

Introduction

Signal Transduction

Charles V. Clevenger

University of Pennsylvania, PA, USA

This issue of *Breast Disease* focuses on the subject of signal transduction and its role in the pathogenesis and progression of human breast cancer. Within the past 10 years, the explosion in our knowledge of these processes has significantly altered our understanding of breast cancer, and resulted in the first receptor-based therapies. This issue examines a variety of relevant signaling pathways in mammary epithelium and explores their mechanisms and functional contribution to the evolution of this disease.

The articles herein explore receptor-based signaling that occurs both at the cell surface and within the nucleus that controls the gene expression required for the breast cancer phenotype. The first review by Rosen examines the effects of sex steroid patterning in the developing mammary gland and the subsequent consequences this may have on the pathogenesis of breast cancer. The contribution by Trauernicht and Boyer evaluates the role of BRCA1 and its interaction with estrogen in the context of breast tumorigenesis. Cross-talk between the progesterone receptor and growth factors within the breast is overviewed in the work by Pierson-Mullany, et al. The structural details of the epidermal growth factor receptor (EGF) superfamily and its significance to ligand binding and receptor blockade is considered in the contribution by Lemmon. The interactions of insulin-like growth factors (IGF) with both receptors and binding proteins are explored in the article by Perks and Holly and consideration of IGF receptor associated signaling pathways and cross-talk is provided. The review by Serra and Crowley exam-

ines the function of transforming growth factor beta (TGF- β) during development, and the biphasic effect this peptide has on early versus late stage tumor progression. Finally, prolactin (PRL) action and signaling in human breast cancer are discussed in the article by Clevenger. We believe that these contributions explore salient areas of breast tumor signaling and serve as ongoing and future bases for targeted drug discovery.

Of course, any good series of reviews should open up more questions than they answer, and the current collection of review provides no exception. Several notable research foci remain ripe for discovery, including: 1) how does cross-talk of the above growth factors coordinate breast differentiation, and how does dysregulation of such mechanisms contribute to the breast cancer phenotype? 2) how is the metastatic phenotype regulated by the interaction of growth factors and hormones in concert with signals from the extracellular matrix? 3) what are the relative and specific roles of growth factors elaborated at the autocrine/paracrine versus endocrine levels in breast neoplasia? and 4) how does the temporal exposure of mammary epithelium and its chromatin to hormone and growth factors alter the spatial differentiation of normal and aberrant breast tissue development? It is our desire that the discussions engendered by the reviews herein stimulate additional research on these topics. Clearly, further mechanistic understanding of these underpinnings of breast neoplasia has been and will be the wellspring for novel therapies of this disease.