce cancer risk include a healthy diet, exercise, antioxidants, and spices (e.g. curcumin).

A new potentially-paradigm shifting direction of inflammation research has emerged with the discovery of the autacoid superfamily of specialized pro-resolving lipid autacoid mediators (SPMs), including resolvins, maresins, protectins, and lipoxins, as key mediators in the resolution of inflammation, possessing potent inflammation clearing activity without being immunosuppressive (Mukherjee, Marcheselli, Serhan, & Bazan, 2004; Serhan et al., 1984;

Serhan et al., 2002; Serhan et al., 2009). The resolution of inflammation is now appreciated to be an active process regulated by SPMs, which are endogenously produced in multiple tissues throughout the human body (Serhan & Levy, 2018). Pro-resolution mediators resolvins may have a dual function in cancer associated-inflammation: inhibiting the pro-inflammation activities of pro-inflammatory cytokines while activating macrophages to phagocytize tumor-promoting cellular debris, thereby preventing chronic inflammation that stimulates tumor growth. Targeting endogenous lipid autacoid mediators such as lipoxins and resolvins offers an entirely new approach to cancer therapy via cell autonomous and non-cell autonomous mechanisms in the tumor microenvironment (Bai et al., 2019; Gilligan et al., 2019; Kuang et al., 2016; Lu, Xu, Yin, Xu, & Jiang, 2018; Panigrahy et al., 2019; Shan et al., 2020; Sulciner, Serhan, et al., 2018; L. Sun et al., 2019; Y. Ye et al., 2018; Zhong, Lee, & Surh, 2018).

**Cyclooxygenase (COX) inhibition**

Selective COX-2 inhibitors (coxibs) and nonselective NSAIDs can reduce the incidence of cancers in humans and in experimental models (D. Wang & Dubois, 2010). The risk for colorectal cancer is increased in patients with inflammatory bowel disease. COX-2 and $PGD_2$ have been identified as potential therapeutic targets for the chemoprevention of colon cancer (D. Wang & Dubois, 2010). However, COX-2 is also a pivotal enzyme necessary to stimulate the resolution of inflammation and production of specialized pro-resolving mediators (SPMs) such as lipoxins (Wallace, 2006). Given the important roles of COX-2 (in part through biosynthesis of $PGD_2$) in the resolution of inflammation, inhibition of COX-2 may be “resolution toxic” (Gilroy et al., 1999; Panigrahy et al., 2019; Serhan & Levy, 2018). Inflammation (e.g. paw swelling) in COX-2 KO mice failed to resolve and exhibited significant leukocyte infiltration. COX-2 is an important source of $PGD_2$ (15-deoxy-$\Delta^{12\text{-}14}PGJ_2$) and is also essential for driving

resolution of the inflammatory response in the lung (Gilroy et al., 1999). Human fibroblasts generate pro-resolving peroxisome proliferator-activated receptor-γ ligands in a COX-2-dependent manner via pro-resolving prostaglandins (Lacy et al., 2016). Thus, inhibition of COX-2 impairs resolution of inflammation because prostaglandins such as $PGE_2$ initiate a lipid mediator class switching to SPMs such as lipoxins to accelerate the resolution of inflammation (Levy et al., 2001).

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for inflammatory diseases, pain, fever and include aspirin, celecoxib, ibuprofen, sulindac, diclofenac, and ketorolac (D. Wang & Dubois, 2010). NSAIDs that block the enzymatic activity of COX and subsequent production of prostaglandins, are widely used to treat inflammation and pain (Marnett, 2009) and exhibit anti-cancer activity (Arber & DuBois, 1999; Gilligan et al., 2019; Hudis, Subbaramaiah, Morris, & Dannenberg, 2012). However, the adverse side effects of NSAIDs such as bleeding prevent their chronic use at high doses (D. Wang & Dubois, 2010). Certain NSAIDs are selective COX-1 and/or COX-2 inhibitors. Aspirin exhibits anti-cancer activity by inhibiting inflammation and triggering the resolution of inflammation (Gilligan et al., 2019; Shiff & Rigas, 1999; D. Wang & Dubois, 2010). NSAIDs inhibit angiogenesis, including suppressing carcinogen-induced angiogenic signaling of cytokines, NF-κB, MMP-2 and MMP-9 in colon cancer progression (Vaish, Piplani, Rana, & Sanyal, 2013).

The NSAID sulindac can prevent carcinogen-induced intrahepatic cholangiocarcinoma in experimental models (Wentz et al., 2009). The loss of 15-hydroxyprostaglandin dehydrogenase,

a prostaglandin-degrading enzyme that inhibits COX-2, stimulate tumor growth. However, sulindac, but not aspirin or celecoxib, overcomes the low 15-PGDH expression to reduce AOM-induced colon carcinogenesis demonstrating a difference in anti-tumor activity with various NSAIDs (Fink et al., 2015). Sulindac partially inhibits NDEA-induced HCC, although statins exhibit more potent anti-inflammatory and anti-cancer activity (Bakiri et al., 2017). $AFB_1$ upregulates COX-2 which activates the inflammasome leading to tumor-promoting inflammation. In contrast, celecoxib reduced this inflammation demonstrating the regulation of inflammation by eicosanoids and inflammatory mediators (L. Y. Zhang et al., 2019). Additionally, etodolac, a COX-2 inhibitor, suppresses N-nitrosobis(2-oxopropyl)amine (BOP)-induced experimental biliary carcinogenesis (Tsuneoka et al., 2005).

While initial studies have focused on colorectal cancers, low-dose aspirin exhibits anti-tumor activity in other tumor-types, including lung, breast, prostate, and metastatic cancers (D. Wang & Dubois, 2010). Aspirin can stimulate resolution by triggering the biosynthesis of resolvins, lipoxins and protectins (Gilligan et al., 2019; Serhan, 2014). Compelling evidence of aspirin's anti-cancer activity stems from patients receiving low-dose aspirin for cardioprevention, in which a substantial fraction (20–30%) benefits from a decrease in cancer incidence. Importantly, the use of low-dose aspirin in cancer patients is limited by adverse side effects, such as gastrointestinal bleeding and hemorrhagic stroke, that necessitate hospitalization (Gilligan et al., 2019). Aspirin-triggered resolvins and lipoxins may account for aspirin's anti-tumor activity at least in part without the toxicity of aspirin (Claria & Serhan, 1995; Gilligan et al., 2019). Because SPMs are not triggered by other NSAIDs besides aspirin, this may explain why aspirin's beneficial anti-tumor activity has not been fully recapitulated with other NSAIDs (Gilligan et al., 2019).

However, NSAIDs can down-regulate pro-tumorigenic cytokines but also generate toxic side effects and may be immunosuppressive resulting in increased risk for infections. Pre-treatment of the NSAID carprofen impaired initiation of inflammatory- and overlapping resolution response and promoted cardiorenal syndrome and heart failure (V. Krishnan et al., 2019). The classic cyclooxygenase inhibitors, celecoxib and indomethacin, that block thromboxanes and prostanoids do not inhibit production of the clot-driven SPM cluster (Norris & Serhan, 2018). Additionally, NSAIDs have been associated with gastrointestinal (GI) injury for a century (D. Wang & Dubois, 2010). It was the discovery by Vane in 1971 that these drugs suppress the biosynthesis of prostaglandins (PGs) that first suggested that autacoids may play a role in the maintenance of GI mucosal injury (Vane, 1971). Coadministration of a selective COX-2 inhibitor with aspirin inhibits pro-resolution lipoxin synthesis in the stomach increasing gastric mucosal damage (Fiorucci et al., 2002). Administration of synthetic $LXA_4$ prior to aspirin resulted in a dose-dependent reduction in the extent of gastric damage. Thus, aspirin-triggered lipoxins reduce injury to the gastric mucosa (Wallace & Fiorucci, 2003).

Standard anti-inflammatories such as steroids, NSAIDs, COX-2 inhibitors, and cytokine antagonists do not clear debris and may be “resolution toxic” (Gilroy et al., 1999; Panigrahy et al., 2019; Serhan, 2014). For example, in a model of CCL4-induced liver fibrosis and inflammation the use of celecoxib reduced $PGE_2$ levels which was not sufficient to inhibit the liver injury and inflammation (Harris et al., 2018). Acetaminophen and indomethacin also generate 18-HEPE production, whereas selective cyclooxygenase-2 (COX-2) inhibitors block 18-HEPE production (Serhan & Levy, 2018). Both 18-HEPE and RvE1 are anti-inflammatory, stopping leukocyte migration and stimulating resolution of inflammation. NSAIDs and COX-2-inhibitors impair inflammation resolution, efferocytosis, and neutralize $PGE_2$ and $PGD_2$-induced class switching to SPMs. Other “resolution toxic” drugs including lipoxygenase (LOX) inhibitors

as 5-LOX plays a critical role in the biosynthesis of two classes of SPMs, lipoxins and resolvins. Lidocaine impairs resolution by inhibiting efferocytosis (Serhan & Levy, 2018). In contrast, frequently used drugs such as aspirin promote resolution through acetylation of COX-2, and triggering production of R-epimer lipoxins, resolvins, and protectins. Statins also boost SPMs and the resolution of inflammation (Serhan, 2014). Glucocorticoids can have mixed activity regarding resolution of inflammation by increasing the pro-resolving annexin A and efferocytosis but are immunosuppressive (Schif-Zuck et al., 2011). Dexamethasone can stimulate SPM production to stimulate resolution of airway inflammation as well as macrophage phagocytosis of apoptotic cells (Maderna, Yona, Perretti, & Godson, 2005; Pyrillou, Chairakaki, Tamvakopoulos, & Andreakos, 2018).

