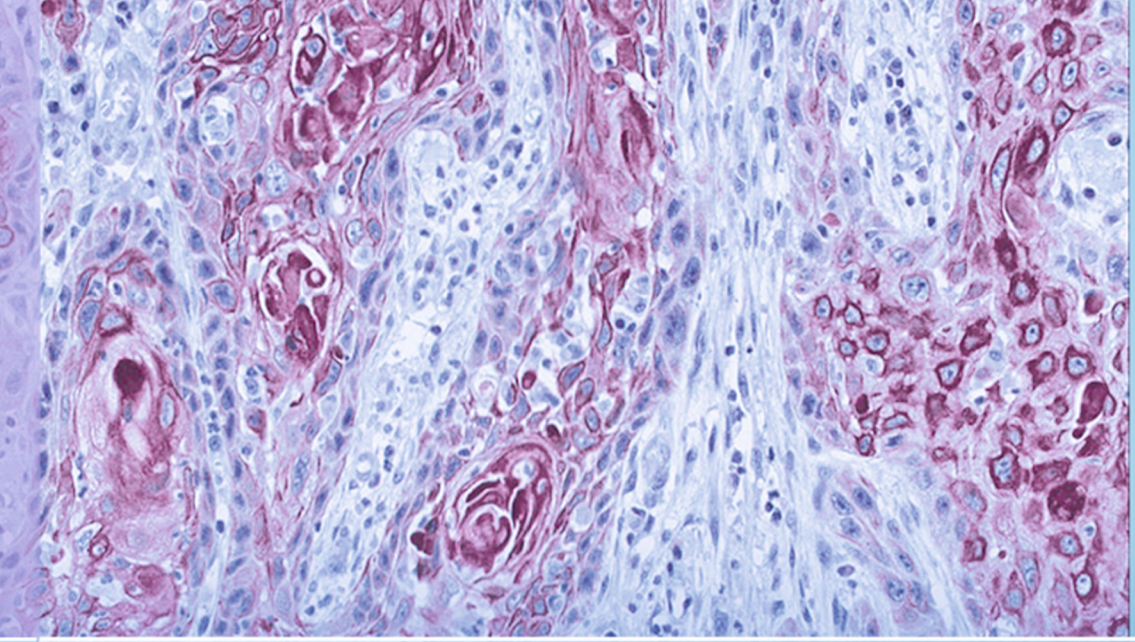

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Preface

Squamous epithelia form the lining surface of tissues in contact with the environment, including the skin, upper aerodigestive, respiratory and genital tracts, and several other specialized tissues. Cancers that form in squamous epithelia are among the most common human solid tumors due to increased exposure to environmental carcinogens such as ultraviolet light, tobacco smoke, and other genotoxic compounds, as well as infectious agents such as human papilloma virus. Late stage cancers of the upper aerodigestive tract, esophagus and cervix have high morbidity and there has been little improvement in survival. Thus there is compelling need to identify critical signaling pathways that regulate the development of squamous cancer and translate these findings into therapeutic targets to improve patient survival. In general, squamous epithelia are multilayered or stratified epithelia in which proliferation is confined to the basal layer in contact with the basement membrane, and squamous differentiation occurs as cells move away from the basal layer. As in any epithelium, proliferation and differentiation are tightly regulated by signaling pathways that respond to the external tissue and cellular microenvironment, and become dysregulated during progression to malignancy. This text addresses some of the most important signaling pathways that regulate normal growth and differentiation in squamous epithelia; how they are altered during progression to carcinoma; and their potential as therapeutic targets. The reviews include studies from human squamous cancers and cancer cell lines, as well as mouse two-stage skin carcinogenesis and genetically engineered mice, which provide meaningful animal models for the development of squamous cancers in multiple tissues. Because these different squamous tissues likely share similar regulatory networks, studies in one tissue or animal model are likely to have general significance for cancer development and therapy in other squamous epithelia.

