

Minireview: Hormones and Mammary Cell Fate—What Will I Become When I Grow Up?

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Systemic hormones are key regulators of postnatal mammary gland development and play an important role in the etiology and treatment of breast cancer. Mammary ductal morphogenesis is controlled by circulating hormones, and these same hormones are also critical mediators of mammary stem cell fate decisions. Recent studies have helped further our understanding of the origin, specification, and fate of mammary stem cells during postnatal development. Here we review recent studies on the involvement of hormone receptors and several transcription factors in mammary stem/progenitor cell differentiation and lineage commitment. (*Endocrinology* 149: 4317–4321, 2008)

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BREAST CANCER is a genetically and clinically heterogeneous disease that may result from the malignant transformation of mammary stem and/or progenitor cells (1). Most of the recent success leading to a decrease in breast cancer mortality is thought to be the result of targeted therapy of hormone-dependent, estrogen receptor (ER) α -positive breast cancers (2, 3), which account for the majority of breast cancers. In ER α -negative breast cancers and those that are resistant to targeted therapy, prognosis declines and patient survival is dramatically decreased. Therefore, it will be crucial to identify the cell of origin in different breast cancer subtypes and to understand the influence of hormonal stimulation on these cells to devise new treatments for all breast cancers.

Mammary gland development is a tightly coordinated series of events that is driven by both systemic hormones and local growth factors (reviewed in Refs. 4 and 5). At each stage of development, the epithelial and stromal compartments respond to different signals that control a balance between proliferation, differentiation, and apoptosis. For example, numerous studies primarily using mouse models have revealed that estrogen is a critical requirement for ductal elongation during puberty, whereas progesterone and prolactin signaling are crucial during pregnancy and lactation (reviewed in Refs. 6 and 7). Likewise, different signals are required for the specification and cell fate determination of mammary stem and progenitor cells during lineage commitment throughout development. In addition to systemic hormones and local growth factors, an important role for cytokines in mammary cell fate and lineage determination has also been established and recently reviewed (8). In this review, we discuss recent studies in both human and mouse,

focusing on the latter, that have helped define how systemic hormones/endocrine factors regulate stem cell fate and lineage commitment during mammary gland development. In addition, we review recent literature that has established a critical role for various transcription factors in epithelial cell lineage commitment during different stages of postnatal development.

Hormonal Cues during Ductal Morphogenesis

The adult virgin mammary gland is comprised of two major types of epithelium, luminal and basal, which together form a ductal network embedded within the stroma. The luminal cells line the ducts as a single layer of epithelia, and the basal component consists of myoepithelial cells that are in direct contact with the adjacent stroma. At the onset of puberty, circulating ovarian and pituitary hormones such as estrogens, progesterins and GH, initiate and drive ductal morphogenesis.

Unlike embryogenesis, postnatal mammary gland development relies on proper spatial patterning of steroid hormone receptors. Approximately 25–30% of the ductal luminal cells are ER α /progesterone receptor (PR)-positive that exhibit a nonuniform pattern of expression. This nonuniform expression pattern is shared by the prolactin receptor (PrlR), and it has been suggested that ER α , PR and PrlR are colocalized to the same cells (9). Importantly, the proliferating cells in the mature gland are steroid receptor negative and are regulated by ER/PR-positive cells by a paracrine mechanism (10, 11). Disruption of hormone receptor patterning results in the inability to respond properly to systemic hormones, leading to a block in lobuloalveolar development during pregnancy (12). It should be noted that luminal epithelial cells in the mature mammary gland exhibit two distinct morphologies (13): tall, columnar-like and round, cuboidal-like. The former are nonproliferating, steroid receptor-negative cells, whereas the latter either express ER α /PR or are proliferating. Although the functional significance of these luminal cell types remains unclear, it is evident that the precise patterning of steroid and prolactin receptors in the normal mammary

First Published Online June 12, 2008

Abbreviations: ALDH, Aldehyde dehydrogenase; ER, estrogen receptor; HMECs, human MECs; MECs, mammary epithelial cells; PR, progesterone receptor; PrlR, prolactin receptor; WAP, whey acidic protein.

