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Review

The Stat family of transcription factors have diverse roles in mammary gland development

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ABSTRACT

The Stat family of transcription factors have diverse roles in mammary gland development. Genetic studies in mice have revealed an essential requirement for Stat5a in development of secretory alveolar cells during pregnancy while Stat6, which is normally associated with differentiation of T helper cells, is important in the commitment of luminal cells to this alveolar lineage. In contrast, Stat3 is specifically activated at the initiation of post-lactational regression when it has an essential function in the regulation of cell death and tissue remodelling. Stat1 and Stat4 have been shown to be regulated during a mammary developmental cycle although whether they have specific, non-redundant roles is not clear. Thus, the adult mammary gland is somewhat unusual in that it is a tissue where different Stats are sequentially activated to orchestrate the processes of functional differentiation, cell death and tissue remodelling.

Contents

1. Historical perspective

The first signal transducer and activator of transcription (Stat), Stat1 (then named ISGF3) was identified in a search for interferon signalling molecules [1]. There followed, from this discovery, the identification of seven closely related proteins that formed the Stat family of transcription factors. Stat5 was first described in mammary gland. Originally observed in sheep and rat mammary tissue during the lactation period, it was named MPBF (for milk protein binding factor) or MGF (Mammary Gland factor), respectively [2,3]. The apparent tissue specificity of Stat5 resulted from the very high levels of Stat5 found in lactating mammary gland tissue compared to other tissues. However, it subsequently became clear that, not only is Stat5 widely expressed, but that there are two closely related proteins, Stat5a and Stat5b that differ primarily in their carboxy termini [4]. Further investigation of other Stat family mem-

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bers revealed that, with the exception of Stat2, all are expressed in mammary tissue [5].

In this review, we will outline briefly the major stages of mammary gland development and then discuss the roles of individual Stat proteins in regulating essential developmental processes in the adult gland.

2. Mammary gland development

There are three principal stages of mammary gland development; embryonic, pubertal, and gestational. Mammary development is similar in most mammals although the number of mammary glands varies. During embryogenesis, the first feature to become evident is the appearance of two ridges of multilayered ectoderm that arise from the embryonic skin (called mammary lines or milk lines) on embryonic day 10.5 (E10.5) in the mouse. These run in an anteroposterior direction from the fore- to the hind-limb buds on the ventral surface of the embryo. At E11.5, 5 pairs of symmetrically positioned mammary epithelial placodes form at reproducible locations, possibly by migration of the ectodermal cells along the mammary line where they coalesce to from the placodes [6]. Morphologically distinct epithelial buds can be distinguished in mouse embryos by E13.5 and 1 day later these buds have sunk into the underlying dermis. In the female, these induce the formation of the mammary mesenchyme and the buds then elongate to form mammary sprouts that branch to form a rudimentary structure with approximately 5 ductules that are embedded within a subdermal fat pad. Development is arrested from E18.5 until after birth.

In the first few postnatal weeks, the mammary tree grows in length commensurate with body growth. Terminal end buds (TEBs), which are club-shaped structures comprised of an outer layer of cap cells and a multilayered inner core of body cells, appear at the tips of the ducts and start to invade the fat pad. Allometric growth ceases when serum levels of estrogen start to rise at puberty. Proliferation within the TEBs results in ductal elongation, and clefting of the TEBs results in bifurcation of the ducts to generate branches. By approximately 10–12 weeks of age, the TEBs have disappeared, the limits of the fat pad have been reached and growth ceases. Once again, development is arrested unless pregnancy ensues, whereupon the gland has to undergo further development and morphological change to prepare for lactation. The hallmarks of this phase of development are the formation of tertiary branches which terminate in alveolar buds, and the rapid proliferation of the luminal epithelium accompanied by differentiation and commitment to the secretory alveolar lineage. The cells of this lineage can synthesize and secrete copious amounts of milk. Two hormones are essential at this stage, progesterone (P) which induces extensive side-branching and alveologenesis, and prolactin (PRL) which promotes differentiation of the alveoli. Notably, the PRLR has been shown to be essential for alveolar differentiation [7].

