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Preface

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Bioactive lipids encompass a diverse array of molecules that regulate a broad range of physiological processes contributing to homeostasis or the pathogenesis of many diseases including cancer. Over the past couple of decades, there has been a growing appreciation for the role of bioactive lipids in cancer initiation, progression, and metastasis. Their diverse molecular structures reflect the complexity of their functions given their ability to promote or suppress cancer. This special double issue of "*Bioactive Lipids*" in Cancer and Metastasis Reviews includes 27 comprehensive review articles authored by leading experts in the lipid biology field.

Stress can accelerate primary tumor growth and tumor metastasis. Prof. Sood and his laboratory explore arachidonic acid-derived eicosanoids in metabolic pathways that are altered in response to psychological stress and inflammation (Umamaheswaran et al.). Physical stress, such as radiotherapy, can activate the synthesis of bioactive lipid mediators which contribute to inflammation and angiogenesis in cancer, as well as the acquisition of resistance to therapy. Kim et al. summarize studies focused on how targeting enzymes involved in the biosynthesis of eicosanoids, such as cyclooxygenase (COX) or lipoxygenase (LOX), could improve the response of cancer patients to radiotherapy. The paradoxical nature of therapy-induced or spontaneous apoptotic cells, as well as the novel roles of apoptotic caspases in cancer, is examined by Zhao et al.

Several outstanding reviews featured in this special issue highlight the critical roles of eicosanoid signaling in various tumor types, including prostate cancer (Panagiotopoulos et al.), malignant melanoma (Tímár et al.), and colorectal cancer (Wang et al.). In addition, Xu et al. provide a unique bioanalytical perspective on eicosanoids in the progression of hepatocellular carcinoma. Further, Chatterjee et al. extensively examine the cross talk between matrix metalloproteinases and eicosanoids in cancer which could lead to novel therapeutic targeting strategies.

Macrophages are critical immune cells that can have pro- or anti-tumor activity. The review by Colby et al. from the M.D. Anderson Cancer Center extensively dissects the complex and diverse effects of bioactive lipids in tumor-associated macrophages in the context of colorectal cancer. Moreover, Weigert et al. summarize current knowledge of COX-2/mPGES-1 and ALOX5/-15 in macrophages and their contribution to cancer progression. Macrophages are one of the immune cell types that express cysteinyl leukotriene receptor 2. Slater et al. comprehensively review the recent identification of an oncogenic mutation in this particular leukotriene receptor in a subset of uveal melanoma patients. Thus, additional research is needed to further delineate the tumor-promoting and tumor-inhibitory roles of bioactive lipid mediators in macrophages.

COX-derived lipid mediators including prostaglandins and thromboxanes have long been shown to be key regulators of inflammation and cancer progression. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin that block the enzymatic activity of COX and subsequent production of prostaglandins have been shown to exhibit anti-cancer activity. Kobayashi et al. at the University of Tokyo summarize the latest studies demonstrating the critical, and in some cases, opposing roles of prostaglandins in the tumor microenvironment. Further, Tong et al. provide an in-depth review on the involvement of the COX-2/PGE_2/EP signaling axis in therapeutic resistance in cancer and current treatment strategies to conquer this resistance in cancer patients. Lala et al. also discuss the role of prostaglandins in tumor-associated lymphangiogenesis (the formation of new lymphatic vessels) in the context of breast cancer. The interaction between biosynthetic enzymes of eicosanoids, such as COX-2, and the epidermal growth factor receptor (EGFR) pathway is central to tumorigenesis. Yang et al. provide an extensive review on this topic with emphasis on the involvement of HB-EGF/EGFR in severe cardiac side effects caused by COX-2 inhibitors.

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Thus, there is an emerging urgency to understand molecular mechanisms underlying toxicities associated with COX inhibition to improve cancer therapy.