While $PGE_2$ and $LTB_4$ initiate inflammation following tissue injury, $PGD_2$ is a pro-resolution prostaglandin that triggers the switch from initiation of inflammation to resolution by inducing 15-LOX and SPM production which is upregulated in colitis patients who undergo long term remission (Serhan, 2014; Vong, Ferraz, Panaccione, Beck, & Wallace, 2010). Thus, pro-resolution prostaglandins inhibit IKKβ to suppress NF-κB induced chronic inflammation, may be a therapeutic approach to carcinogen-induced inflammation (Rossi et al., 2000). Alternatively, more specific inhibition of microsomal PGE synthase (mPGES-1) suppressed carcinogen-induced colon cancer without broadly blocking prostaglandin signaling as a potential mechanism to reduce NSAID-associated toxicity (Nakanishi et al., 2011). Thus, inhibition of eicosanoid enzyme pathways may disrupt inflammation resolution in carcinogen-induced cancers which can be restored via supplementation of pro-resolution lipid mediators.

**Specialized Pro-resolving Mediators (SPMs)**

A paradigm shift is emerging in our understanding of the resolution of inflammation as an active biochemical process with the discovery of novel endogenous specialized pro-resolving lipid autacoid mediators (SPMs), such as resolvins, lipoxins, protectins and maresins (Serhan, 2014). Resolvins and other pro-resolution lipid mediators stimulate macrophage-mediated clearance of cellular debris and counter pro-inflammatory cytokine production, a process called inflammation resolution. Resolution indices utilized temporal lipidomics, proteomics, and flow cytometry to establish relationships between cell trafficking, eicosanoids, pro-resolving lipid mediators and chemokines/cytokines (Bannenberg et al., 2005; Schwab, Chiang, Arita, & Serhan, 2007). Tumor-associated macrophages (TAM) family members (TYRO3, AXL and MerTK) play important roles in the resolution of inflammation in many diseases including infections and cancer via efferocytosis (Y. Duan et al., 2019). MerTK signaling also has an important role in the resolution of inflammation by stimulating production of SPMs, including lipoxin $A_4$ ($LXA_4$) and RvD1 (Cai et al., 2018). MerTK-deficient mice exhibit impaired phagocytosis of apoptotic cells contributing to development of allergic inflammation(Felton et al., 2018), atherosclerosis (Thorp, Cui, Schrijvers, Kuriakose, & Tabas, 2008), or autoimmune diseases (Rothlin, Carrera-Silva, Bosurgi, & Ghosh, 2015).

SPMs (e.g. resolvins, protectins, and maresins) are biosynthesized from omega-3 fatty acids EPA and DHA and consist of families including resolvins (D and E series), maresins and their conjugates in tissue repair, protectins, and arachidonic acid-derived eicosanoid lipoxins (Serhan & Levy, 2018). SPMs function via G protein coupled receptors including GPR32, GPR18, ChemR23, GPR37, and LGR6 have been identified for RvD1, RvD2, RvE1, PD1, and Mar 1, respectively (Bang et al., 2018; Chiang, Dalli, Colas, & Serhan, 2015; Chiang, Libreros,

Norris, de la Rosa, & Serhan, 2019; Krishnamoorthy et al., 2010; Ohira et al., 2010). In a metabololipidomics LC-MS/MS analysis screening included products of the DHA-derived bioactive metabolome (resolvins of the D series, maresins, protectins), EPA-derived bioactive metabolome (lipoxins, resolvins of the E series), and AA-derived mediators (lipoxins, leukotrienes, prostanoids) all of which regulate specific inflammatory disease processes. SPMs function potently in other inflammatory diseases including reducing thrombosis (Cherpokova et al., 2019). SPMs inhibit the recruitment of neutrophils that produce DNA damaging oxygen radicals, which may inhibit the carcinogen-induced inflammation promoting oxidative damage and mutagenesis. Limiting neutrophil tissue damage may also inhibit regenerative proliferation triggered as an injury response. SPMs, including protectins such as protectin DX, can reduce the production of reactive oxygen species and downregulate the activity of COX-2 in neutrophils (M. Liu et al., 2014). Notably, electrical stimulation of the vagus nerve is an alternate approach to stimulate the local production of SPMs while reducing prostaglandins and leukotrienes (Serhan, de la Rosa, & Jouvene, 2018).

Lipoxins are the first SPMs discovered although it took a long time to uncover their role in resolution of inflammation as potent, active stop signals for immune cell (e.g. neutrophil) infiltration and are biosynthesized from arachidonic acid (Serhan et al., 1984). Lipoxins (LX) are trihydroxytetraene-containing eicosanoids typically generated through transcellular biosynthetic pathways involving either 5- and 15-lipoxygenases (LOX) or 5- and 12-LOX. Lipoxins are produced relatively early during resolution of self-limited acute inflammatory responses (Serhan, 2014). Lipoxins are biosynthesized by immune cells such as neutrophils and macrophages in response to stresses such as inflammatory stimuli, injury, or infection. Endogenous lipoxins are the only arachidonic acid-derived SPM, and act as antagonists of pro-inflammatory and pro-tumorigenic leukotrienes. The Serhan laboratory utilized lipid mediator metabololipidomics, proteomics (liquid chromatography–tandem mass spectrometry [LC-MS/MS]), and cell

trafficking in self-limited exudates to identify three more new families of pro-resolving mediators, termed the “resolvins” (short for resolution phase interaction products), “protectins,” and “maresins” (short for macrophage mediators in resolving inflammation) (Mukherjee et al., 2004; Serhan et al., 2002; Serhan et al., 2009). Each family is structurally distinct and biosynthesized from essential fatty acid precursors eicosapentaenoic acid (EPA), docosapentaenoic acid (n-3DPA), or docosahexaenoic acid (DHA).

Aspirin stimulates the biosynthesis aspirin-triggered specialized pro-resolving mediators (AT-SPMs) from omega-3 polyunsaturated fatty acid substrates, including eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA) by acetylation of COX-2 (Serhan et al., 2002). AT-SPMs include endogenous production of aspirin-triggered lipoxins, aspirin-triggered resolvins and aspirin-triggered neuroprotectins (Claria, Lee, & Serhan, 1996; Claria & Serhan, 1995; Petasis et al., 2012; Serhan, 2014; Serhan, Dalli, Colas, Winkler, & Chiang, 2015; Takano, Clish, Gronert, Petasis, & Serhan, 1998). Stable analogues of lipoxin $A_4$, lipoxin $B_4$, and aspirin-triggered lipoxin $A_4$ inhibit neutrophil infiltration more potently than aspirin and rescue resolution deficits in various inflamed tissue injury models (Clish et al., 1999; Schwab et al., 2007; Serhan, 2005; Takano et al., 1997). Aspirin-triggered resolvin D3 are potent immunoresolvents, including blocking neutrophil transmigration as well as stimulating macrophage phagocytosis and efferocytosis (Dalli et al., 2013). Aspirin-triggered resolvins can mediate the anti-proliferative and anti-tumor activity of aspirin (Claria et al., 1996; Gilligan et al., 2019). Aspirin-triggered resolvins can mediate the anti-tumor activity of aspirin at >10,000 fold lower doses than aspirin without toxicity in experimental cancer models via resolution of inflammation (Gilligan et al., 2019). Preoperative administration of the NSAID ketorolac and/or resolvins (RvD2, RvD3, and RvD4) activate endogenous resolution programs before surgery to eliminate micrometastases and reduce tumor recurrence (Panigrahy et al., 2019).

Importantly, as NF-κB is central to inducing tissue injury and inflammation in carcinogenesis, SPMs have been shown to downregulate this signaling via activation of NF-κB regulators, including 15-epi-lipoxin $A_4$ induction of A20 and SIGIRR via its ALX/FPR2 receptor signaling following LPS-induced inflammation (Sham et al., 2018). Resolvin D1 protects from LPS-induced inflammation in a lung injury model via inhibition of damaging oxidative stress (L. Wang et al., 2014). Upregulation of the ALOX-15/LXA4 pathway in a PMA-induced skin inflammation model can promote the resolution of inflammation via inhibition of IFN-γ (G. Zhang, X. Liu, et al., 2013). Resolvin D1 in colitis-associated cancer inhibits c-Myc and TNF-α in colon cancer cells (Zhong et al., 2018). In an inflammatory intestinal model, protectin $D1_{n\text{-}3DPA}$ and resolvin $D5_{n\text{-}3DPA}$ protected against colitis and intestinal injury, both of which are risk factors for intestinal carcinogenesis (Gobbetti et al., 2017).