While each chapter focuses on a specific pathway and its role in squamous cancer, it is clear that these represent a network of interacting pathways that control many different aspects of normal keratinocyte homeostasis. Alterations in any one pathway during cancer progression are likely to impact several others. Interaction of epithelial cells with the extracellular matrix in the basement membrane through integrin receptors is critical for tissue integrity and control of epithelial cell proliferation. Chapters by Dr. Kramer, University of Pennsylvania and Dr. DiPersio, Albany Medical College and colleagues review recent studies on the alterations in

expression and adhesive interactions between integrins and their ECM ligands that drive local tissue invasion and progression squamous cell carcinoma. Equally important, extracellular signals that regulate cell growth come from both positive and negative growth factor signaling pathways. The epidermal growth factor receptor family and its ligands are critical regulators of both normal keratinocyte proliferation and differentiation, and aberrant expression and activation of this pathway is a consistent feature of squamous cancers. Chapters by Dr. Hansen, Creighton University and Dr. Grandis, University of Pittsburgh and their colleagues discuss recent data on the role of the epidermal growth factor receptor in mouse models of squamous cancer, human head and neck squamous cell carcinoma (HNSCC) and targeting this signaling pathway for therapy of HNSCC. The role of another important growth factor pathway, HGF/cMet, in the development of squamous cell cancer, and therapeutic targeting of this pathway is also discussed in a chapter by Dr. Zhong Chen, NIDCD, NIH. Transforming growth factor beta (TGFβ1) is a critical negative regulator of keratinocyte proliferation but with important autocrine and paracrine roles in cancer pathogenesis that may both inhibit and enhance the malignant phenotype. The chapter by Drs. Reiss and Xie, UMDNJ-Robert Wood Johnson Medical School, examines the role of the TGFβ1 signaling pathway and mutations in this pathway in HNSCC. Many of these growth factor pathways activate intracellular signaling molecules that are the center of important regulatory nodes controlling proliferation differentiation and inflammatory signaling in keratinocytes. Thus, this book contains several chapters which review studies in humans and mouse models that indicate an important role of Ras (Drs. Cataisson and Yuspa, NCI), Protein Kinase C (Dr. Denning, Loyola University), AKT and mTOR (Dr. Nathan et al., LSU; Drs. Lin and Rocco, Harvard Medical School; Dr. Gukind et al., NIDCR) and Cox-2 (Drs. Rundaug and Fischer, UT M.D. Anderson Cancer Center) in the development of squamous cancer, and the potential of these molecules as therapeutic targets. These signaling pathways converge on two transcription factor families AP-1 and NF-κB that play critical roles in gene expression that regulates keratinocyte proliferation, differentiation and inflammatory signaling. Drs. Bowden and Alberts, University of Arizona, and Hess and Angel, German Cancer Research Center review studies on ultraviolet activation of AP-1 signaling and potential therapeutic targets in this pathway and the role of AP-1 in mouse skin carcinogenesis, while Dr. Karin and colleagues, University of California, San Diego discuss recent studies on the role of NF-κB and IκB kinases in squamous cancer and the interaction with other signaling pathways. Other nuclear transcription factor families play critical roles in normal keratinocyte homeostasis and are frequently altered during progression to squamous cell carcinoma. Chapters on PPARs (Drs. Peters and Gonzalez, Pennsylvania State University and NCI), p. 63 (Drs. Roop and Koster, University of Colorado, Denver), retinoic acid receptors (Drs. Kadara and Lotan, UT M.D. Anderson Cancer Center) and vitamin D receptors review the important role of these transcription factor families in the regulation of epidermal proliferation and differentiation their role in squamous cancer. Finally the chapter by Drs. Zhou, Hu, and Wong, University of California at Los Angeles, describes

recent advances in high throughput molecular profiling as a means to identify new genomic alterations and therapeutic targets for oral cancer.

While this is not an exhaustive survey of all signaling pathways that regulate squamous cancer development we hope that pulling together this diverse research into one monograph will provide potential for cross-fertilization between researchers studying different aspects of squamous cancer, stimulate new research directions and highlight potential new targets for therapeutic intervention. The editors would like to thank their colleagues who contributed chapters to this book and to everyone in the research community that have made significant contributions to our understanding of this disease.

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