Endocrinology is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

gland is required to elicit the appropriate paracrine response to local growth factors.

Mouse Mammary Stem Cells and ER

The existence of adult mammary stem cells was established nearly 50 yr ago when DeOme *et al.* (14) observed that tissue fragments of epithelium isolated from several different regions of the mammary gland were able to reconstitute the entire mammary ductal tree upon transplantation. Later, serial transplantation experiments by Charles Daniel and colleagues (15) demonstrated that stem cells exist throughout the life span of the mouse. Further studies by Smith and Medina (16) suggested that mammary stem cells were present in all portions of the ductal mammary tree at all developmental stages. However, in both mouse and human, studies have been hindered by the inability to identify definitive and exclusive stem/progenitor cell markers.

Despite these obstacles, considerable progress has recently been made in the field of mammary gland stem cell biology. In 2006, two complementary studies demonstrated that a single cell from either the CD24⁺ (heat-stable antigen)/CD29^{hi} (β 1-integrin) (17) or CD24⁺/CD49f^{hi} (α 6-integrin) (18) epithelial population isolated from an adult virgin mouse could generate a functional mammary gland when transplanted into the cleared fat pad of recipient mice. Further analysis of the CD24⁺CD29^{hi} cells revealed that this was a basal population of cells that was ER α -negative (19). Limiting dilution transplantation experiments by Smalley and co-workers (20) illustrated that CD24^{lo} ER α -negative basal cells displayed the highest stem cell activity (as defined by mammary repopulating units), whereas ER α -positive luminal cells exhibited very little stem cell activity.

Conversely, Booth and Smith (21) suggested that long-lived, slow-dividing, label-retaining ER α -positive cells comprise a stem/progenitor cell population that can directly respond to hormones. The relationship of these cells characterized *in situ* to the CD24^{lo} cells identified by fluorescence-activated cell sorting remains to be established. Using an elegant genetic chimeric approach, Brisken and co-workers (22) transplanted cells derived from ER α knockout mice to demonstrate that estrogen facilitates epithelial proliferation and morphogenesis by a paracrine mechanism. The results of their study suggested that nonproliferating ER α -positive cells are required to stimulate the proliferation of neighboring stem/progenitor cells during ductal outgrowth. These results raise an important question: how then can a single ER α -negative stem cell give rise to a fully functional mammary gland upon transplantation? Wicha and colleagues (23) hypothesized that ER α -negative stem cells can give rise to undifferentiated steroid receptor-positive cells, which subsequently proliferate in response to estrogen and secrete paracrine factors that regulate adjacent ER α -negative cells. Likewise, we proposed that a basal ER α -negative stem cell may divide asymmetrically once to give rise to a luminal ER α -positive progenitor cell (24). This undifferentiated cell would then secrete paracrine factors in response to estrogen stimulation to feedback on ER α -negative stem cells and induce their proliferation. Additionally, these same paracrine factors may induce the proliferation and/or differ-

entiation of adjacent ER α -negative and ER α -positive progenitor cells (Fig. 1).

Lineage Commitment during Puberty and Pregnancy

These and other studies provide evidence for a hierarchical model in which all types of epithelial cells in the mammary gland, including ductal luminal, alveolar luminal, and myoepithelial originate from a common multipotent stem cell. Although several such models have been proposed, the precise genetic mechanisms that regulate stem/progenitor differentiation and lineage commitment during mammary gland development remain ill defined. A series of recent publications, however, have helped elucidate a critical role for several different transcription factors in mammary lineage specification.