An important function of pro-resolution mediators or signaling pathways is the induction of macrophage phagocytosis and efferocytosis. Clearance of microbes as well as apoptotic cells is important in multiple inflammatory diseases, including carcinogen-induced cancers as dead cells or increased microbe uptake can stimulate chronic inflammatory cycles. Peroxisome proliferator-activated receptors (PPARs) stimulate macrophage phagocytosis to promote clearance of infection and inhibit pro-inflammatory mediators in macrophages, which may be key to “resolve” inflammation-driven cancers (DuBois et al., 1998; Penas et al., 2015). As targeting specific macrophage phenotypes is crucial to the resolution of inflammation in carcinogen-induced cancers, a MerTK macrophage phenotype has been demonstrated to induce phagocytosis and prevent liver damage (Triantafyllou et al., 2018). Additionally, $LTB_4$, a potently pro-inflammatory mediator, can be detected via PPAR-α binding which signals for its metabolism and clearance in the liver to control pro-inflammatory signaling (Devchand et al.,

1996). Thus, exploring multiple targets involved in the resolution of inflammation may elucidate novel therapeutics in carcinogen-induced inflammation and cancer.

SPMs also induce a macrophage phenotype switch from a generally M1 to M2 phenotype which promotes efferocytosis and phagocytosis functions (Werz et al., 2018). Hypoxia activates resolution metabolomes (SPM-biosynthetic circuits) which stimulate resolution including resolvins in M2-like human macrophages via interactions with erythrocytes which store omega-3 fatty acids to increase phagocytosis and efferocytosis (Norris, Libreros, & Serhan, 2019). This clearance of dead and damaged cells would inhibit the increased inflammatory response to DAMPs and reduce the debris induced macrophage-derived cytokine storm. SPMs, including resolvins, have functioned to clear therapy-generated dead cells to prevent their generation of tumor promoting inflammation, as well as prevent micrometastases to prolong survival in surgery-stimulated tumor dormancy escape models (Panigrahy et al., 2019; Sulciner, Serhan, et al., 2018). In addition, phagocytosis of inflammatory microbes which may have increased in the tissue via carcinogen exposure and failed barrier function may prevent synergistic tumorigenic inflammation. Macrophage phenotype is of utmost importance in the tumor microenvironment, as M1-like macrophages produce prostaglandins and leukotrienes generating an inflammatory and pro-tumorigenic microenvironment, while M2-like macrophages translocate 5-LOX and 15-LOX-1 to produce resolvins and maresins in response to inflammatory bacteria stimuli (Werz et al., 2018).

A critical difference between pro-resolution mediators (“resolving” inflammation) compared to anti-inflammation (“blocking” inflammation) is that while most anti-inflammatory agents can lead eventually to immunosuppression, the resolution of inflammation in an active endogenous reprogramming of the immune response to turn off inflammation without being immunosuppressive. In surgery-stimulated and chemotherapy-stimulated cancer models

preoperative stimulation of inflammation resolution via resolvins (RvD2, RvD3, and RvD4) inhibited metastases and induced T cell responses (Panigrahy et al., 2019). SPMs also promote the differentiation of B cells to be antibody-producing thus endogenously enhancing the adaptive immune system (Ramon, Gao, Serhan, & Phipps, 2012). SPMs not only inhibit macrophage-derived pro-inflammatory cytokines but prevent activated CD8+ and CD4+ cells from releasing inflammatory cytokines without inhibiting T regulatory cells (Aoki et al., 2008; Aoki et al., 2010). Thus, the resolution of inflammation via SPMs may be a novel approach to preventing carcinogen-induced cancers via downregulation of pro-inflammatory cytokines, suppression of neutrophil infiltration, reduced oxidative damage and clearance of carcinogen-generated debris (Figure 4).

**Lipoxins**

The most extensively studied SPMs in cancer biology at this time are the lipoxins (e.g. $LXA_4$). Lipoxins suppress cancer cell proliferation in culture and in animal xenograft models inhibit tumor cell invasion (Y. Chen et al., 2010; Claria et al., 1996; Schottelius et al., 2002; X. Y. Zhou et al., 2009). Lipoxins exhibit anti-inflammatory actions by inhibiting NF-κB signaling pathway (Gewirtz et al., 2002). Lipoxins inhibit pro-inflammatory cytokines (IL-8) and adhesion molecule (i.e., ICAM-1) expression in human astrocytoma brain tumor cells (Decker, McBean, & Godson, 2009). $LXA_4$ potently inhibits the leukocyte trafficking to the inflammatory site and stimulates the phagocytosis of apoptotic cells by tissue macrophages (Ariel, Chiang, Arita, Petasis, & Serhan, 2003; Y. Chen et al., 2010). ATL-1, a synthetic analogue of 15-epi-lipoxin $A_4$, inhibited melanoma tumor progression via switching tumor associated macrophages (TAM) from an M2- to an M1-cytotoxic like profile, promoting inhibitory activity on tumor cell proliferation and survival, and triggering tumor cell apoptosis (Simoes et al., 2017). $LXA_4$ can inhibit MAPK signaling to suppress aberrant COX-2 expression induced by IL-1β signaling in endometriosis,

an inflammatory risk factor for endometrial cancer (S. Dai et al., 2019). However, ATL-1 had no direct effect on cancer cell proliferation (Simoes et al., 2017). Additionally, $LXA_4$ did not exert any direct anti-proliferative effect on liver cancer (H22 cells) (Y. Chen et al., 2010).

Cancer progression including leukemia and colorectal cancer is associated with down-regulation of lipoxins (H. Liu et al., 2019; Stenke et al., 1991). Downregulation of lipoxin $A_4$ ($LXA_4$) plays a role in Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) infection pathogenesis and KS-related cancer (Chandrasekharan, Huang, Hwang, & Sharma-Walia, 2016). Serum $LXA_4$ levels were decreased in colorectal cancer patients and specifically in the tumor tissue, while cancer patients expressed higher serum levels of $LTB_4$, IL-1β, IL-6, CXCL8, TNF-α, and CCL2. $LXA_4$ suppresses the colorectal tumor levels of pro-inflammatory mediators IL-1β, IL-6, TNF-α and $LTB_4$ while up-regulating anti-inflammatory IL-10 expression (H. Liu et al., 2019). $LXA_4$ also inhibited the infiltration of CD45+ leukocytes and CD68+ macrophages in the colorectal tumor tissue. $LXA_4$ suppresses the expressions of p-ERK, p-P38 and NF-κB in the xenograft, inhibit the proliferation and migration of colorectal cancer cells stimulated by activated macrophage-conditioned media(H. Liu et al., 2019). Kaposi's sarcoma (KS) occurs is frequently identified in HIV infected patients (Chandrasekharan et al., 2016). The lipoxin receptor ALX/FPR was expressed on human KS tissue sections (Chandrasekharan et al., 2016). Treating KS-IMM cells with lipoxins ($LXA_4$ or 15-epi-$LXA_4$) reduced the levels of pro-inflammatory cytokines IL-6 and IL-8, enzymes COX-2, 5-LO, and their metabolites (Marginean & Sharma-Walia, 2015).

Lipoxins and their analogues are potent inhibit tumor growth including hepatocellular carcinoma, melanoma, and Kaposi's sarcoma by suppressing angiogenesis such as endothelial cell proliferation, endothelial cell migration, VEGFA-induced angiogenesis, VEGF-induced permeability, VEGF-stimulated VEGFR2 (KDR/FLK-1) phosphorylation, COX-2, 5-LO, $PGE_2$ and $LTB_4$ (Baker, O'Meara, Scannell, Maderna, & Godson, 2009; Cezar-de-Mello et al., 2008; Y. Chen et al., 2010; Fierro, Kutok, & Serhan, 2002; Hao et al., 2011; Jin et al., 2009; Marginean &

Sharma-Walia, 2015; Simoes et al., 2017; Vieira et al., 2014). $LXA_4$ inhibits VEGF and HIF-1α production by H22 hepatocellular carcinoma tumor cells in a dose-dependent manner (Y. Chen et al., 2010). The lipoxin analogue BML-111 inhibited serum VEGF production *in vivo* in H-22 tumor bearing mice (Y. Chen et al., 2010). In murine hepatocarcinoma, melanoma and CRC xenograft models, $LXA_4$ suppressed tumor growth by targeting regulatory B cells (Bregs) through the inhibition of important signaling pathways (Z. Wang et al., 2015). Bregs inhibit functions of $CD8^+$ cytotoxic T cell in the tumor microenvironment. Thus, $LXA_4$ may induce sustained anti-tumor immunity favoring the $CD8^+$ T cell response. Lipoxin metabolically stable analogs may protect from tumor extravasation by inhibiting VEGF-induced endothelial permeability (Vieira et al., 2014).

SPMs also exhibit cell-autonomous activity on cancer cells, independent from their anti-inflammatory action. In a murine model of liver cancer, $LXA_4$ inhibits hepatocarcinoma tumor growth by regulating the induction of MDSCs in response to T-reg depletion and inhibiting tumor angiogenesis (Y. Chen et al., 2010; B. Zhang et al., 2010). $LXA_4$ also suppresses acute myeloid leukemia cell migration and stimulates the phagocytic clearance of apoptotic cells by all-trans retinoic acid (ATRA)-treated alveolar macrophages (Tsai et al., 2012). Interestingly, $LXA_4$ shares structural similarities with estrogen 17-estradiol and possesses anti-estrogenic activity by competing for estrogen receptors, suggesting a potential effect in estrogen-associated diseases, such as endometrial cancer (Canny & Lessey, 2013).

