

Introduction

Transcription Factors

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One of the early issues of the *Journal of Mammary Gland Biology and Neoplasia* from 1997 dealt with "Transgenic Models of Mammary Gland Development and Function." In the past 6 years, enormous progress in this area has resulted from the characterization of numerous transgenic and knockout mice which display mammary phenotypes, as well as an increasing number of investigators realizing the potential of the mammary gland as a model system for studying signal transduction and development. In particular, this issue is focused on transcription factors because of the significant new insights that have resulted from studying their roles in mammary gland development and breast cancer.

Studies conducted during the 1980s using milk protein gene promoters to target the expression of heterologous genes to the mammary glands of transgenic mice suggested that there might be a mammary-specific transcription factor involved in hormonal and tissue-specific regulation of these genes. However, the search for the holy grail of a "master regulatory" factor proved fruitless. Instead, in the 1990s detailed analyses of the milk protein gene promoters and enhancers revealed that their spatially and temporally restricted expression patterns resulted from combinatorial interactions at the protein-protein and protein-DNA level of members of several families of commonly expressed transcription factors whose activities were controlled by both systemic hormones and local growth factors. These studies identified members of the signal transducers and activators of transcription (Stat), nuclear factor 1 (NF1), CCAAT enhancer binding protein (C/EBP),

nuclear factor of κ B (NF- κ B), Ets and nuclear receptor families of factors as being involved in the regulation of milk protein gene expression. A second class of transcription factors discussed in this issue is those which have been implicated in embryogenesis and organogenesis and, more recently, in the regulation of stem cells and cell fate determination. These include members of the homeobox, the helix loop helix (HLH), and the β -catenin/T-cell factor (TCF) families of transcription factors.

All of these transcription factors are encoded by genes that generate multiple protein isoforms, resulting not only from differential transcription, but also from alternative splicing and even alternative translational start sites. Many of these factors also undergo unique posttranslational modifications, including phosphorylation, glycosylation, sumoylation, and acetylation. Thus, the number of combinatorial interactions among these factors at composite response elements is quite large, and there are dramatic changes observed in their activities throughout mammary gland development and in breast cancer. Not too surprisingly, germline or conditional deletion of the transcription factors interacting with composite elements in the milk protein genes has resulted not only in effects on milk protein gene expression but, in many cases, in profound effects on earlier stages of mammary gland development.

Conceptually, it makes sense to discuss transcription factors beginning with their effects during embryonic mammary gland development, then ductal morphogenesis, lobuloalveolar development, lactation, and finally involution. However, most of the transcription factor families discussed in this volume exert pleiotropic effects at multiple stages of mammary gland development, as well as in breast tumorigenesis. For example, the first chapter by

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Hatsell *et al.* illustrates that β -catenin acts in concert with Lef/Tcf factors to determine cell fate and promote cell survival and proliferation at several stages of mammary gland development. This is followed by a summary of the role of homeobox-containing genes in mammary gland development and breast tumorigenesis by Chen and Sukumar outlining the fundamental role these genes play in embryogenesis. The chapter by Kurpios *et al.* suggests an unexpected role for PEA3 Ets factor in progenitor cell renewal in the terminal end buds, while Grimm and Rosen summarize the role of C/EBP β as a member of the family of bZIP transcription factors, with an emphasis on its role in the specification of progenitor cell fate in the mammary gland. The next three chapters deal with factors involved primarily in lobuloalveolar development,

including characterization of the differences in response to the A and B isoforms of the progesterone receptor by Conneely and colleagues, NF- κ B by Cao and Karin, and finally different Id proteins by Desprez *et al.* The final chapter describes potential roles of members of the NF1 transcription factor family primarily in lactation and involution. Clearly, we are just beginning to scratch the surface in understanding the transcriptional programs regulating mammary gland development and tumorigenesis. In closing, I thank the authors of these papers for their timely contributions, in many cases containing new data just submitted for publication. Finally, I need to apologize to those investigators whose important work on other transcription factors could not be included because of a lack of space.