The Gata family of zinc-finger transcription factors plays fundamental roles in cell fate determination in multiple systems, including kidney, skin, nervous system, and the immune system. The Werb (25) and Visvader (26) laboratories have recently demonstrated that Gata-3 is essential for mammary gland development. Conditional deletion of Gata-3 using mouse mammary tumor virus-Cre resulted in the failure of terminal end bud formation and consequently, a significant reduction in ductal outgrowth. Notably, this phenotype is reminiscent of that observed in ER α -null mammary glands, and ER α expression was reduced in the Gata-3 null glands. Gata-3 was shown to bind directly to the promoter of the forkhead transcription factor FOXA1, which has been suggested to be essential for estrogen signaling in the mammary gland and required for binding of ER α to chromatin (27). Using breast cancer cell lines, Myles Brown and colleagues (28) demonstrated that Gata-3 is required for estrogen-mediated cell growth. Furthermore, ER α was shown to directly stimulate Gata-3 transcription, suggesting a positive cross-regulatory feedback loop between these two factors. Whether this feedback loop exists in the normal mammary gland remains to be established. Collectively, these studies indicate that Gata-3 is part of a unique transcriptional feedback network that may control important cell fate decisions in response to estrogen during ductal morphogenesis.

In addition to regulating ductal branching and elongation, Gata-3 plays a key role in mammary luminal cell differentiation. Gata-3 expression is profoundly decreased in PrlR and PR knockout mice, which also display failed alveolar development and lactogenesis (29, 30). Several conditional deletion strategies have been employed to ablate Gata-3 at different stages of pregnancy. Acute loss of Gata-3 by a doxycycline-inducible whey acidic protein (WAP)-rtTA-Cre line led to the expansion of undifferentiated luminal cells (25). Similarly, WAP-Cre driven Gata-3 deficiency resulted in a block in alveolar differentiation and failed lactogenesis (26). Fluorescence-activated cell sorting analysis of a luminal progenitor population (CD29^{lo}CD24⁺CD61⁺) in Gata-3-null glands revealed that the proportion of CD61⁺ (β 3-integrin) cells was significantly increased in the absence of Gata-3. Retroviral reintroduction of Gata-3 into this unique stem cell-enriched population promoted maturation along the alveolar luminal lineage, because β -casein and WAP transcripts were induced even in the absence of lactogenic hor-