Lipoxin $A_4$ as an endogenous lipid mediator can reprogram the tumor stroma to target pancreatic and liver cancer. $LXA_4$ inhibited pancreatic cancer cell invasion by inhibiting the

reactive oxygen species as well as MMP9 and MMP2 (Zong et al., 2016). In patients with pancreatic cancer, a low Lipoxin effect score (LES) has been observed. Specifically, a low LES tended to correlate with lymph node and distant metastasis. The “Lipoxin effect score” (LES) was the product of the immunohistochemistry scores of both 15-LOX and FPRL1. LES was correlated with aggressive metastatic potential in pancreatic tissue from pancreatic cancer patients (Zong et al., 2017). In PDAC, human pancreatic stellate cells (hPSCs), the main precursors of pancreatic cancer associated fibroblasts (CAFs), become activated and induce fibrosis by secreting extracellular matrix, which presents a barrier to anti-cancer drugs (Schnittert, Heinrich, Kuninty, Storm, & Prakash, 2018). Lipoxin $A_4$ can disrupt the pro-tumoral paracrine signaling of human (hPSCs) (Schnittert et al., 2018). $LXA_4$ inhibited the activation of hPSCs into CAF-like myofibroblasts in vitro and inhibited hPSC-induced tumor-promoting activity (Schnittert et al., 2018). $LXA_4$ can also inhibit renal and lung fibrosis (Mitchell et al., 2004; Roach, Feghali-Bostwick, Amrani, & Bradding, 2015). Lipoxin $A_4$ also inhibited pancreatic tumor growth via anti-fibrotic mechanisms such as reduced collagen I expression and thus may increase the efficacy of chemotherapy and radiation in pancreatic cancer (Schnittert et al., 2018). $LXA_4$ also reduced tumor angiogenesis as determined by a reduction in the endothelial marker CD31 (Schnittert et al., 2018). In a liver metastasis model in nude mice, the $LXA_4$ analogue mimetic BML-111, could inhibit the metastasis of pancreatic cancer cells (Zong et al., 2017). Lipoxin reverses mesenchymal phenotypes to attenuate invasion and metastasis via inhibition of autocrine TGF-β1 signaling in pancreatic cancer (Zong et al., 2017). EMT is a metastasis-promoting process in which cancer cells lose epithelial phenotypes such as E-cadherin expression and acquire mesenchymal characteristics including elevated expression of N-cadherin and vimentin expression (Zong et al., 2017).

Aspirin-triggered-lipoxin, 15-epi-$LXA_4$ analog, is a potent inhibitor of endothelial cell

responses and angiogenesis in vitro and in vivo. Lipoxin and AT-$LXA_4$ treatment of a cancer-induced bone pain model results in suppression of spinal pro-inflammatory cytokines including IL-1 and TNF-α (S. Hu et al., 2012). $LXA_4$ administration also promoted the regression of DMBA/TPA– induced papillomas and reduced several pro-inflammatory cytokines including IFN-gamma in papilloma tissue (C. Wang et al., 2013). IFN-gamma maintains inflammation and papilloma growth by repressing $LXA_4$, demonstrating a dynamic balance between pro-inflammatory factors and pro-resolution lipid mediators (C. Wang et al., 2013). Lipoxins promote resolution of inflammation increasing papilloma regression independent of upregulating IFN-gamma by enhancing anti-tumor immunity. Thus, lipoxins are a potential treatment for papillomas and other cancer types.

**Resolvins**

SPMs such as resolvins are entirely unique from traditional anti-inflammatory agents in that they actively promote resolution of inflammation via activation of macrophages to clear inflammatory cell debris and killing/clearing microbes, counter-regulate pro-inflammatory cytokines, and halt leukocyte infiltration to reduce the propagation of inflammation at pico-nanogram concentrations (Serhan, 2014). Reduced resolvins have already proven to be critically involved in a number of autoimmune diseases characterized by uncontrolled inflammation (Serhan, 2014; Serhan & Levy, 2018). Resolvins are highly effective in treating diseases driven by excessive inflammation at picogram levels *in vivo* (logs lower than aspirin or dexamethasone) in a wide variety of experimental pre-clinical models of inflammatory diseases(Aoki et al., 2008; Arita et al., 2005; Bannenberg, 2009; Bento, Claudino, Dutra, Marcon, & Calixto, 2011; Connor et al., 2007; Duffield et al., 2006; Gonzalez-Periz et al., 2009; Hansson, Robertson, & Soderberg-Naucler, 2006; Hassan & Gronert, 2009; Hasturk et al.,

2007; Haworth et al., 2008; S. Hong, Gronert, Devchand, Moussignac, & Serhan, 2003; Jin et al., 2009; Kasuga et al., 2008; Merched et al., 2008; Serhan et al., 2002; Spite et al., 2009; H. Tian, Lu, Sherwood, Hongqian, & Hong, 2009; Van Dyke & Serhan, 2003). Clinical trials show increasing resolvin activity in inflammatory diseases such as dry eye inflammation and periodontal diseases can reduce local inflammation (Serhan & Levy, 2018).

Demonstrating the importance of resolvins in cancer, the neutralization of Resolvin D1 receptor GPR32-mimics FPR1-silencing which increases angiogenesis and tumorigenesis of gastric cancer cells (Prevete et al., 2017). Formyl peptide receptors (FPR1, 2, and 3) are pattern recognition receptors of the G-protein-coupled (GPCR) family that recognize both exogenous and endogenous “danger” signals, and can trigger inflammation while FPR2/ALX activates resolution (R. D. Ye et al., 2009). Genetic deletion of FPR1 in gastric cancer cells promoted angiogenesis and enhanced the response to pro-inflammatory cytokines and impairing inflammation resolution (Prevete et al., 2015). The resolvin receptors (GPR32 for RvD1 and GPR 18 for RvD2) are down regulated during cancer progression in oral cancer cells (Y. Ye et al., 2018). While both RvD1 and RvD2 inhibited oral tumor cell proliferation in vitro, RvD2 suppressed tumor growth in an oral squamous cell carcinoma xenograft models via macrophage efferocytosis and reduced tumor-derived cytokines/chemokines (TNF-α, IL-6, CXCL10, and MCP-1), $CD11b^{b}Ly6G$ myeloid cell infiltration, nociception, reduction of tumor necrosis, and decreased neutrophil infiltration (Y. Ye et al., 2018). Tissue resolvin of the D series was identified as potential biomarker in endometrial cancer patients and correlated with improved patient survival (Eritja et al., 2017). Resolvin D1 (RvD1) also increases miR-138-5p expression by over 60-fold compared to control directly targeted FOXC1 to reduce cancer cell growth and invasion in NSCLC in vitro (Bai et al., 2019). RvD1 decreased cell viability and cell invasion in A549, H1299 and LLC cells in a dose-dependent manner and affected Akt and

Erk1/2 phosphorylation (Bai et al., 2019). Specifically, in lung cancer, FOXC1 plays a critical role in tumor microenvironment to promoted cancer progression (Cao et al., 2018; Lin et al., 2017). RvD1 regulates the expression of several miRNAs. These studies establish the mechanistic linkage between miR-138-5p and inflammation resolution (Bai et al., 2019). RvD1 also inhibits skin inflammation via reducing cytokine levels including IL-1β, IL-6, IL-33, TNF-α, and oxidative stress induced by ultraviolet irradiation (Saito et al., 2018).

Epithelial mesenchymal transition (EMT) is a biological process that plays a critical role in cancer progression (C. H. Lee, 2018). Resolvins (RvD1 and RvD2) inhibit TGF-β1-induced epithelial mesenchymal transition (EMT) in lung cancer cells via their receptors ALX/FPR2 and GPR32 receptors, resulting in inhibition of ZEB1 expression (H. J. Lee, Park, Lee, & Lee, 2013). TGF-β1, one of the featured mediators in the resolution of inflammation and key components comprising the tumor microenvironment, can induce EMT of lung cancer cells. AT-RvD1 suppresses the TGF-β1-induced EMT by mTOR pathway inhibition reducing the expression of PKM2, which affects cellular energy metabolism and oxidative stress (Y. Liu, Yuan, Li, Cao, & Shu, 2016). Blocking the process of EMT can be an essential strategy in the development of anti-cancer drugs. EMT involves down-regulation of epithelial proteins such as E-cadherin and keratins and the acquisition of mesenchymal marker proteins, including vimentin and EMT-related transcription factors such as Snail1 and zinc-finger E-box binding 1 (ZEB1) (C. H. Lee, 2018). Snail, Twist, and ZEB transcription factors are well-known transcription factors involved in the EMT process. A cancer stem cell (CSC) is a cancer cell that undergoes a self-renewal and differentiation. Activation of EMT in cancer cells is closely related to the entry of cancer cells into CSC state (Chaffer, San Juan, Lim, & Weinberg, 2016). Resolvins (e.g. RvD1) impaired paracrine of activity of carcinoma-associated fibroblasts (CAFs)-derived COMP by targeting FPR2/ROS/FOXM1 signaling to inhibit EMT and cancer stemness in HCC in a

receptor-dependent manner (L. Sun et al., 2019). Thus, RvD1 may be a potential agent to inhibit many cancers dependent on cancer stem cells such as hepatocellular carcinoma (L. Sun et al., 2019). CAFs-derived COMP induced EMT and cancer stem cell-like properties to promote invasion and metastasis of HCC (L. Sun et al., 2019), which was in accordance with previous findings that IL-6 secreted by CAFs confers stem-like properties in HCC via the upregulation of stemness-correlated transcription factors including Sox2, Oct4 and Nanog (Y. Li et al., 2019).

