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PREFACE

Preface

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The identity of mammary progenitors and stem cells is still a subject of debate, while the concept of hormonal regulation of these cell types has gained prominence in recent years. This regulation is important as growing evidence suggests that the stem and progenitor cells in the breast are particularly susceptible to tumorigenesis. These data, which are primarily derived from animal models, demonstrate transient expansion of the mammary stem cell compartment during pregnancy and the reproductive cycle, thereby providing a potential mechanism for the window of increased susceptibility to transformation during these stages. This issue of The Journal of Mammary Gland Biology and Neoplasia brings together a number of reviews that provide a detailed overview of, and new insight into, how hormone signaling, and alterations to this signaling (such as that which occurs when taking hormone replacement therapy), may drive increased breast cancer risk and also how this signaling may impact established breast cancers.

"Form and function: how estrogen and progesterone regulate the mammary epithelial hierarchy"

In this issue, Arendt and Kuperwasser comprehensively review the current understanding of how estrogen and progesterone regulate stem and progenitor cells within the epithelial hierarchy of the mammary gland during pubertal mammary development, as well as during the menstrual cycle and pregnancy. Importantly, they discuss what is known of how this occurs in the mouse mammary gland, and which mechanisms are thought to be similar or different in the human breast. In addition, their review acknowledges the challenges in this subject area: for example, the propensity for steroid receptors to be lost during in vitro experimentation and, more notably in the human breast, the difficulty in being able to study specific cell subpopulations due to the transient existence of some cell subsets during particular developmental periods, such as pregnancy. Moreover, this review includes discussion surrounding conflicting reports which have identified diverse phenotypes

Additional contributor to this preface We thank Professor Joyce Taylor-Papadimitriou for her commentary in this preface on the review by Dontu and Ince "*Of mice and women: a comparative tissue biology perspective of breast stem cells and differentiation*"

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of stem and progenitor cells that have been identified using a variety of different cell surface markers and functional assays.

"Impact of progesterone on stem/progenitor cells in the human breast"

This review by Hilton and Clarke provides a detailed report and discussion of the emerging role for progesterone in regulating stem and progenitor cells in the human breast, with a particular emphasis on progesterone control of progenitor cell proliferation and expansion, and how this may increase risk for tumorigenesis. These authors discuss similarities and differences between progesterone's actions on progenitor cells in mouse and human models, and how both paracrine and autocrine signaling downstream of progesterone may impact human breast progenitor cells. Importantly, they discuss evidence for the existence of progesterone receptor (PR) + progenitor cells in the human breast basal layer that may proliferate upon progesterone signaling, and how this may extend to breast cancer, where progesterone promotes a basal phenotype and increases breast cancer stem/progenitor markers. Finally, they tie together how an expanded progenitor population from progesterone exposure during pregnancy or synthetic progestins during hormone replacement therapy may impact the relative risk for developing breast cancer.

"Steroid hormones, steroid receptors, and breast cancer stem cells"

The review by Finlay-Schultz and Sartorius provides a thorough and comprehensive overview of how steroid hormones regulate breast cancer stem cells. The action of natural and synthetic steroid hormones and their receptors on breast cancer stem cell numbers and functionality is discussed with a special focus on the mechanisms of steroid hormone-induced cancer stem cell modulation. Recent findings on the roles of downstream factors in steroid hormone signaling are outlined with respect to breast cancer and its stem cells. Specifically, the mechanistic functions of steroid hormone-induced transcription factors and microRNAs are highlighted. Furthermore, agreed as well as controversial perspectives on the postulated roles of autocrine and paracrine progesterone signaling and their effects on breast cancer stem cell expansion are discussed, and their potential relevance in tumor heterogeneity is highlighted. Most importantly, the fine balance between interacting signaling pathways is explored, and areas for future investigations are unfolded.