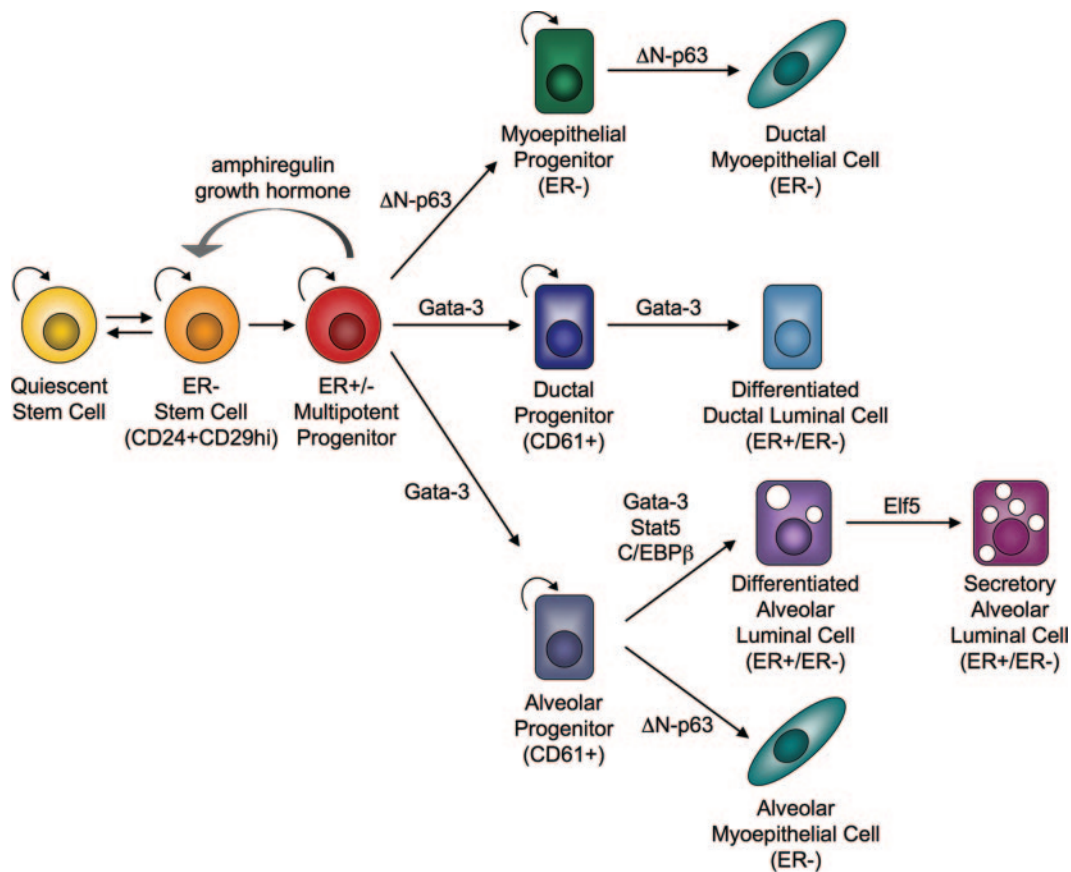


FIG. 1. Regulation of mammary stem cells by hormones, growth factors, and transcription factors during lineage commitment. ER-negative stem cells undergo asymmetric division to give rise to undifferentiated, ER-positive progenitor cells, which in response to estrogens, secrete paracrine factors that regulate ER-negative stem cells. These multipotent progenitor cells may also differentiate into basal-restricted (*green*) or luminal-restricted progenitors (*dark blue*), and alveolar-restricted lineages (*gray*) (36, 37). As a result of estrogen stimulation during ductal morphogenesis, Gata-3 may specify luminal cell fate, whereas ΔN -p63 is important for basal cell lineages. During pregnancy, prolactin-mediated Gata-3 may contribute to alveolar cell development, and Elf5 establishes the secretory alveolar lineage.

mones (26). Collectively, these data indicate that loss of Gata-3 blocks luminal progenitor cell differentiation and that Gata-3 promotes the differentiation of lineage-restricted progenitor cells.

Impaired alveolar differentiation is a phenotype shared by several other knockout models, including Stat5, Id2, CCAAT/enhancer binding protein β , and Elf5. Elf5 is an Ets transcription factor and member of the PrlR signaling pathway that was recently shown to play a key role in alveolar cell fate specification (31). Like Gata-3, Elf5 levels are drastically reduced in PrlR-null mammary glands, suggesting that it is an important mediator of alveolar differentiation (32). Elf5-deficient mice are embryonic lethal due to placental defects, but Elf5 heterozygotes display defective lobuloalveolar development and reduced milk secretion during pregnancy. Harris *et al.* (33) demonstrated that retroviral re-expression of Elf5 in PrlR-null mammary epithelial cells (MECs) followed by transplantation rescued alveolar morphogenesis, compensating for the loss of PrlR signaling. Ormandy and colleagues (31) demonstrated that forced overexpression of Elf5 using a doxycyclin-inducible model resulted in disrupted ductal morphogenesis and precocious alveolar differentiation and milk secretion in virgin mice. Analysis of luminal progenitor cells ($CD29^{lo}CD24^{+}CD61^{+}$)

in transplanted glands revealed that there was a significant accumulation of this population in Elf5-null MECs during pregnancy compared with wild type, a result that was shared by midpregnant Elf $^{+/-}$ mice. The authors concluded that Elf5 deficiency causes a block in $CD29^{lo}CD24^{+}CD61^{+}$ luminal cell differentiation, and that Elf5 specifies secretory alveolar cell fate from this progenitor cell population. Although Gata-3 and Elf5-null mammary glands display similar phenotypes, Gata-3 appears to regulate luminal cell specification, whereas Elf5 is required to establish the secretory alveolar lineage during pregnancy. Whether Gata-3 and Elf5 cooperate in luminal progenitor cells to regulate alveolar differentiation remains to be determined.

