

Viewpoint

Gata-3 and mammary cell fate

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Abstract

Genomic regulatory networks specify how cellular gene expression responds to external temporal and spatial stimuli, ensuring that correct cell fate decisions are made and the appropriate cell phenotypes are adopted. In mammary epithelial cells, the hierarchy of stem and progenitor cells and the genetically specified program of transcriptional activity are beginning to be elucidated and integrated. A novel role for Gata-3 in specifying and maintaining mammary cell fate has recently been identified. These reports offer an understanding of how mammary cells assume and maintain a variety of cell behaviours and functions, and how a mammary cell may potentially subvert these constraints during carcinogenesis.

Toward a combined understanding of cell hierarchy and genomic regulatory networks

Genomic regulatory networks are composed of two principal features, regulatory motifs (response elements, cis-regulatory elements) and the genes that these motifs control. The arrangement of regulatory motifs within gene promoters provides a way to program the induction and repression of gene expression in response to external signals. A key feature is the use of cascading transcription factor networks to control families of functional genes. An elegant demonstration of a complete genomic regulatory network has been provided for *Saccharomyces cerevisiae* [1], while in mammals the network responsive to oestrogen has been described using a breast cancer cell line [2]. Given its developmental characteristics, the mammary gland has emerged as a system in which transcriptional networks and the extrinsic factors regulating them can be investigated [3]. These networks are heritable, both via the germline and also somatically. Thus, a cell's potential is specified, though not completely, by the cell that produced it. It is clear that we have to combine these fundamental aspects of inheritance and the genomic regulatory network if we are to understand how external stimuli, such as a hormonal change or cell context, can exert the profound changes in gene expression and tissue composition that we observe in the mammary gland.

Gata-3

The Gata family comprises six zinc-finger transcription factors that have a well-defined role in cell-fate specification in the

immune system, kidney and other tissues. Constitutive null mutation of Gata-3 results in embryonic lethality. In the mammary gland Gata-3 is expressed only by the epithelium and its expression increases during early pregnancy [4]. Recent work from Zena Werb's laboratory [5] reports that Gata-3 was the most highly enriched transcription factor in a microarray analysis of terminal end-buds and ducts compared to epithelium free stroma. Gata-3 expression can be detected as early as E12.5 in primordial mammary buds of Gata-3/LacZ knockin mice [6]. Expression in mammary epithelium continues throughout puberty and pregnancy and Gata-3 expression is restricted to luminal cell lineages. The expression and localisation of Gata-3 indicates a potential role in the regulation of epithelial cell phenotype throughout several stages of mammary gland development.

Gata-3 knockout

Using the Cre/lox system, both the Werb and Visvader labs demonstrated a critical role for Gata-3 in the regulation of several stages of mammapoiesis. Deletion of Gata-3 driven by K14-Cre (expressed in mammary primordia) resulted in the failure to form mammary placodes [6]. This finding is similar to that observed following loss of the LEF1, Msx1 and Msx2 transcription factors [7] and may indicate a transcriptional network or complex between these molecules.

Defects in ductal elongation and invasion through the mammary fat pad were observed in both studies following MMTV-Cre induced deletion of Gata-3 [5,6]. This phenotype is similar to that observed following loss of oestrogen receptor α . Interestingly, Gata-3 has previously been shown to orchestrate transcriptional networks in other systems [8], and it appears to have a similar function in the mammary gland. Gata-3 binds to the promoter of FoxA1, a forkhead factor that is required for chromatin binding of oestrogen receptor [2,5]. This indicates a transcriptional network in which Gata-3 regulates the transcriptional activity of oestrogen receptor α , and identifies Gata-3 as a potential master regulator of ductal elongation at puberty.

In addition to regulating mammary placode formation and ductal elongation, a direct requirement for Gata-3 in epithelial

cell differentiation was demonstrated. Deletion of Gata-3 following mammary ductal development resulted in failure of the expansion of the luminal progenitor population required for lobuloalveolar development during pregnancy [6]. This finding was supported by the ability of Gata-3 expression to drive a stem cell enriched population along the alveolar luminal lineage. This is one of the first findings linking a transcription factor to the enriched luminal cell progenitor population it regulates. In this context it will be interesting to determine which progenitor cell populations are acted upon by other known transcriptional regulators of mammary development such as Stat5 or C/EBP β .

The failure of the luminal progenitor population expansion following Gata-3 loss resulted in the accumulation of undifferentiated luminal cells, characterised by an absence of differentiation markers such as β casein [5,6]. The resulting outcome was a failure of differentiation manifested as impaired lactation. Several other knockout mice also display a similar phenotype, most notably members of the prolactin signalling pathway, such as Stat5 and Elf5, and molecules that feed into this pathway or are markers of mammary stem cells, such as β 1 integrin. In prolactin receptor knockouts, which also display a failure of lobuloalveolar development, Gata-3 expression is greatly reduced [4,9]. Whether or not Stat5, Elf5 or Gata-3 or others physically interact or are members of the same transcriptional network remains to be determined, as does their order in the cascade from hormonal stimulus to execution of *de novo* transcription. Reduced Gata-3 expression in prolactin receptor null mammary glands may simply indicate the loss of Gata-3 cell populations in these glands or, conversely, that Gata-3 is a true downstream target of the prolactin pathway. What is clear, however, is that although many transcription factors will prove essential for this process, no one transcription factor is likely to act alone. Rather, these transcription factors will act as part of a coordinated transcriptional network, providing an integrated response to multiple extracellular stimuli.

In addition to demonstrating that Gata-3 is a key regulator of mammary gland development, the Werb and Visvader studies also raise the interesting question of the role of Gata-3 in breast cancer. Consistent with similar mammary gland phenotypes and the link to FoxA1, expression of Gata-3 correlates with estrogen receptor- α in microarray studies of human breast cancer [10]. High Gata-3 expression was a marker for well-differentiated tumours, while low Gata-3 expression was strongly associated with markers of poor patient prognosis, such as oestrogen receptor and progesterone receptor negative status, high histological grade and ErbB2 over-expression. The potential utility of Gata-3 as a prognostic indicator has also been verified by meta-analysis [11]. In addition, mutations in Gata-3 have been reported in a subset of breast tumours, indicating a potential tumour suppressor role [12]. These studies, together with the Gata-3 regulatory role during mammary

gland development strongly support further studies into the role of Gata-3 in human breast cancer.

Competing interests

The authors declare that they have no competing interests.

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