"Of mice and women: a comparative tissue biology perspective of breast stem cells and differentiation"

The article by Dontu and Ince presents a timely and incisive critique of past and current attempts to define the phenotypes of the human mammary gland and how these might relate to mammary epithelial stem cells and to breast cancer. The problems of obtaining relevant data from working with the mouse mammary gland are raised and the importance of first defining the differentiated phenotypes in the human mammary epithelial cell compartment is emphasized. The Ince laboratory used multiplex immuno-staining of tissue sections to focus on antigens showing a bimodal distribution rather than a gradient pattern of staining. They also documented the position of the staining in the mammary ductal system. This latter dimension is particularly relevant in correcting the commonly held view that the keratins 5,14/17 are markers for basal myoepithelial cells, since the multiplex data shows that these keratins are expressed in luminal cells in lobules and in myoepithelial cells surrounding ducts. The new data defines 11 luminal cell phenotypes based on the expression of the estrogen, androgen, and vitamin D receptors expressed together or singly in connection with+ve or –ve expression of K5. In relating the new phenotypes to the commonly used pathological classification of breast cancer (ER+; HER2+; and triple negative breast cancer subclasses), an important basic observation is that 95 % of all human breast cancers have a pure luminal phenotype, with only a small percentage of triple negative breast cancers expressing the myoepithelial smooth muscle actin/CD10 markers. The inclusion of references to new data and to misconceptions that have arisen through the years make this necessary reading for all investigators of differentiation and malignancy in the human mammary gland.

"ERrrr…where are the progenitors? Hormone receptors and mammary cell heterogeneity"

The review by Tornillo and Smalley provides a detailed summary of the evidence regarding the cellular distribution of hormone receptors within functionally distinct cell compartments within the mammary gland, with a focus on the increasing evidence that hormone receptors are expressed in a subset of progenitor cells. The profile of this expression has important implications regarding the mechanisms of hormone action during both normal breast development as well as during carcinogenesis. This review also includes discussion surrounding the high degree of cell heterogeneity and complexity within these tissues, and the different cell sorting strategies and approaches (as well as their caveats) employed to identify the different cell types in the mammary glands of both mice and humans.

"Hormone-sensing mammary epithelial progenitors: emerging identity and hormonal regulation"

The review by Tarulli and colleagues defines the properties of hormone-sensing mammary epithelial cells, an ERα+, PR+ sub-population of the mammary epithelium which they term hormone-sensing mammary epithelial cells (HS-MECs). They describe the capacity for proliferation of these cells under defined physiological circumstances, and their harbouring of rare cells with stem/progenitor properties. The authors also review paracrine mediators of the HS-MEC phenotype,

including prolactin and transforming growth factor beta (TGF-β) as well as combining the current knowledge of androgen action in the mammary gland, and the expression of the androgen receptor in MECs. This review also focuses on a number of the transcription factors known to be involved in lineage determination in the mammary gland. The evidence for the roles of these factors in mammary lineage determination is presented, and the regulation of these molecules by hormones is summarized.

"Hormone signaling requirements for the conversion of non-mammary mouse cells to mammary cell fate(s) in vivo"

The review by Boulanger and colleagues highlights the determinant role of the niche in fostering the cell fate and functional specialization of mammary epithelial cells. These authors summarize and discuss studies based on assays testing regeneration of the mammary ductal network upon allo-implantation of epithelial cells into theepithelium-free mammary fat pads of mice. Mixtures of wild-type and knock-out mammary epithelial cells (specifically where steroid receptors, amphiregulin, or prolactin receptors have been knocked out), or mixtures of mammary epithelial cells and cells of other origins (testicular) have been utilized in these allo-transplantation studies, many of which were conducted in the authors' laboratory. Taken together, the data indicate that only signaling through ERα is indispensable for establishing the mammary epithelial fate, even when cells of non-mammary origin are utilized for re-transplantation. These intriguing conclusions raise the challenge to further identify the factors that constitute the mouse mammary niche, to enquire if these results apply to the human gland and importantly, to investigate the implications of these findings for breast cancer.

This timely issue of The Journal of Mammary Gland Biology and Neoplasia compiles a number of reviews covering a range of aspects related to the hormonal regulation of stem and progenitor cells, and the expression of hormone receptors within these cell types, with a focus on the human breast. These topics have important implications not only in understanding normal mammary development, but also how fluctuations in circulating hormone levels may make this tissue particularly susceptible to oncogenic mutation, and/or to the development of specific breast cancer subtypes. We would like to thank all the contributing authors for their comprehensive and insightful submissions, as well as the reviewers who gave their time to ensure that this subject was covered sufficiently and accurately. We would also like to thank the Editorial Board of The Journal of Mammary Gland Biology and Neoplasia for the opportunity to assemble this issue, and the editorial staff for their assistance in coordinating its production.