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Review

Mammary gland: From embryogenesis to adult life

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ABSTRACT

The aim of this review is to focus on the molecular factors that ensure the optimal development and maintenance of the mammary gland thanks to their integration and coordination. The development of the mammary gland is supported, not only by endocrine signals, but also by regulatory molecules, which are able to integrate signals from the surrounding microenvironment. A major role is certainly played by homeotic genes, but their incorrect expression during the spatiotemporal regulation of proliferative, functional and differentiation cycles of the mammary gland, may result in the onset of neoplastic processes. Attention is directed also to the endocrine aspects and sexual dimorphism of mammary gland development, as well as the role played by ovarian steroids and their receptors in adult life.

Introduction

In mammals, including humans, the mammary gland has a development that begins during prenatal life, but it also consists of several stages during postnatal life (neonatal, puberty up to pregnancy) (Richert et al., 2000; Castrogiovanni et al., 2014; Musumeci et al., 2013). The mammary glands are modified and highly specialized sweat glands. The whole system of mammary ducts is included in the context of an adipose mesenchyme that exerts considerable influence on its growth and evolution (Giordano et al., 2014). These influences are the result of a complex multifactorial process that progresses through both prenatal and postnatal stages (Richert et al., 2000; Musumeci et al., 2014, 2015). The histogenesis of the mammary gland begins early in the embryonic period with the development, in females, of a draft consisting of a small-branched channels system located in the mammary adipose tissue. Although its development proceeds with the isometric growth until the neonatal period, a greater impulse is in the prepubertal period; it continues in the peripubertal phase with elongation and branching of the ducts; finally, it culminates in the pubertal stage characterized by full sexual maturity, period in which the branching of the ducts increases and on their tips, the alveolar buds will form. Pregnancy represents the last developmental stage of the mammary gland during which the functional differentiation of the glandular parenchyma takes place in order to prepare the lobule–alveolar structure to lactation (Richert et al., 2000). This structure undergoes involution in response to the interruption of pregnancy and the cessation of menstrual cycles (Fig. 1).

The regulation of all the stages of mammary gland development, characterized by repeated cycles of morphological growth and functional differentiation, is given by a series of systemic endocrine signals (Neville et al., 2002; Need et al., 2014; Musumeci et al., 2014, 2015). Nevertheless, it seems also necessary to consider the existence of other regulatory molecules capable of integrating all the involved signals, both the endocrine ones and those

Abbreviations: AR, androgen receptor; AP1, APETALA1; BMP4, bone morphogenetic protein 4; CEBPB, CCAAT/enhancer binding protein (C/EBP), beta; Dvl1, disheveled segment polarity protein 1; EDA-R, death receptor; ER, estrogen receptor; ETS2, v-ets avian erythroblastosis virus E26 oncogene homolog 2; FGF-10, fibroblast growth factor-10; GFs, growth factors; GSK3b, glycogen synthase kinase 3b; ID2, inhibitor of DNA binding 2, dominant negative helix-loop-helix protein; IgG, immunoglobulin G; IKK-α, inhibitor of nuclear factor kappa-B kinase-α; JAK, Janus kinase; LEF-1, lymphocyte enhancer factor-1; LMO4, LIM-domain only protein 4; Msx, muscle segment homeobox; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PEA3, phosphatidylinositol-4-phosphate 5-kinase and related FYVE finger-containing proteins signal transduction mechanisms; PR, progesterone receptor; PRLR, prolactin receptor; PTHrP, parathyroid hormone-related protein; PTHR1, parathyroid hormone/parathyroid hormone-related protein receptor 1; RANK, receptor activator of nuclear factor kappa-B; RANKL, RANK-ligand; RTK, tyrosine kinase receptor; Sp1, specificity protein 1; SRC-3/AIB1, steroid receptor co-activator-3; STAT3, signal transducer and activator of transcription-3; TBX3, T box3; TEBs, terminal epithelial buds.

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originating from the surrounding microenvironment (mesenchymal cells, cellular matrix, growth factors, hormones, paracrine/autocrine factors, cytokines, etc.). Only the integration and coordination of all these factors ensures the optimal development of the mammary gland, the maintenance of its own evolutionary destiny and tissue identity.

The coordination of this complex process is largely organized and supported by the Homeobox genes (Chen and Sukumar, 2003; Satoh et al., 2004; Pagani et al., 2010). However, even if the spatiotemporal regulation of the proliferative, differentiative and functional cycles of the mammary gland by the homeotic genes may be effective, it is always possible that their wrong expression in mammary cells may lead to a defective or insufficient cell differentiation or, on the contrary, to an uncontrolled proliferation, contributing to the onset of a neoplastic process (Ligresti et al., 2008; Douglas and Papaioannou, 2013; Howard and Lu, 2014).