Resolvins (e.g. RvE1) also inhibit the oncoprotein c-Myc expression which is overexpressed in a large variety of human cancers such as colon cancer (Zhong et al., 2018). The suppression of TNF-α-induced upregulation of c-Myc in normal cells was mediated through attenuation of NF-κB signaling (Zhong et al., 2018). RvD1 stimulated c-Myc degradation through direct interaction with the ALX/FPR2 receptor (Zhong et al., 2018). RvD1 induces cytotoxic activity and elevated caspase-3 activity in natural killer (NK) cells in pancreatic ductal adenocarcinoma cells (PDAC) cells (Haber et al., 2015). RvD1 and RvD2 also exhibited anti-inflammatory activity by inhibiting LPS-interferon (IFN)-γ-induced M1 polarization as well as promoting interleukin-4 (IL-4)-mediated M2a polarization. These differential polarization processes were mediated, at least in part, by protein kinase A. Thus, regulation of macrophage polarization using RvDs may be a potential therapeutic approach in the management of prostate cancer (Shan et al., 2020). The communication between human monocyte-derived M2-like macrophages (MDM) and cancer cells in co-incubations can strikingly modulate the biosynthetic capacities to produce bioactive LM including lipoxin $A_4$, resolvin D2 and D5 were elevated after coculture with human A549 epithelial lung carcinoma cells (Werner et al., 2020).

Current therapy for HCC and hepatoblastoma includes resection, transplantation,

radiofrequency ablation, chemoembolization and sorafenib (Villanueva, Hernandez-Gea, & Llovet, 2013). Resolvin D1 and E1 prevent liver injury and progression from hepatitis to liver cancer in murine models (Kuang et al., 2016). Resolvins protect from acute liver injury (e.g. carbon tetrachloride) (X. Chen et al., 2016). Resolvin D1 and E1 prevent concanavalin A (Con A)-induced liver injury and the changes of hepatitis to liver cancer in mice by inhibition of inflammatory cytokine secretion and NF-κB/AP-1 activity (Kuang et al., 2016). RvD1 and RvE1 inhibit Con A-induced liver injury, the production of TNF-α, IFN-γ, IL-2, IL-1β and IL-6, NF-κB and AP-1 signaling, TLR4, IκBα, IKKβ, MyD88, JNK, ERK and p38, and necrosis in mice (Kuang et al., 2016). Resolvins (e.g. 17(R)-Resolvin D1) can regulate Toll-like receptor 4-mediated inflammatory responses of human macrophages to LPS and E. coli (Palmer et al., 2011). Resolvins (e.g. RvD1) also inhibits the proliferation of LPS-treated liver cancer cells and reduces the expression and release of TNF-α, IL-1β and IL-6 at the protein and mRNA levels in LPS-treated liver cancer cells (Lu et al., 2018). In addition, RvD1 decreases p-ERK, p-JNK and p-p38 levels in LPS-treated liver cancer cells (Lu et al., 2018).

Resolvins may have the potential to resolve damaging inflammation generated by tobacco smoke, one of the most widespread worldwide carcinogens. Chronic secondhand exposure to tobacco smoke stimulated the levels of pro-inflammatory cytokines IL-17A, IL-6, IL-1β, and TNF-α in the lungs and impairs bacterial clearance from the lungs (Bhat et al., 2018). Pro-resolution mediators such as resolvins suppressed macrophage production of smoke-induced pro-inflammatory cytokines, enzymes, and lipid mediators (Croasdell et al., 2015). Resolvins also increased anti-inflammatory cytokines, promoted an M2 macrophage phenotype, and restored cigarette smoke-induced defects in phagocytosis (Croasdell et al., 2015). Resolvin D1 (RvD1) suppressed production of pro-inflammatory mediators by primary human cells in a dose-dependent manner. RvD1 administered with cigarette smoke exposure reduced

neutrophilic lung inflammation and production of pro-inflammatory cytokines, while upregulating the anti-inflammatory cytokine IL-10 in mice (Hsiao et al., 2013).

Alarmins such as high-mobility group box 1 (HMGB1) can disrupt the resolution of inflammation by inhibiting macrophage efferocytosis induced by SPMs (G. J. Kang et al., 2015). HMGB1 plays an important role in maintaining inflammation and can be actively released from various immune cells such as macrophages, monocytes, NK cells, dendritic cells, and endothelial cells, as well as from dead (e.g necrotic) cells (Scaffidi, Misteli, & Bianchi, 2002). HMGB1 enhances inflammatory reactions by potentiating the activity of pro-inflammatory mediators such as LPS and cytokines, and by suppressing the phagocytosis of apoptotic neutrophils (Banerjee et al., 2011; G. Liu et al., 2018). HMGB1 suppresses resolvin D1-induced phagocytosis via induction of resolvin D1-inactivating enzyme, 15-hydroxyprostaglandin dehydrogenase (G. J. Kang et al., 2015). HMGB1 suppressed RvD1-enhanced phagocytosis of MDA-MB-231 cancer cells and gene silencing of HMGB1 restored the phagocytic capability of MDA-MB-231 cells (G. J. Kang et al., 2015). Hepatocellular carcinoma ensues in the presence of excessive hepatic apoptosis and necroptosis in the tumor microenvironment which directs lineage commitment to either hepatocellular carcinoma or intrahepatic cholangiocarcinoma (Seehawer et al., 2018). The clearance of necroptotic cells are inefficiently taken up by macrophages in diseases characterized by impaired inflammation resolution (Gerlach et al., 2020). Necroptotic cells are inefficiently taken up by macrophages because they have increased surface expression of CD47, a "don't eat me" signal (Gerlach et al., 2020). Resolvin D1 enhanced the clearance of necroptotic cells in advanced murine plaques by the release of the "eat me signal" calreticulin from macrophages in a CDC42 dependent manner (Gerlach et al., 2020).

**SPMs in humans**

Evidence in humans demonstrates the importance of pro-resolving lipid mediators in the cancer patients. The pro-inflammatory response in response to hepatobiliary surgery is associated with low circulating concentrations of lipoxin $A_4$ and resolvins of the D series which were the opposite of IL-6 and cortisol which were elevated after surgery for liver tumors (Cata et al., 2017). The systemic inflammatory markers in the plasma C-reactive protein (CRP) and interleukin-6 were decreased in lung cancer patients administered EPA and DHA supplementation undergoing chemotherapy in a double-blind placebo-controlled study (Finocchiaro et al., 2012). In another study, compared with healthy volunteers, the levels of serum pro-inflammatory cytokines in colon cancer patients increase while the level of RvD1 decreased significantly associated with higher TNM stage of colon cancer (Zhuang, Meng, Xi, & Wu, 2018). Concentrations of IL-6, IL-1β, IL-10 and TNF-α gradually increased with the advancement of TNM staging (Zhuang et al., 2018). In stage III, concentrations of IL-6, IL-1β, and IL-10 were the highest, TNF-α concentration was the highest in stage IV. RvD1 concentration gradually decreased with the advancement of TNM staging (Zhuang et al., 2018).

Resolvin E1 (RvE1) plays an key role in the resolution of acute inflammation when immunonutrition is supplemented with EPA in patients undergoing a severely stressful operation (Uno et al., 2016). Pre-operative immunonutrition reduced pro-inflammatory responses and protected against the aggravation of post-operative complications in patients undergoing major hepatobiliary resection (Uno et al., 2016). In clinical randomized trials focused on dietary interventions that can boost SPMs, omega-3 fatty acids increased resolvins (e.g. RvE1) in patients undergoing hepatobiliary surgery for liver cancer, resulting in lower rates of infections, complications, and disease progression (Uno et al., 2016). The omega-3 fatty acid Lovaza

stimulates SPM production in coronary artery disease patients (Elajami et al., 2016). SPMs were also boosted in military personnel and in traumatic brain injury patients administered with substrate supplementation (Bisicchia et al., 2018). Peripheral blood markers of inflammation as well as inflammation resolution markers (e.g. resolvins) have been identified in cancer patients. ω-3 PUFAs exhibit anti-tumor activity in a variety of cancers such as breast cancer. SPMs may account for the anti-inflammatory and anti-cancer activity of ω-3 PUFA at least in part.

Maresins (e.g. MaR1) can also inhibit EMT of mouse type II alveolar epithelial cells and improve bleomycin-induced lung fibrosis (Y. Wang et al., 2015). Protectin DX (PDX), a PD1 isomer that is a double lipoxygenation product, reverses bleomycin-induced lung fibrosis by reversing EMT and alleviates acute kidney injury (Duffield et al., 2006; H. Li et al., 2017). Docosahexaenoic acid (DHA) with A549 lung cancer cells can generate maresins (e.g. MaR1) and protectins (e.g. PD1/NPD1). The role of maresins and protectins in cancer remain of interest in the years ahead now that they are widely available.



