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Preface

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Protein growth factors and cytokines are typically thought to drive the proliferative/invasive/survival hallmarks of cancer. However, it has become apparent that bioactive lipids are equally involved, and like their protein counterparts, generally do so thorough the activation of their cognate membrane receptors. It has also recently become apparent that protein growth factor and lipid signaling are not independent events but rather are integrated such that growth factors upregulate eicosanoid synthetic enzymes while at least some bioactive lipids can activate growth factor receptors, resulting in a complex array of biological outcomes.

Bioactive lipids, particularly, but not limited to the eicosanoids derived from arachidonic acid, have actions at every stage of cancer, from prevention to progression to metastasis. The knowledge that has been generated in recent years on the identification of the roles and mechanisms of action of specific lipids is highly significant in that it offers the opportunity for the development of prognostic and predictive biomarkers as well as therapeutic intervention into the neoplastic process. This issue is a compendium of reviews on the most recent information on the formation and function of the eicosanoids and other bioactive lipids in the development of cancer.

Three major enzymatic pathways can metabolize arachidonic acid into signaling hormones: the cyclooxygenases (COX), the lipoxygenases (LOX), and the P450 monooxygenases. As described in the following review chapters, components of all three enzymatic pathways are upregulated in either tumor cells or in the surrounding microenvironment. The roles in neoplasia of the eicosanoid products of each of these pathways are well described in the first chapter by Schneider and Pozzi. The following three chapters, by Berquin et al., Das, and Comba et al., focus on the fatty acid precursors to the eicosanoids and describe how alteration of their abundance and type affect eicosanoid synthesis and thus biological processes associated with gene expression, stem cell and cancer cell biology. Three chapters by Müller-Decker, Cathcart et al., and Thiel et al., describe the importance of COX-2 upregulation to specific processes involved in the development of skin and gastrointestinal cancers. This is followed by a chapter by Ekambaram et al. on the little studied but significant contribution of the thromboxane products of the COXs in cancer progression and metastasis. A subsequent chapter by Tai describes the important contribution of the catabolic enzyme prostaglandin dehydrogenase (PGDH) to controlling the tissue level of prostaglandins and thus tumor development. This is followed by a chapter by Moore et al. on the regulation of COX, the EP receptors for prostaglandin E_2, and PGDH by microRNAs; this information offers new approaches to controlling eicosanoid synthesis. Speed and Blair describe the formation of mutagenic DNA adducts by COX-2 and 5-LOX metabolism of arachidonic acid. Two chapters by Reader et al. and Fischer et al. describe the function of the EP receptors and their complex mechanisms of action in breast and skin cancer. The following two chapters by Lee et al. and Tucker et al. describe the pro- and antitumorigenic action of specific lipoxygenases in inflammation and several types of cancer. Two chapters by Pace-Asciak and Janakiram et al. focus on the formation and function of hepoxilins and resolvins, novel products of the LOXs. The little studied but emerging significance of the epoxyeicosatrienoic acids (EETs),

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products of cytochrome P450 enzymes, are described by Panigrahy et al. and by Fleming. Chapters by Houben and Moolenaar, Furuya et al., and Yester et al. describe the function of several non-eicosanoid bioactive lipids, the autotaxins and sphingolipids, while Hermanson and Marnett focus on the endocannabinoids. The involvement of eicosanoids in tumor hypoxia is the subject of a chapter by Krishnamoorthy and Honn. The anti-inflammatory and anti-carcinogenic activity of peroxisome proliferator-activated receptors is explored by Peters et al. In the final chapter, Wang et al. discuss the activation of the NSAID-activated gene (NAG-1) by COX inhibitors and the role of NAG-1 in cancer prevention.

Thus, this volume of *Cancer and Metastasis Reviews* is intended as an up-to-date reference on the role of a wide variety of bioactive lipids in the development and progression of cancer. It is hoped that the information provided in this volume will encourage additional studies that will lead to improved approaches to the prevention and treatment of cancer.