Finally, following lactation, removal of the now surplus alveolar cells is accomplished by cell death. This post-lactational regression, or involution, is the most dramatic example of physiologically regulated cell death in an adult tissue. In an exquisitely regulated series of events, approximately 80% of the epithelium is removed within 6 days. Importantly, involution can be halted by returning the pups to the mother to re-initiate lactation. This reversible phase of involution lasts for approximately 48 h, whereupon the process becomes irreversible with loss of the alveolar structures and remodelling of the stroma accompanied by re-differentiation of the adipocytes. These distinct stages and features of mammary gland development are summarised in Fig. 1.

3. Expression and activation of Stats during a mammary developmental cycle

Little is known of Stat activity in the embryonic mammary gland but since glands form in the absence of Stats 1, 2, 4, 5 and 6, these Stats cannot be essential for embryonic development. Due to the embryonic lethality encountered upon Stat3 gene deletion, it is not possible to determine whether Stat3 is important at this early stage

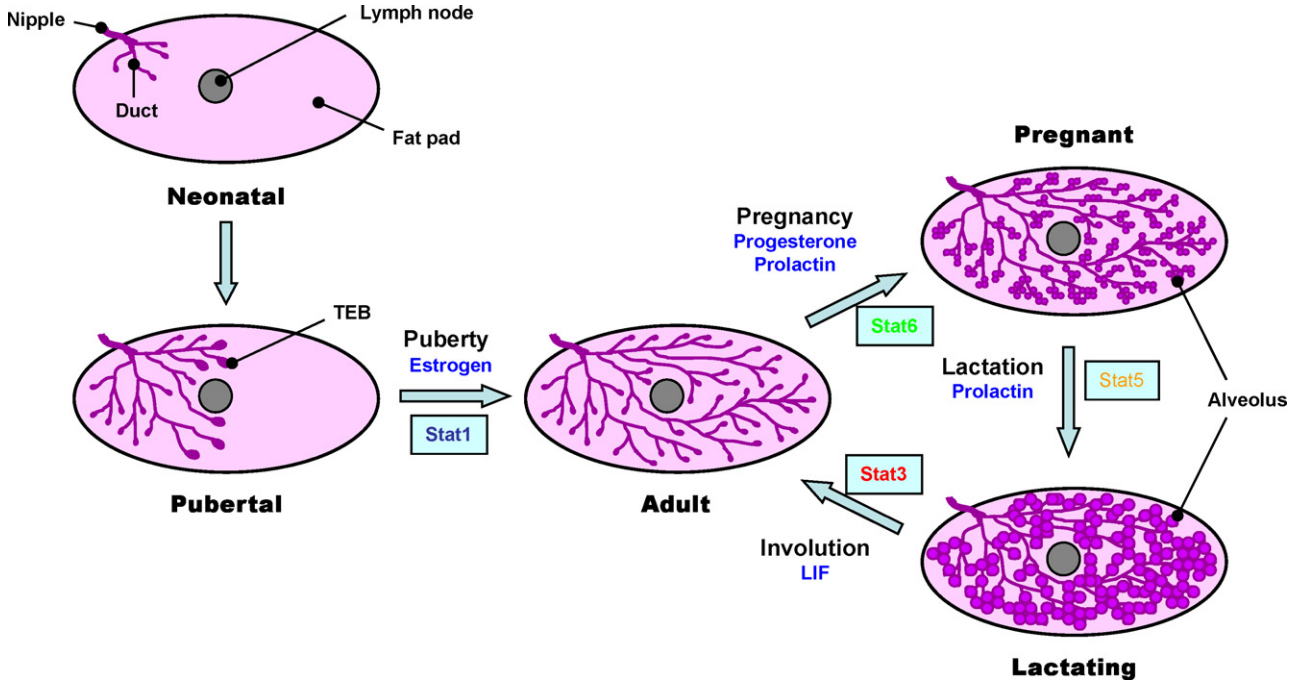

Fig. 1. Postnatal mammary gland development. Schematic overview of postnatal mammary gland development in the mouse. The cycle of mammary gland development from mature non-pregnant adult through pregnancy and involution is indicated on the right of the diagram. *Abbreviations*: TEB, terminal end bud; LIF, leukaemia inhibitory factor. Based on a figure from Wiseman and Werb [44].