**Annexin A1 and Gaseous mediators**

In addition to SPMs, inflammation resolution is also controlled by a variety of endogenous mediators including protein/peptide mediators, such as annexin A1 and annexin A1–derived peptides which stimulate inflammation resolution (Perretti et al., 2002). Interestingly, estrogen can stimulate resolution of inflammation in macrophages (Villa, Rizzi, Vegeto, Ciana, & Maggi, 2015). Other pro-resolution mediators are IL-10, gases (e.g. carbon monoxide and hydrogen sulfide), TGF-β, formyl-Peptide Receptors, Selenoproteins, Galectin-1, and nucleotides (e.g. adenosine and inosine) (Arbiser, Bonner, Ward, Elsey, & Rao, 2018; Nelson et

al., 2016; Wallace, Ianaro, Flannigan, & Cirino, 2015). Drugs that stimulate resolution include aspirin, statins, omega-3 fatty acids, annexin A1 and annexin A1-derived peptides, statins, glucocorticoids, diclofenac, α-melanocyte stimulating hormone, erythropoietin, kinase inhibitors, galectins, chemerin, adrenocorticotropic hormone, gaseous mediators (e.g. hydrogen sulfide and carbon monoxide), purine (adenosine) as well as neuromediators and pioglitazone (Serhan & Levy, 2018). Drugs that may be resolution toxic include NSAIDs, COX-2 inhibitors, and lidocaine which impair efferocytosis (Serhan & Levy, 2018).

**Diet, exercise and supplementation**

Both omega-3 fatty acids and aspirin, which are known to reduce cancer risk, trigger the body's production of resolvins (Y. P. Sun et al., 2007). Although resolvins inhibit primary tumor growth at doses over *10,000 fold less* than omega-3 fatty acids, due to their rapid metabolism *in vivo*, an alternative approach for clinical application of SPMs in cancer is to increase their endogenous synthesis through dietary and pharmacologic intervention (Serhan, 2014). Omega-3 polyunsaturated fatty acids are precursors for many SPMs; for example, DHA is the substrate that aspirin-acetylated COX-2 converts to aspirin-triggered resolvins (e.g. AT-RvD1). In human subjects, dietary intake of DHA and EPA with aspirin treatment effectively increased plasma resolvin levels (Serhan, 2014). Similarly, mice fed a high omega-3 diet exhibited high levels of resolvins and omega-3 fatty acids in their tissues, serum, and plasma.

Thus, dietary interventions have been suggested as an approach to carcinogen associated inflammation. For example, in a DMBA-induced mammary carcinogenesis model low dose EPA and DHA demonstrated chemopreventive activity (Noguchi et al., 1997). A diet high

in omega-3s opposes the western diet, high in omega-6 fatty acids, which promotes inflammatory macrophage- and colitis-associated colon carcinogenesis (I. W. Kim et al., 2010). Importantly, DHA supplementation may increase the efficacy of HCCA patients receiving sorafenib via increased anti-angiogenic and anti-tumorigenic lipids such as 19,20-epoxydocosapentaenoic acid (EDP) (Leineweber et al., 2020; G. Zhang, D. Panigrahy, et al., 2013). Additionally, diets, based off elite crop varieties containing anticancer effects have been demonstrated to reduce hepatocarcinogenesis from NDEA by downregulating TNF-α/IL-6, increasing antioxidants, and increasing apoptosis without stimulating regenerative proliferation (J. Zheng et al., 2019). Additionally, EPA suppressed IL-6-induced chronic inflammation in high fat diet and carcinogen-induced HCC (Inoue-Yamauchi, Itagaki, & Oda, 2018). In a colon cancer model EPA also reduced MMP9 cytokine production via NOTCH1 signaling to exhibit protective effects (Fazio et al., 2016). Alternatively, caloric restriction has been suggested as a mechanism to alter metabolic pathways in NDEA-induced HCC rather than diet leading to altered inflammation, oxidative stress, cell migration, injury and oncogenesis (Ploeger, Manivel, Boatner, & Mashek, 2017). Human plasma and serum found to consist of eicosanoids and SPMs, additional omega-3 or acetylsalicylic acid supplementation also increased plasma SPM levels inducing increased phagocytosis (Colas, Shinohara, Dalli, Chiang, & Serhan, 2014). In a randomized double blinded placebo controlled study marine oil supplements containing fatty acid precursors increased SPM levels in blood samples and reprogramed blood cells to a pro-resolution phenotype (Souza et al., 2020). An additional clinical trial demonstrated efficacy of fish oil to benefit patients undergoing gastrointestinal surgery via regulation of TNF-α and NF-κB (J. Wang, Yu, Kang, & Ma, 2012). Stretching of connective tissue stimulates murine production of SPMs including resolvins, suggesting the potential for beneficial cancer protective activity of exercise (Berrueta et al., 2016).

However, benefits of dietary intervention and fatty acid supplements results are not always validated. In one study dietary fish oil enhanced azaserine-induced pancreatic carcinogenesis in rats (Appel & Woutersen, 1996). Fish oil supplementation may require additional regulation of what lipids specifically are in the product as it is not one specific compound. In a model of carcinogen-induced inflammatory colon cancer the EPA:AA lipid ratio helped predict $PGE_2$ levels in the tumor tissue of mice fed with a fish oil diet or western fat diet. Thus, the beneficial activity of diets on lipid production may depend on the pre-existing tumor lipid microenvironment (Djuric et al., 2017). While fish oils have been suggested as an important source of antioxidants one group found environmental pollutants to outweigh the benefits of antioxidants in fish oil without proper regulation of persistent organic pollutants (M. Y. Hong et al., 2017). In a study of women diagnosed with breast cancer omega-3 fatty acid intake did not affect overall breast cancer risk, although it did marginally reduce the risk of estrogen and progesterone receptor positive breast cancers, which was increased with omega-6 fatty acid intake (Kiyabu et al., 2015).

**Epoxyeicosanoids and sEH inhibition**

Epoxyeicosatrienoic acid (EETs) are lipid signaling molecules which act as autocrine and paracrine mediators of proliferation, migration, and inflammation in several tissues (Spector & Norris, 2007). EETs are fatty acid epoxides (EpFA) produced via the epoxidation of arachidonic acid catalyzed by cytochrome P450 (CYP) enzymes. Most CYP enzymes are general oxidases showing varying degrees of selectivity for the substrate and the product formed. In normal animals CYP2C8 or CYP2J2 appear largely responsible for production of EpFA and are metabolized by soluble epoxide hydrolase (sEH) to the corresponding 1, 2-diols. Members of the CYP4A, CYP2C, and CYP2J families of epoxygenases are among the most extensively studied(Fleming, 2007), however, in animals with induced cytochrome P450s other

families may dominant production of EpFA. While CYP4A enzymes produce the vasoconstrictor 20-hydroxyeicosatrienoic acid (20-HETE), the CYP2C and CYP2J enzymes convert arachidonic acid to the bioactive epoxyeicosatrienoic acids (EETs), including 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. EETs are metabolized by soluble epoxide hydrolase (sEH) to less active dihydroxyeicosanoic acids (DHETs). EETs, which function primarily as autocrine and paracrine mediators of arachidonic acid-induced relaxation in the cardiovascular and renal systems, are short-lived and quickly metabolized in most tissues (Campbell & Falck, 2007; Fleming, 2008). EETs secreted mainly by endothelial cells have critical roles in cellular proliferation, migration and inflammation; their major target cells are blood vessels (Spector & Norris, 2007). The EET producing enzymes of the CYP2C and CYP2J subfamilies have been found in endothelial cells (ECs) *in vitro* and *in vivo* (Fleming, 2007; Pozzi et al., 2005). Indeed, CYP2C enzymes are induced by hypoxia, and endothelial cells are a major source of EETs during inflammation and angiogenesis. Targeted inhibition of the EET inactivating enzyme sEH raises the levels of the cardioprotective EETs. Thus, soluble epoxide hydrolase (sEH) inhibitors are in clinical development being evaluated in phase II clinical trials for hypertension. The role of EETs and soluble epoxide hydrolase inhibitors as classical mediators of inflammation offer targets for drugs directed towards the tumor stroma for cancer therapy.

sEH inhibition and epoxy fatty acids are dual functioning to inhibit inflammation-induced carcinogenesis and enhance NSAID-induced ulcer healing at the site of inflammation via suppressing reactive oxygen species, improved mitochondrial function (R. D. Jones et al., 2019). sEH is overexpressed in ulcerative colitis (UC)-associated dysplasia and adenocarcinoma (W. Zhang, H. Li, et al., 2013). EETs are anti-inflammatory and inhibit cytokine-mediated endothelial cell adhesion preventing leukocyte infiltration via NF-κB (Node et al., 1999). sEH inhibition inhibits inflammatory bowel disease (IBD) and IBD-tumor development including dextran sulfate sodium (DSS)-induced carcinogenesis via suppressed

cytokines/chemokines including MCP-1, iNOS, VCAM-1, IL-1β and TNF-α (W. Zhang, H. Li, et al., 2013; W. Zhang et al., 2012; W. Zhang, J. Liao, et al., 2013).