In addition to COX, biosynthetic enzymes LOX and cytochrome P450 (CYP450) have also been the focus of potential therapeutic interventions. Orafaie et al. from Mushhad University of Medical Sciences in Iran review recent publications highlighting the importance of 15-lipoxygenase inhibitors in cancer treatment. Targeting cancer-associated CYP450 enzymes with a particular focus in cancer cell mitochondria is reviewed by Guo et al.

As characterized by Dr. Judah Folkman, the formation of new blood vessels (angiogenesis) is necessary for the growth and survival of tumors. Eicosanoids have been shown to be critical regulators of angiogenesis. Hu et al. from Goethe-University Frankfurt in Germany review the involvement of bioactive lipids, in particular CYP450- and soluble epoxide hydrolase (sEH)-derived metabolites, in angiogenesis and cancer progression. Platelets are key players in inflammation, angiogenesis, and thrombosis, as well as cancer progression and metastasis. Kanikarla-Marie et al. elegantly highlight our current knowledge of bioactive lipid metabolism in platelet and cancer biology, while Dovizio et al. discuss the exciting potential diagnostic and therapeutic implications of platelets and platelet-derived microparticles in cancer. Further, Ramirez et al. offer a thorough review of the complex interactions of thrombospondin-1 (TSP-1) and eicosanoids in cancer and inflammation. Anquetil et al. focus on the roles of bioactive lipid mediators derived from phosphoinositide 3-kinase (PI3K) isoforms in cancer and thrombosis. Therefore, targeting bioactive lipids in the vasculature may be a potential therapeutic strategy for cancer treatment.

The importance of bioactive lipids extends far beyond arachidonic acid-derived metabolites. Julian Gomez-Cambronero provides exceptional insight into the lack of translational regulation of phospholipase D (PLD) expression in triple negative breast cancer, and also discusses the important role of PLD and phosphatidic acid (PA) in macrophage polarization, exosome biogenesis, and regulation in the tumor microenvironment. Lee et al. address autotaxin (ATX) and lysophosphatidic acid (LPA) signaling in the intriguing subpopulation of cancer stem cells, which possess increased resistance to therapy and the ability to differentiate and self-renew.

The potential benefits of omega-3 polyunsaturated fatty acids (PUFAs) in cancer are of popular interest. Erazo-Oliveras et al. highlight how the fatty acid composition in the plasma membrane can affect critical cellular signaling processes and that if dysregulated can contribute to a pro-tumor environment. They also address the current literature demonstrating how certain dietary PUFAs can potentially reduce cancer risk by reorganizing the arrangement of critical proteins/lipids in the cell membrane. Further, as a clinical scientist, Dr. Mark Hull provides unique insight into the latest pre-clinical mechanistic studies and clinical research on dietary intake or supplementation of omega-3 PUFAs in colorectal cancer (Volpato et al.). Included in this review are observations from ongoing clinical trials that point to direct correlation between omega-3 PUFA intake and improved patient outcomes.

The review by Sulciner et al. focuses on targeting bioactive lipid mediators in cancer, including the endogenous specialized pro-resolving lipid autacoid mediators (SPMs) derived from omega-3 PUFAs. SPMs are a novel superfamily of lipid mediators that exhibit anti-inflammatory, pro-resolving, and anti-tumor activity. SPMs stimulate the resolution of inflammation by promoting macrophage phagocytosis of cellular debris and counter-regulating pro-inflammatory cytokines. Enhancing the demonstrated anti-tumor activity of SPMs provides a new therapeutic avenue for improving cancer therapy.

This impressive collection of scientific reviews highlights the cutting-edge research of bioactive lipids in cancer and cancer therapy. However, to this day, new bioactive lipids are still being discovered, giving rise to more questions that are yet to be addressed. Continued research is necessary to advance our understanding of bioactive lipids and elucidate their mechanistic involvement in cancer. Targeting specific bioactive lipids, either by inhibiting inflammatory and pro-tumorigenic lipid mediators, or by enhancing the anti-tumor activity of specialized pro-resolving mediators in resolution inflammation, represents a promising and novel therapeutic approach for cancer treatment.