Steroid Hormones in Human Mammary Stem Cells

Although the molecular mechanisms of hormonal regulation of mouse mammary stem/progenitor cells are just beginning to be unraveled, the interactions between endocrine factors and human stem cells remain largely unexplored. While numerous putative stem and progenitor cell markers have been proposed, the effects of estrogen on these populations, for example, have yet to be determined. Dontu and colleagues (1) recently reported that increased

aldehyde dehydrogenase (ALDH)-1 activity is associated with increased stem cell properties in human MECs (HMECs). Limiting dilution transplantation into humanized cleared fat pads of NOD/SCID (nonobese diabetic/severe combined immunodeficient) mice showed that only ALDEFLUOR-positive HMECs, indicative of high ALDH1 activity, could generate ductal outgrowth. Likewise, ALDEFLUOR-positive breast cancer cells were enriched in tumor-initiating ability when xenografted at limiting dilution. Finally, ALDH1 activity was associated with poor clinical outcome when a panel of 577 breast cancers was examined. In summary, these data demonstrate that in both normal and cancer human mammary epithelial cells, ALDH1 activity marks a population that displays increased stem cell activity (1).

What then is the relationship between ER α and ALDH1 activity in human mammary stem cells? In a recent study by Wicha and colleagues (34), the breast cancer susceptibility gene BRCA1, which has well-established roles in DNA repair and chromosome stability, was shown to be a mediator of mammary cell fate specification. Deletion of BRCA1 in primary HMECs resulted in the expansion of stem cell populations defined by ALDH1 activity. Additionally, ER α -positive cells were decreased in BRCA1-null HMECs *in vitro*, and transplantation of these cells produced outgrowths that uniformly expressed ALDH1 but lacked ER α expression. These results suggest that BRCA1 plays a role in the differentiation of ALDH1-positive/ER-negative stem/progenitor cells into ER-positive luminal epithelial cells. Wicha and colleagues (34) proposed that loss of BRCA1 causes impaired luminal epithelial cell differentiation and results in an accumulation of ALDH1-positive/ER-negative stem cells. These studies suggest that loss of BRCA1 function may cause a block in epithelial cell differentiation and the expansion of undifferentiated, ER-negative stem cells.

Conclusions

Although considerable progress has been made in the characterization of mammary stem cells, the molecular and genetic mechanisms that regulate their self-renewal, maintenance, differentiation and survival remain poorly understood. Here we summarized various reports that suggest that endocrine factors and steroid hormones have significant roles in cell fate specification, although elucidation of these mechanisms has only just begun. In response to hormonal stimulation during different stages of development, luminal progenitor cells may commit to either a ductal or alveolar fate. A model for a hierarchy of stem/progenitor cell differentiation and lineage commitment is presented in Fig. 1.

Estrogen signaling is fundamental to normal mammary gland development and plays a central role in promoting the proliferation of neoplastic breast epithelium. ER α is one of the most important prognostic factors of breast cancer and its expression can dictate clinical outcome. However, the precise role(s) of ER α in normal and cancer stem cells remains controversial. Several important questions remain unanswered: In the mouse, how can a single ER-negative stem cell give rise to a functional mammary gland when ductal outgrowth and epithelial cell proliferation require ER α ? Is there a population

of quiescent mammary stem cells and what is the local microenvironment or “niche” for these cells? Recent studies have suggested that the Δ N-p63 isoform may be involved in commitment of the basal mammary epithelial cell lineage (35), but the mechanisms that regulate the expression of this isoform remain to be established. What are the local factors that regulate basal and luminal epithelial cell commitment and are these regulated by systemic hormones? Answering these questions will be essential to devising new therapeutic strategies that target tumor-initiating cells in both hormone-responsive and hormone-negative breast cancers.

Acknowledgments

Received April 1, 2008. Accepted May 12, 2008.

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Studies in our laboratory are supported by National Institutes of Health Grant CA030195-22 (to J.M.R.), and Heather LaMarca is the recipient of an American Cancer Society Tricam Industries Postdoctoral Breast Cancer Fellowship (PF-06-252-01-MGO).

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