Inhibition of sEH inhibits chronic pancreatitis and the progression of pancreatic intraepithelial neoplasms (PanIN) via dual inhibition of sEH and RAF1 proto-oncogene serine/threonine kinase (c-RAF)(J. Liao et al., 2016). Omega-3 epoxy fatty acids combined with a sEH inhibitor inhibited pancreatic carcinoma via anti-inflammatory, anti-proliferation, reduced mutant Kras-activated signals, and anti-angiogenic activity (Xia et al., 2019). Soluble epoxide hydrolase (sEH) inhibitors stabilize arachidonic acid-derived epoxyeicosatrienoic acids (EETs), which also stimulate inflammation resolution by promoting the production of pro-resolution mediators (e.g. lipoxins), activating anti-inflammatory processes, and preventing the cytokine storm. sEH inhibition can inhibit vascular permeability to prevent diabetic retinopathy (J. Hu et al., 2017).

Poly-unsaturated fatty acids also generate EETs which are metabolites of the omega-6 fatty acid arachidonic acid (Lopez-Vicario et al., 2015; G. Zhang, D. Panigrahy, et al., 2013). EETs may potently downregulate endoplasmic reticulum (ER) stress responses as demonstrated in response to cigarette smoke damage (Yu et al., 2015). Thus, inhibition of sEH may allow for their stability and prolonged effects and has demonstrated pro-resolution activity such as stimulation of SPMs and activating anti-cytokine programs in multiple inflammatory diseases, including those which are risk factors for cancer induction (Schmelzer et al., 2005; W. Wang et al., 2018; L. Yao et al., 2019; Yu et al., 2015). Importantly, the sEH eicosanoid pathway has been suggested to be involved in the progression of colorectal cancer, including obesity-associated cancer (J. Zhang, Sanidad, & Zhang, 2019). Inflammatory mediators, including

angiotensin, TNF-α and NF-κB can upregulate sEH expression in immune cells (Bastan et al., 2018). sEH inhibitors (sEHI) downregulate NF-κB and other inflammatory markers leading to decreased pro-inflammatory cytokines and nitric oxide metabolites and upregulates lipoxins to generate resolution (Schmelzer et al., 2005). In addition to downregulating a series of pro-inflammatory cytokines, EETs promote macrophage phagocytosis (Bystrom et al., 2013), which may have implications for the clearance of carcinogen-generated dead cells. Importantly, inhibition of sEH also promotes the generation of SPMs such as lipoxin generation (Ono et al., 2014). A metabolomics approach identified a critical role for cytochrome P450 (CYP)-generated epoxygenerated fatty acids and sEH-mediated eicosanoids were elevated in the plasma and colon of azoxymethane (AOM)/dextran sodium sulfate (DSS) induced colon cancer (W. Wang et al., 2019).

However, the role of EETs in cancer is complex as these epoxyeicosanoids may stimulate pro-angiogenic and pro-tumorigenic mechanisms (Imig & Hammock, 2009; Panigrahy et al., 2012). The CYP3A4 produced EETs play a role in breast cancer progression, including in tamoxifen-resistant subsets via proliferation, angiogenesis, and migration (Thuy Phuong et al., 2017). While EETs can be mildly pro-angiogenic, inhibition of sEH prevents angiogenic diseases such as diabetic retinopathy (J. Hu et al., 2017). Interestingly, EET-induced angiogenesis is suppressed by simultaneous inhibition of COX-2 by preventing COX mediated metabolism to pro-angiogenic lipids (Rand et al., 2019). Importantly, sEHIs may also reduce the toxicities of NSAIDs and COX-2 inhibitors via anti-inflammation and inhibition of oxidative injury as well as barrier breakdown (R. D. Jones et al., 2019). To minimize the pro-angiogenic activity of sEH inhibitor and the GI toxicity of COX-2 inhibitors, a novel COX-2/sEH inhibitor (PTUPB) was synthesized which potently inhibits inflammation (Hwang et al., 2011). Cancer progression is stimulated by inflammation, fibrosis, and oxidative stress. Dual COX-2/sEH inhibition via

PTUPB inhibits allergic airway inflammation, pulmonary fibrosis, kidney injury and sepsis via anti-oxidative stress (Dileepan et al., 2019; Hye Khan et al., 2016; C. Y. Zhang et al., 2019; Y. F. Zhang et al., 2020). Dual COX-2/sEH inhibition inhibits primary tumor growth including glioblastoma growth, metastasis and potentiates the antitumor efficacy of chemotherapeutic agents such as cisplatin (J. Li et al., 2017; F. Wang et al., 2018; G. Zhang et al., 2014). A novel dual COX-2/sEH inhibitor (PTUPB) inhibits debris-stimulated ovarian tumor growth by preventing an eicosanoid and cytokine surge of pro-inflammatory and pro-angiogenic mediators (Gartung et al., 2019). PTUPB inhibits high-fat diet-induced non-alcoholic fatty liver disease via inhibition of fibrosis, collagen deposition and pro-inflammatory cytokines (C. C. Sun et al., 2020). sEH is a therapeutic target as it is upregulated in obesity-induced colonic inflammation and sEH inhibition reduces obesity-induced activation of Wnt signaling in mice (W. Wang et al., 2018). Notably, carcinogen-induced cell death dose-dependently promotes tumor dormancy escape and progression by triggering oxidative stress as well as an eicosanoid/cytokine storm of pro-inflammatory mediators (Fishbein et al., 2020). In contrast, dual COX-2/sEH inhibition prevents inflammation-initiated tumor growth by preventing the eicosanoid/cytokine storm and reducing oxidative stress, as well as by promoting macrophage-mediated efferocytosis of tumor debris (Fishbein et al., 2020). Thus, inhibition of sEH may synergize with COX-2 inhibition while reducing the toxicity of COX-2 inhibition.

Thus, EETs may additionally be a novel approach to resolving carcinogen-induced inflammation via anti-inflammatory signaling and stimulation of macrophage phagocytosis. Importantly, in bronchiolar cells in which oxidative stress reduced lipoxin production, sEHIs stimulated pro-resolution mechanisms by stimulating the levels of lipoxins (Ono et al., 2014). Stimulation of resolution of inflammation, via SPMs or EETs, may be a novel chemopreventive

approach to carcinogen-induced cycles of inflammation, cell death, oxidative stress, and carcinogenesis (Figure 4).

## 4. Outlook

Cancer accounts for over 8 million deaths annually worldwide and presents one of the largest disease morbidity and mortality (Cortes et al., 2020). The prognosis for patients with cancer remains poor. Despite many exciting advances in research, many cancers remain deadly unless diagnosed early before advanced metastatic disease. The most effective treatment for patients is prevention and early detection. While carcinogens induce inflammation, a hallmark of cancer and a key characteristic of their pro-tumorigenic activity (Hanahan & Weinberg, 2011; Mantovani et al., 2008; M. T. Smith et al., 2016), they also disrupt the resolution of inflammation. Thus, the loss of inflammation resolution is an emerging mechanism of cancer pathogenesis (Gilligan et al., 2019; H. Liu et al., 2019; Panigrahy et al., 2019; Serhan & Levy, 2018; Sulciner, Gartung, et al., 2018; Sulciner, Serhan, et al., 2018; Y. Ye et al., 2018). Carcinogens continue to play a large role in the disease and social burdens of cancer globally. However, genotoxic mechanisms alone may not be sufficient for carcinogenesis and increased tumor risk (Bogen, 2019; Johnson et al., 2014), and more studies are required to further characterize nongenotoxic mechanisms including “failed” inflammation resolution. There is a malignant pro-tumorigenic feedback loop between apoptosis, inflammation, DNA damage, and carcinogenesis. Chronic inflammation and oxidative stress are largely intertwined processes which contribute via feedback loops to a microenvironment of stress, injury, and regeneration (Nowsheen et al., 2012). Initial carcinogen exposure induces inflammatory pathways and signaling through NF-κB leads to cytokine production, inflammatory infiltrates, and reactive oxygen species in a pro-tumorigenic environment. Controlling the local and systemic inflammatory response will be essential to prevent carcinogen-induced cancers. Stimulation of

resolution via supplementation of specifically pro-resolution lipid mediators may be a potent and less toxic non-immunosuppressive approach to reduce and prevent carcinogenesis at an early stage (Gilligan et al., 2019). Importantly, SPMs, including resolvins, lipoxins, and protectins, as well as sEH inhibitors are currently in clinical trials for other inflammatory diseases and could be rapidly translated for the management of carcinogen-induced cancers. Pro-resolution therapies can complement current anti-carcinogen strategies via debris clearance and inflammatory cytokine suppression. Further studies including human cancer trials are needed to evaluate the stimulation of resolution of inflammation to prevent and treat carcinogen-induced cancers.

