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Review

Growth and development of the mammary glands of livestock: A veritable barnyard of opportunities

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ABSTRACT

The mammary glands of all mammals are rich and diverse in their histomorphogenesis, developmental biology, genomics and metabolism. Domesticated livestock comprise a unique population for the analysis of mammary gland and lactation biology, where much of what has been learned about these topics originates from studies of these species. However, with the strong trend toward using rodents as flexible and attractive models for normal mammary biology and cancer, there is a growing void of new information related to biology of the mammary glands in these relevant and informative domestic livestock. In turn, this trend threatens to reduce opportunities to either capitalize on an abundance of pre-existing data or to apply this information to studies of lactation and cancer. Herein we review the unique and discerning features of mammary gland development in several domestic livestock species including cows, sheep and pigs and provide an overview of the factors regulating it. At the same time we discuss some of the key considerations for studying these species, their limitations, and the associated opportunities. From such an analysis it quickly becomes clear that much remains to be learned about the mammary glands of domestic livestock, particularly given their many similarities to the human breast, the unique biological mechanisms they employ, and the phenotypic variation they afford.

Contents

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1. Introduction

The course of normal mammary gland development can be broadly characterized as a progression of events that begins in embryogenesis and ends with post-lactational involution. Ironically, many descriptions of these processes in the review literature are often broad-stroked, and generally outline events and mechanisms that have been resolved in a subset of rodents, namely rats and mice. Yet, mice and rats are within but one order among >5600 mammals. Hence it seems far from appropriate to limit any summary of the processes underlying mammary development to these few species.

Domesticated livestock, which for the purpose of this review includes pigs, cattle, sheep and goats, are dual-toed ungulates in the order Artiodactyla. While estimates vary, there are approximately 1.3 billion cattle, 1 billion each of sheep and pigs, and 700 million goats worldwide. The global economic value of these four species combined is tremendous and ultimately hinges on their mammary glands, either through their capacity to provide dairy products, or because their growth and production of milk underlies successful animal production, welfare and survival. At the same time, the widespread abundance of domestic livestock highlights their potential as a model for diseases such as human breast cancer, where recent advances on fronts such as whole genome sequencing and proteomics stand to overcome many of the perceived obstacles for utilizing these species.

In this review we seek to summarize the key processes of mammary gland development in domesticated livestock. We focus specifically on developmental changes and their regulation during embryogenesis, prior to and during puberty, during gestation and during post-lactational involution. As becomes quickly evident, their mammary glands are notably different from those in rodents, and in fact bear several similarities to the human breast. Many of these comparisons are outlined in Table 1. We also consider the pros and cons of studying the mammary glands of these species.

2. Fetal development

The mammary glands arise from the ectoderm during embryonic development to yield a rudimentary epithelial anlagen by birth. These origins involve complex epithelial–mesenchymal interactions and confer sexual dimorphism of the mammary glands, which is species-dependent.

2.1. Pigs

Each gestation in pigs lasts approximately 115 d. Development of the mammary glands of embryonic pigs was first described by Schultze in 1892 and Rein in 1882, as last reviewed by Turner [1]. The future mammary glands begin to develop through cell migration along two ventral mammary lines that extend from the front limb to the inguinal area [1]. This movement leads to ectodermal thickening and emergence of the mammary hillock, which is apparent around embryonic (e) d45. Each hillock transitions from a flat disc to an elongated flask, ultimately giving rise to an epithelial bud that is visible by e65 (Hovey et al., unpublished data). These buds ascend at discrete sites destined to become the future nipple, coincident with regression of the mammary line [1]. Nipple formation ensues by a coordinated process including proliferation of the underlying mesenchyme, protrusion of the mammary bud [1] and invagination into the dermis. It is worth noting that while there has been discrepant use of the terms teat and nipple in the literature, our convention herein is that a teat has a single galactophore (as found in mice, cows and sheep) whereas the nipple contains multiple galactophores (as found in pigs, humans and most of the order Carnivora).

By e85 the two mammary ducts extend from the nipple, ramifying into the underlying mesenchyme (Hovey et al., unpublished data). The ducts continue to increase in complexity by e105, where proliferation of epithelial cells at the distal ends permits their branching into the surrounding mesenchyme. By the time of birth each of the two primary sprouts has formed a 3–4 mm streak canal with an underlying, widened lactiferous sinus [1]. Ducts emanating from the mammary bud are solid, uncanalized cords while the distal ends of the mammary ducts have a wide lumen [1].

The ventral nipples along the "mammary chain" are usually paired regularly and symmetrically, although it is also common to find them irregularly unpaired, or offset [1]. Interestingly, arrangement of the nipples in pigs is sexually dimorphic, where males tend to have a more regular arrangement than females, leading Turner to suggest that offset arrangement of the nipples may benefit piglet access during nursing [1]. Furthermore, polythelia (supernumerary nipples) on the hind legs is common in pigs, consistent with their origins from the mammary line (Fig. 1).

The average number of nipples per pig is approximately 12, but ranges from 8 to 18 [1]. The number of nipples is also breed-dependent, ranging from an average of 12.5 in Durocs to almost 15 in Landrace, and correlates with litter size across breeds [2]. This variation is particularly important for piglet growth and lactation performance given that the average litter size for pigs has increased notably in recent decades as the result of genetic selection. Interestingly, several studies have identified a variety of genetic markers for nipple number in pigs, although no single candidate has been identified [3]. Another determinant of nipple number in pigs is sex ratio within a litter, where a greater number of male littermates leads to females having fewer nipples [4]. This is likely due to intrauterine exposure to androgens, as occurs in mice [4,122,123].

Inverted nipples, where the cratered nipple fails to protrude from the body surface, occur in 7.6% to 30% of pigs, is heritable, and varies in incidence across breeds [5]. This phenomenon is of significant economic impact given the dysfunction of these teats and an increased risk for mastitis [6]. Interestingly, inverted nipples in pigs appear to arise from inadequate mesenchymal proliferation, consistent with defective epithelial-stromal signaling in these animals [6]. Several candidate genes have been identified as pertaining to this phenotype [7], where a polymorphism in the PTHR1 gene correlated with its incidence [7]. A recent microarray analysis further highlighted the influence of various growth factor-regulated pathways in these processes [5].

2.2. Cattle

Turner [8] provides a thorough characterization of mammary development in the embryo and fetus of cattle during an average gestation of approximately 280 d. At approximately e30 there are noticeable parallel thickenings of the ectoderm in the inguinal region along the ventral side that constitute the mammary bands. Almost as soon as they are formed, the mammary bands become known as mammary lines after e35 at a time when the mammary anlagen are first discernable. Formation of the mammary crests by e37 reflects the regional proliferation of cells along the paired mammary lines, while neighboring cells along the line do not proliferate. Two crests arise per mammary line, eventually giving rise to the four "quarters" of the udder. The mammary hillock stage (~e40) follows, during which time the proliferative epithelial zones in each crest become rounded off and simultaneously sink further into the mesenchyme. The last stage of embryonic mammary development is the bud stage that occurs around e43. At this stage sexual dimorphism becomes evident, where mammary buds in females are smaller than in males. Mammary buds