Embryogenesis of the human mammary gland

In humans, as well as in other mammals, the tegumentary ectodermal epithelium, after the interaction with the mesenchymal cells of the underlying dermis, originates the epidermis and activates the differentiation of various specialized dermal–epidermal structures such as hair, nails, teeth and several exocrine glands such as sebaceous, sweat and mammary glands. These latter arise, since the end of week 4 of embryonic development, from bilateral thickenings that extend from the axillary to the inguinal region, called mammary ridges or "milk lines" (Moore et al., 2011; Macias and Hinck, 2012). These regress, except for those in a small region of the chest, where they form the mammary placodes (Fig. 2) (Moore et al., 2011; Macias and Hinck, 2012). These areas, characterized by a lenticular form, subsequently expand in the underlying mesenchyme and constitute the primordium of the mammary gland (Cowin and Wysolmerski, 2010; Moore et al., 2011). The development of the milk lines continues until week 6. Between weeks 7 and 8, the mammary parenchyma begins to invade the underlying stroma forming a primitive mammary disk. A further proliferative surge of mammary parenchyma starts at week 9, and a simultaneous discrete rarefaction of the epithelial layers of the overlying skin occurs. Between weeks 10 and 12 some epithelial buds originate from the mammary proliferation. These buds branch out and extend to the epithelial–mesenchymal boundaries (Macias and Hinck, 2012; Moore et al., 2011). The additional ramification between weeks 13 to 20 leads to the formation of about 15–20 solid epithelial cords. These give rise to other epithelial cords (lactiferous) that converge in the nipples. During the next ramification processes that continue to week 32, the solid epithelial cords undergo apoptosis of the internal epithelial cells. Between weeks 32 to 40 of gestation, starting from the ends of the epithelial gems, a tubule-alveolar proliferation is established (Cowin and Wysolmerski, 2010; Moore et al., 2011). The alveoli are covered by a monolayer of epithelial cells and circumscribed by a mesenchyme-connective stroma. Before birth, the mammary glands are equally developed in the male and female and each of them consists of about 20 lactiferous ducts that open into a dimple. In a few weeks, the proliferation of the underlying mesoderm transforms the dimple into an everted nipple and the skin surrounding it proliferates forming the areola (Moore et al., 2011).

The spatiotemporal sequence of these phases in the mammary gland development is subjected to control and regulation by different genetic and transcriptional factors such as nuclear regulatory proteins (transcription factors) that play a key role in the development of the mammary gland, and if deregulated can contribute to breast cancer (Ligresti et al., 2008; Douglas and Papaioannou, 2013; Howard and Lu, 2014; Musumeci et al., 2014, 2015).

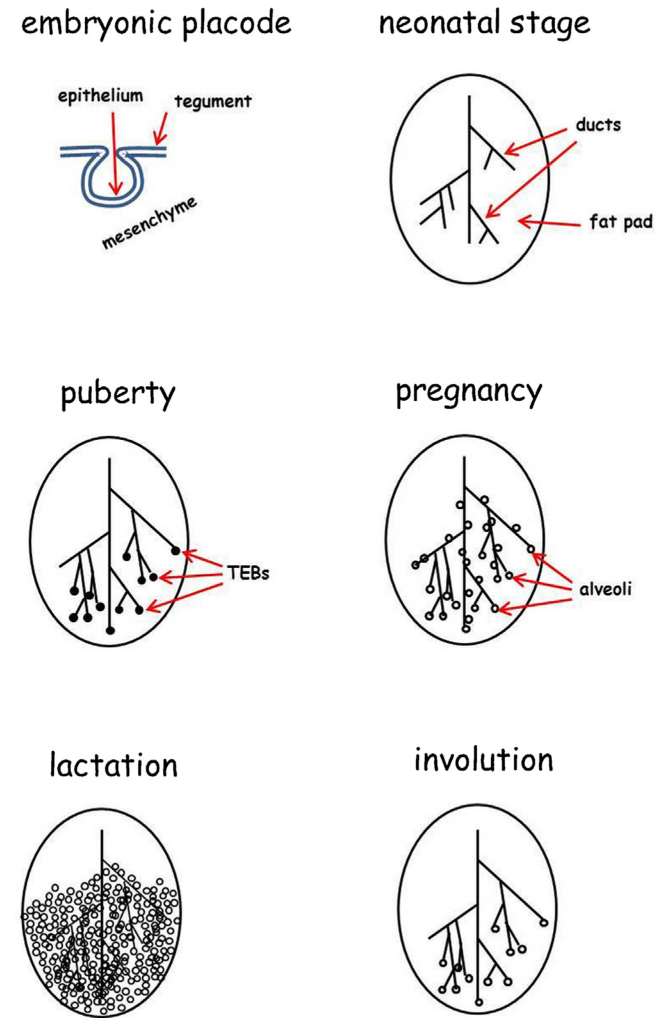

Fig. 1. The diagram shows the different stages of mammary development starting from the embryonic mammary primordium, followed by the various postnatal developmental stages, up to the menopause. The mammary placode differentiates into mammary buds that penetrate the underlying surrounding mesenchyme, sprout and develop a lumen. In the neonatal period the arborized gland invaded the developing fat pad. At puberty morphogenesis begins under control of estrogen and progesterone that regulate side branching. In pregnancy, estrogen, progesterone and prolactin play roles in alveolar expansion. In the late stages of pregnancy and during lactation, prolactin plays a key role in establishing the secretory state. After lactation, the gland involutes.

Endocrine aspects of mammary development and sexual dimorphism

The development of the mammary gland is determined by endocrine interactions that begin during the early stages of

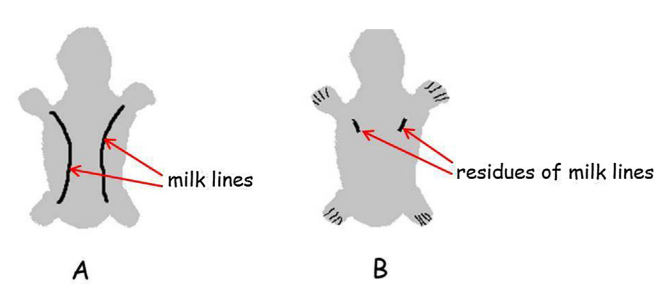

Fig. 2. Development of mammary glands. (A) Diagram of the embryo at about 28 days, which shows the mammary ridges (milk lines). (B) Diagram of embryo at week 6, showing what remains of the mammary ridges.

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