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**Figure and Table legends**

**Figure 1. Key characteristics of carcinogens.**

Represents the 10 key characteristics of carcinogens adapted from Table 1 in (M. T. Smith et al., 2016). Aflatoxin $B_1$ as an example of a carcinogen which undergoes 1. Metabolic activation 2. Is genotoxic 3. Alters DNA repair 4. Leads to epigenetic alterations 5. Generates oxidative stress, 6. Chronic inflammation, and 7. Immunosuppression 8. Activates receptor mediated signaling 9. Causes cell immortalization and 10. Increases cell proliferation. Adapted from Smith et al Environmental Health Perspectives 124:6 2016.

**Figure 2. Experimental models of carcinogen-induced cancers.**

**A)** Intraperitoneal injection of male Sprague-Dawley rats with 30 mg/kg Diethylnitrosamine (DEN) twice a week for 11 weeks led to hepatocellular carcinoma. **B)** Male C57BL/6J mice or BALB/c mice injected intraperitoneally week one with 10 mg/kg azoxymethane (AOM) and one week later given 1.5% or 2% dextran sodium sulfate (DSS) in the drinking water for one week leading to colon carcinomas. **C)** Male F344 rats given 40 p.p.m. 4-nitroquinoline 1-oxide (4-NQO) in drinking water for 10 weeks led to tongue squamous cell carcinoma or papilloma. **D)** NMRI mice exposed to single epicutaneous application of 0.1 µmol 7,12-dimethylbenz[a]anthracene (DMBA) in acetone and two weeks later exposed twice a week to 5nmol phorbol 12-myrisate 13-acetate (PMA) for 28 weeks leading to skin papilloma and carcinoma. **E)** Male A/J mice were injected intraperitoneally with 50 mg/kg 4-(methylnitrosamino)-1 (3-pyridyl)-1-butanone (nicotine-derived nitrosamine ketone (NNK)) for 4 weeks led to lung adenocarcinoma. **F)** Male F344 rats injected subcutaneously with 1mg/kg N-nitrosomethylbenzylamine (NMBA) 5 times a week for 5 weeks and then once a week for 5 more weeks led to esophageal papilloma and carcinomas.

**Figure 3. Nongenotoxic mechanisms of carcinogenesis.**

Following carcinogen exposure inflammation is induced leading to inflammatory infiltrates at the location of exposure. With the upregulation of NF-κB, COX-2, and 5-LOX inflammatory cells are triggered to release a storm of pro-inflammatory and tissue regenerative eicosanoids, cytokines, and reactive oxygen species. The factors generate DNA mutations, cell damage, and epigenetic alterations leading to cellular transformation. In addition, the inflammation and oxidative stress leads to upregulated anti-apoptotic mechanisms, angiogenesis, and DNA damage but downregulated DNA repair, immune surveillance, and resolution. Together, these processes driven by carcinogen induced inflammation alter the microenvironment allowing for extracellular matrix remodeling, cytotoxicity and damage-associated molecular pattern (DAMP) signaling, and regenerative proliferation resulting in tumor growth.

**Figure 4. Inflammation resolution in carcinogen-induced cancer.**

Carcinogen (NDEA) induced inflammation causes tissue damage and cell death of normal cells (hepatocytes) generating cellular debris. These dead cells activate local macrophages (Kupffer cells) to a pro-inflammatory phenotype generating a cytokine storm. This chronic inflammation reduces pro-resolving mediators including SPMs and EETs and signals for angiogenesis, fibrosis, and inflammatory cell infiltration. Infiltrating white blood cells add to the tissue injury by producing reactive oxygen and nitrogen species triggering the upregulation of NF-κB, COX-2, 5-LOX, and MMPs in surrounding hepatocytes generating a vicious cycle leading to tumor growth. However, resolution of inflammation via SPMs or sEH inhibition may break this pro-tumorigenic

cycle. Resolution promotes macrophage phagocytosis of cellular debris, inhibits the cytokine storm, suppresses inflammatory infiltration, and is not immunosuppressive leading to the downregulation of NF-κB, COX-2, 5-LOX, and MMPs and inhibition of carcinogenesis.

**Table 1. SPM cancer-related mechanisms.**

Summary of publications demonstrating the anti-cancer role of SPMs via multiple mechanisms.

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Table 1. SPM cancer-related mechanisms

| TUMORIGENIC PROCESS | SPECIALIZED PRO-RESOLVING MEDIATORS | MECHANISMS | REFERENCES |
|---|---|---|---|
| **ANTI-TUMOR ACTIVITY** | AT-RvD1, AT-RvD3, AT-LXA4 | Aspirin-triggered SPMs suppress tumor growth | Gilligan et al |
| | RvD2, RvD3, RvD4 | Pre-operative supplementation eliminates micrometastases | Panigrahy et al |
| | Resolvin receptor FPR1 | Regulation of inflammation, angiogenesis, and gastric tumorigenesis | Prevete et al |
| | RvD1 | Inhibition of lung cancer growth and metastasis (miR138-5p/FOXC1) | Bai et al |
| | RvD1 | Inhibits c-MYC in colon cancer cells | Zhong et al |
| | 15-epi-LXs | Produced by lung adenocarcinoma cell-leukocyte interactions inhibit proliferation | Claria et al |
| **CANCER ASSOCIATED LOSS OF SPMS** | RvD1, $LXA_4$ | Loss during human colon cancer progression | Zhuang et al, Liu et al |
| | Resolvin receptors GPR18, GPR32 | Resolvin receptors downregulated in oral cancer cells | Ye et al |
| | $LXA_4$ | Downregulated via IFN-γ signaling during inflammatory papilloma persistance | Wang et al |
| | Lipoxins ($LXA_4$) | Lipoxin deficiency in leukemia, lymphoma and kaposi's sarcoma | Stenke et al, Chandrasekharan et al |
| **ANGIOGENESIS** | $LXA_4$, BML-111 | Inhibits VEGF and HIF-1α to suppress hepatocarcinoma growth | Chen et al |
| | $LXA_4$, 15-epi- $LXA_4$ | Anti-angiogenic and anti-inflammatory in Kaposi's sarcoma tumor cells | Marginean et al |
| | ATL-1 (15-epi- $LXA_4$) | Inhibit VEGF-induced permeability and tumor cell migration | Vieira et al |
| **INFLAMMATION** | $PD1_{n\text{-}3DPA}$, $RvD5_{n\text{-}3DPA}$, $LXA_4$ | Protect inflammatory colitis induced injury | Gobbetti et al, Gewirtz et al |
| | RvD1, RvD2 | Inhibition of oral cancer derived cytokines and inflammatory cells | Ye et al |
| | RvD1, RvE1 | NF-κB suppression prevention of liver hepatitis transition to cancer | Kuang et al |
| | RvD1 | LPS induced cancer cell proliferation inhibited via MAPK pathway targeting | Lu et al |
| | RvD2, RvD3, RvD4, RvE1, AT-RvD1, AT-RvD3, AT-LXA4 | Resolution and phagocytosis of inflammatory tumor-cell debris | Sulciner et al, Gilligan et al, Panigrahy et al |
| | $LXA_4$ | Inhibits IL-8 and ICAM-1 in brain tumor cells | Decker et al |
| **EPITHELIAL-MESENCHYMAL TRANSITION** | RvD1, AT-RvD1 | Inhibition of TGF-β1 for suppression of ZEB1, mTOR signaling | Lee et al, Liu et al |
| | RvD1, AT-RVD1 | Inhibition of carcinoma associated fibroblast signaling to inhibit EMT | Sun et al |
| | Mar1, PDX | Inhibition of bleomycin induced fibrosis and EMT | Wang et al, Li et al |
| **FIBROSIS AND INVASION** | $LXA_4$ | Inhibits pancreatic cell invasion via ROS/MMP and TGF-β1 | Zong et al |
| | $LXA_4$ | Inhibits pancreatic cancer fibroblast activation | Schnittert et al |
| | $LXA_4$ | Inhibits hepatocyte growth factor induced invasion | Zhou et al |
| | $LXA_4$ | Inhibit leukemia cell migration and induces phagocytosis of apoptotic cells | Tsai et al |

| | | | |
|---|---|---|---|
| **IMMUNOSUPPRESSION** | RvD2, RvD3, RvD4 | Induction of anti-tumor T-cell response | Panigrahy et al |
| | RvD1 | Induction of NK cell cytotoxicity to pancreatic cancer cells | Halder et al |
| | RvD2, RvD5, $LXA_4$ | SPMs produced by cancer cell interaction with macrophages | Werner et al |
| | ATL-1, $LXA_4$ | Induction of tumor cell apoptosis by TAMs to inhibit melanoma | Simoes et al |
| | $LXA_4$ | Target Breg cells to allow for CD8+ immunosurveillance and regulate MDSCs | Wang et al, Zhang et al |

## Figure and Table legends

### Figure 1. Key characteristics of carcinogens.

Represents the 10 key characteristics of carcinogens adapted from Table 1 in (M. T. Smith et al., 2016). Aflatoxin $B_1$ as an example of a carcinogen which undergoes 1. Metabolic activation 2. Is genotoxic 3. Alters DNA repair 4. Leads to epigenetic alterations 5. Generates oxidative stress, 6. Chronic inflammation, and 7. Immunosuppression 8. Activates receptor mediated signaling 9. Causes cell immortalization and 10. Increases cell proliferation. Adapted from Smith et al Environmental Health Perspectives 124:6 2016.