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Journals Club

Review of: The Ets transcription factor Elf5 specifies mammary alveolar cell fate

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S. R. Oakes, M. J. Naylor, M. L. Asselin-Labat, K. D. Blazek, M. Gardiner-Garden, H. N. Hilton, M. Kazlauskas, M. A. Pritchard, L. A. Chodosh, P. L. Pfeffer, G. J. Lindeman, J. E. Visvader, C. J. Ormandy. ***Genes Dev*** 2008; **22**(5): 581–586.

Abstract of the original article:
Hormonal cues regulate mammary development, but the consequent transcriptional changes and cell fate decisions are largely undefined. We show that knockout of the prolactin-regulated Ets transcription factor Elf5 prevented formation of the secretory epithelium during pregnancy. Conversely, overexpression of Elf5 in an inducible transgenic model caused alveolar differentiation and milk secretion in virgin mice, disrupting ductal morphogenesis. CD61+ luminal progenitor cells accumulated in Elf5-deficient mammary glands and were diminished in glands with Elf5 overexpression. Thus Elf5 specifies the differentiation of CD61+ progenitors to establish the secretory alveolar lineage during pregnancy, providing a link between prolactin, transcriptional events, and alveolar development.

Review

The mammary gland is a compound tubulo-alveolar gland composed of a series of branched ducts that drain alveolar structures that are generated during pregnancy. The epithelium of the gland is classically considered as being composed of two main lineages of cells, the luminal cells and the myoepithelial cells. Luminal cells are the cells that synthesize milk proteins during pregnancy, and the myoepithelial cells are the contractile cells that squeeze the milk down the ductal system and out of the gland. However, evidence is emerging that the mammary epithelium in both humans and mice is much more complex than initially described and is composed of a hierarchy of cells that span from stem cells to progenitor cells to differentiated luminal and myoepithelial cells (Fig. 1) [1–9]. By combining fluorescence-activated cell sorting (FACS) with a variety of functional mammary stem and progenitor cell assays, many of the cells of this hierarchy have been identified and can be prospectively isolated based on their cell surface phenotype. Analysis of flow-sorted luminal epithelial cells has demonstrated that this population is particularly heterogeneous and that it may be more appropriate to consider the mammary epithelium, at least in the mouse, as being composed of three lineages of epithelial cells: myoepithelial, steroid hormone receptor$^+$ luminal cells and milk protein$^+$ luminal cells [5].

There is much interest in identifying the molecular mechanisms that regulate the cell fate decisions of the mammary stem and progenitor cells and how

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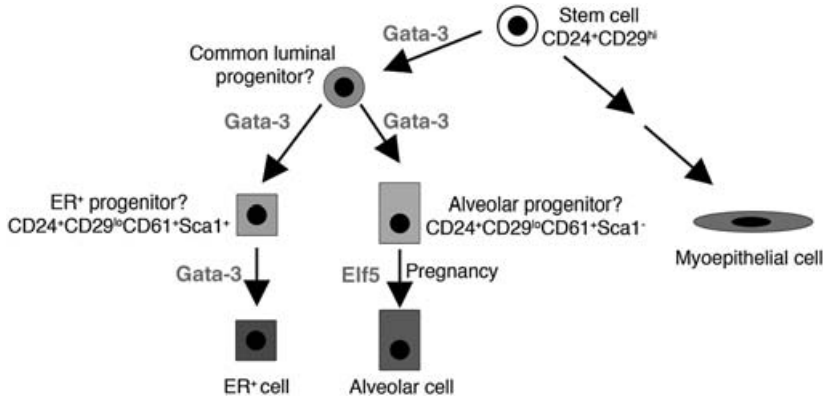

Figure 1.
Proposed epithelial hierarchy present in the mouse mammary gland. The parent–progeny relationships between many of the components of this hierarchy have yet to be firmly established. Luminal progenitors have a CD24^{+}CD29^{lo}CD61^{+} phenotype, and it has been suggested that this population may be further subdivided into estrogen receptor (ER)$^{+}$ and milk protein^{+} lineages on the basis of expression of Sca-1 [15]. The stages where Gata-3 and Elf5 are believed to function are indicated.

these decisions impact mammary gland structure, function and breast cancer susceptibility. The article by Oakes and colleagues examines the influence of the Elf5 transcription factor on mammary epithelial cell function. Elf5 is a transcription factor that appears to function downstream of the prolactin receptor and is essential for proper lobulo-alveolar development during pregnancy [10,11]. Oakes *et al*. demonstrated that deletion of *Elf5* from the mammary epithelium does not influence mammary stem cell function or the formation of ductal structures in virgin mammary glands. However, *Elf5*$^{-/-}$ mammary epithelium displays impaired alveolar development during pregnancy. Forced over-expression of Elf5 in the mammary epithelium resulted in reduced size of the ductal tree generated during puberty. More interestingly, the forced over-expression of Elf5 in the virgin mammary gland resulted in precocious alveolar development and milk protein synthesis.

Analysis of the types of cells present in these genetically modified mammary glands by flow cytometry demonstrated that there was an increase in the frequency of cells that had a luminal progenitor (CD24^{+}CD29^{lo}CD61^{+}) phenotype in the *Elf5*$^{-/-}$ mammary glands and that the reverse was true in the mammary glands of transgenic mice that over-express Elf5. In vitro colony-forming cell (CFC) assays also demonstrated that the Elf5 over-expressing glands had a lower frequency of progenitor cells. The authors conclude that over-expression of Elf5 results in the erosion of the alveolar progenitor cell pool, which is an incorrect conclusion based on the data presented. The problem with the data is that it reports the frequency of CD24^{+}CD29^{lo}CD61^{+} cells and CFCs, not absolute numbers. Frequency is a relative measurement and it may be, for example, that the frequency of CD24^{+}CD29^{lo}CD61^{+} cells and CFCs is decreased not because there are less of them in the mammary gland, but because there may be an expansion of another epithelial cell population (such as differentiated alveolar cells). Regardless of this, the data demonstrate that there is a pool of alveolar progenitors that have a CD24^{+}CD29^{lo}CD61^{+} phenotype and that Elf5 induces their differentiation into secretory alveolar cells.

GATA-3 is a transcription factor that has gained recent attention because it is a defining marker of the luminal (ER^{+}) subtypes of human breast cancer [12,13]. Interestingly, when the distribution of Elf5 and Gata-3/ER were examined among tissue sections of mouse mammary glands, it was observed that Elf5 and Gata-3/ER are expressed in mutually exclusive cell types. This is somewhat surprising since Gata-3 has been identified as an important regulator of the differentiation of both estrogen receptor (ER^{+}) and secretory alveolar cells, and as a result it would be expected that Gata-3 would be expressed in both cell types [1,14]. One explanation for this paradox is that Gata-3 influences the function of a more primitive luminal progenitor that gives rise to alveolar progenitors, which in turn do not express this transcription factor (Fig. 1). However, this is speculation and what is required is the identification of new cell surface markers that will further resolve the different mammary cell populations and in vivo lineage tracing experiments to determine the developmental fates of these cells.

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