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Review

Interplay between progesterone and prolactin in mammary development and implications for breast cancer

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ABSTRACT

Progesterone and prolactin remodel mammary morphology during pregnancy by acting on the mammary epithelial cell hierarchy. The roles of each hormone in mammary development have been well studied, but evidence of signalling cross-talk between progesterone and prolactin is still emerging. Factors such as receptor activator of NFkB ligand (RANKL) may integrate signals from both hormones to orchestrate their joint actions on the epithelial cell hierarchy. Common targets of progesterone and prolactin signalling are also likely to integrate their pro-proliferative actions in breast cancer. Therefore, a thorough understanding of the interplay between progesterone and prolactin in mammary development may reveal therapeutic targets for breast cancer. This review summarises our understanding of Pg and PRL action in mammary gland development before focusing on molecular mechanisms of signalling cross-talk and the implications for breast cancer.

Contents

1. Introduction

The mammary gland undergoes dramatic tissue remodelling events in response to hormonal stimuli during puberty and pregnancy (Richert et al., 2000; Hovey et al., 2002). Oestrogen and growth hormone drive the elongation of the mammary ductal network during puberty, while progesterone (Pg) and prolactin (PRL) co-operate during pregnancy to stimulate the formation of alveolar structures that produce milk post-partum. Underlying these tissue-remodelling events is a mammary cell hierarchy composed of multipotent stem and lineage restricted progenitor cells (Shackleton et al., 2006; Stingl et al., 2006; Asselin-Labat et al., 2007; Visvader, 2009). Hormones elicit morphological changes in the mammary gland by acting on a complex regulatory network of paracrine signals and transcription factors to modulate the activity of mammary stem cells (Asselin-Labat et al., 2010; Joshi et al., 2010; Schramek et al., 2010).

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Like normal mammary gland development, breast carcinogenesis is commonly a hormonally dependent process. Since the original observation that bilateral ovariectomy was effective in treating breast cancer, more than a century of research has been devoted to understanding how hormones control this disease (Medina, 2005). Therefore, a thorough understanding of how hormones co-operate to promote mammary development will have applications not only to normal physiology but also to carcinogenesis.

This review focuses on Pg and prolactin PRL, the two key drivers of mammary development during pregnancy. Since early endocrine ablation and replacement studies first established progesterone Pg and PRL as master regulators of mammary gland development (Lyons, 1958), genetically modified animal models and tissue recombination techniques have been used to clarify the role of each hormone. The marked similarity between the phenotypes of PRL receptor (PRLR) and Pg receptor (PR) deficient mammary glands, and the significant overlap in transcriptional targets of Pg and PRL (Fernandez-Valdivia et al., 2008), indicate that these hormones act synergistically to drive mammary development during pregnancy. Our current understanding of the role of each hormone in mammary development is summarised below before potential interactions are investigated. The implications of these interactions for breast carcinogenesis are also discussed.

2. Progesterone action in the mammary gland

In mammary glands deficient for PR, ductal elongation proceeds as normal, demonstrating that Pg is not essential for pubertal mammary development (Lydon et al., 1995; Humphreys et al., 1997). Rather, Pg plays a critical role in inducing ductal side-branching of the mammary gland (Atwood et al., 2000), which is essential for lobuloalveolar development during pregnancy (Brisken et al., 1998). PR null mammary glands fail to undergo alveolar morphogenesis during pregnancy, and this effect is epithelial cell autonomous, as demonstrated by transplants into cleared mammary fat pads of wild-type (WT) mice (Brisken et al., 1998). Conversely, forced over-expression of PR resulted in increased ductal side-branching in adult virgin animals (Shyamala et al., 1998).

Animals with selective knockout of PR-A and PR-B have been used to study the effects of each PR isoform. Ablation of PR-A had no effect on mammary gland development in animals treated with oestrogen and Pg (Mulac-Jericevic et al., 2000, 2003), whereas there was reduced ductal side-branching in PR-B null mammary glands (Mulac-Jericevic et al., 2003). Similarly, mammary glands from PR-B null mice exhibited limited ductal side-branching and lobuloalveologenesis during pregnancy (Mulac-Jericevic et al., 2003). These results suggest that PR-A is not essential for mammary gland development, and that PR-B is the primary mediator of progesterone's proliferative effects during pregnancy.

3. Prolactin action in the mammary gland

Disruption of the PRL gene in mice did not effect mammary gland development during puberty but prevented the formation of alveolar buds upon reaching adulthood (Vomachka et al., 2000). Similarly, deletion of the PRLR had no influence on pubertal mammary development but resulted in failure to form secondary branches and alveolar buds in adults (Ormandy et al., 1997a,b; Brisken et al., 1999). Since PRLR null mice have reduced serum Pg levels, it was unclear whether these defects were direct effects or due to the endocrine disturbance in these animals. Pg replacement was able to rescue the failed side-branching of PRLR null mammary glands, but could not compensate for the defect in alveolar bud formation (Ormandy et al., 2003). This result indicates that PRL has a direct effect on alveolar bud formation, but not on ductal side-branching in adult mammary glands. Animals carrying only one allele of the PRLR were fertile but failed lactation following their first pregnancy (Ormandy et al., 1997a,b; Brisken et al., 1999). This phenotype was characterized by incomplete lobuloalveolar development during pregnancy, with alveoli failing to expand and engorge with milk at parturition (Brisken et al., 1999). Since PRLR null mice are infertile, epithelial transplants into cleared mammary fat pads were performed to study development in pregnant hosts. These mammary glands underwent normal ductal side-branching but failed alveologenesis, indicating that epithelial PRLR is required for mammary development during pregnancy. Conversely, recombined glands with PRLR null stroma and WT epithelium developed normally in pregnant hosts, indicating that stromal PRLR is not required for mammary development (Ormandy et al., 2003).

4. Signalling interactions between Pg and PRL in the mammary gland

4.1. Progesterone and prolactin interactions at the level of their receptors

PR is a ligand-activated transcription factor that binds to DNA as a protein dimer, and activates transcription of a suite of target genes (Fernandez-Valdivia et al., 2008). PR is restricted to the luminal cell lineage with no expression in the myoepethelial and stromal compartments of the mammary gland (Shyamala et al., 2002). In adult virgin mice, PR is expressed in approximately 55% of luminal epithelial cells (Seagroves et al., 2000), but during pregnancy this proportion decreases dramatically to around 5% (Shyamala et al., 2002). Importantly, PR and oestrogen receptor (ER) are usually co-expressed in the mammary gland and define a steroid receptor positive subset of epithelial cells (Mukherjee et al., 2010).

The PRLR is a membrane-bound protein of class I of the cytokine receptor superfamily (Bole-Feysot et al., 1998), that is closely related to the growth hormone receptor (GHR). Lack of a reliable antibody has precluded attempts to analyse PRLR expression during mouse mammary gland development in detail, however PRLR has been detected in both the stroma and epithelium of the rat mammary gland (Camarillo et al., 2001). Interestingly, microarray analysis of sorted epithelial populations has indicated that PRLR is expressed predominantly in the steroid receptor positive luminal cells in virgin mice (Kendrick et al., 2008). Whether or not PRLR expression is restricted to this population throughout development remains to be seen.

Interactions between PRL and Pg have been described at the level of cross-regulation of their receptors. Progestin treatment causes increased PRLR expression in MCF-7 cells, and conversely PRL treatment upregulates PR (Ormandy et al., 1997c). Similarly, ectopic expression of PR in a normal mammary epithelial cell line led to increased PRLR expression (Goldhar et al., 2011). The mechanism by which PRL induces PR expression is unknown; however, it has been shown that Pg induction of PRLR expression involves co-operative activation of Sp1 and C/EBP signalling (Goldhar et al., 2011). Studies *in vivo* have also demonstrated that acute Pg exposure can upregulate PRLR expression in virgin mice (Fernandez-Valdivia et al., 2008), however there is also evidence indicating that Pg can suppress PRLR expression in late pregnant mammary glands (Nishikawa et al., 1994). These results suggest that PR and PRLR interactions may depend upon the cellular and physiological context.

4.2. Convergence of progesterone and prolactin signals on STAT5

The PRLR lacks intrinsic kinase activity but associates constitutively with Janus kinase (JAK2) (Campbell et al., 1994; DaSilva