Mammary Gland: Growth, Development and Involution

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Introduction

Mammary glands are accessory reproductive organs that develop to nourish the young. Mammary gland development and lactation may occur multiple times in a mammal's life. In fact, the mammary gland is one of a few body organs that undergo repeated cycles of structural development, functional differentiation, and regression. Careful management of this cycle is the basis for successful lactation in dairy animals. Growth and development of the mammary gland (mammogenesis) occur through a series of phases that are intimately associated with the specific physiology of the animal's growth and reproduction. Each mammary growth phase is regulated systemically by hormones and locally by growth factors produced in the gland. The specific hormones responsible for mammary growth vary with the developmental phase. To understand mammary gland growth and regulation, one needs to have a clear picture of the tissue components that give rise to the growing gland.

Mammary Tissue Components

Mammary parenchyma of the lactating gland is composed of epithelial structures, such as alveoli and ducts, and the associated stromal connective tissue surrounding those structures.

The mammary parenchyma (formed by epithelial structures, the ducts and alveoli) is the portion of the mammary tissue that gives rise to the mammary alveoli and associated ducts that lead to the teat or nipple in the mammary gland of the lactating cow.

Stroma of a lactating gland is primarily composed of cellular and noncellular components of the connective tissue surrounding the epithelial structures. Cellular components of the stroma include fibroblasts, endothelial cells associated with blood vessels, and leukocytes localized in the tissue, while noncellular components include collagen and other connective tissue proteins. In contrast to the lactating gland, considerable white adipose tissue exists in the gland from the early phases of fetal development and it extends through much of pregnancy. This fat pad is often included as part of the stroma of the developing gland, but is considered extraparenchymal tissue.

Alveoli are the basic structures that produce milk during lactation (Fig. 1). The extensive system of mammary ducts provides a pathway for removal of milk from alveoli. Ducts and alveoli are the defining structures of the mammary gland. Understanding their development has been the primary historical focus of research. Groups of alveoli are organized into clusters, with each cluster constituting a lobule (Fig. 2). Each alveolus in a lobule drains into an intralobular duct, and intralobular ducts in turn are connected by interlobular ducts. Development of this lobular structure is a fundamental process of mammary growth. Prior to puberty, ductules arising from rudimentary epithelial structures near the base of the teat will elongate by growing into the fat pad. After puberty, these ductules continue to elongate in the cycling heifer, but also begin branching to form structures called terminal ductule lobular

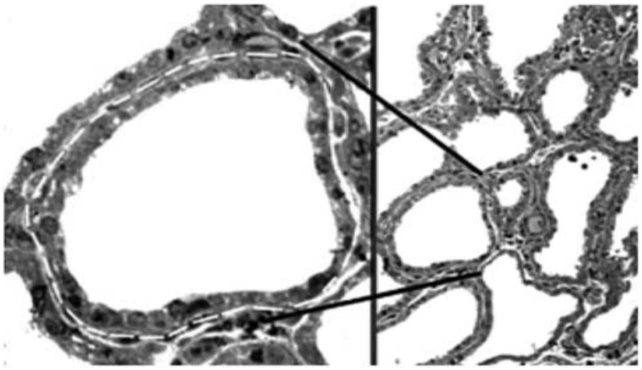

Fig. 1 Histological structure of mammary alveoli from a lactating cow. A single alveolus (outlined with a *white dotted line* in the left panel) is composed of a lumen surrounded by a single layer of epithelial cells. The *dotted line* is approximately defining the interalveolar connective tissue between adjacent alveoli. Myoepithelial cells (contractile cells) would be between the basal side of the epithelial cells and the basement membrane, but are not typically visible in this type of histological section. The right panel is a group of alveoli within a lobule.

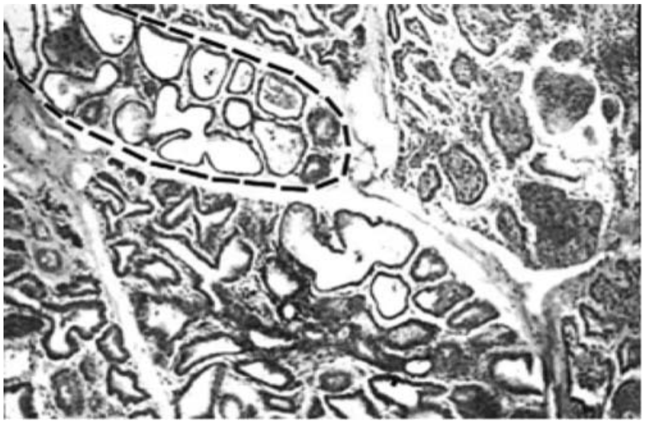

Fig. 2 Histological structure of mammary lobular structure from a lactating cow. One lobule is outlined with a *dotted line*, which is drawn over the interlobular connective tissue. There are portions of as many as five additional lobules present in this section, each with numerous alveoli.

units (TDLUs). These structures are characteristic of postpubertal mammary development in the human breast. Similar structures can be observed in the ruminant udder (**Fig. 3**). A TDLU makes up a developmental and functional unit of parenchymal tissue. Epithelial components of a TDLU are held in place by loose intralobular connective tissue and are surrounded by a denser interlobular connective tissue sheath. While the lobular organization of mammary tissue is apparent in the cycling heifer, it is during pregnancy that a TDLU will develop further to form a cluster of alveoli in what is recognizable histologically as a lobuloalveolar unit (**Fig. 2**).

Development of the epithelial components of TDLU and subsequent differentiation into functioning alveoli are essential elements of mammary development. The importance of nonepithelial tissue components has been highlighted by recent research. For example, growth of mammary epithelium requires the presence of the fat pad in order to form ductal structures (**Fig. 4**A). Therefore, the ultimate number of epithelial cells in the gland is limited by the size of the fat pad.

The ruminant's mammary fat pad has an abundance of interlobular fibroblastic connective tissue. Of particular note is the network of connective tissue fibrils, which are distributed through the adipose tissue as thick interconnected sheets (**Fig. 4**B). These connective tissue sheets contain extensive networks of collagen, fibroblasts, and blood vessels. Growing ducts and their associated lobular epithelial structures are thought to grow by advancing preferentially through these fibrous connective tissue sheets. Ducts and TDLUs are often surrounded by layers of connective tissue (**Fig. 4**B and C). This contrasts with mammary development in the mouse, which has often been used as a model to study mammary growth. The mouse mammary fat pad is composed of thin fibrous connective tissue septa, which are irregularly interspersed among the adipocytes. Duct elongation in the mouse results from actively growing epithelial structures in close proximity to adipose cells and surrounded by relatively little fibrous connective tissue.

During the early postnatal period of mammary gland development, ruminant mammary parenchymal tissue grows into the fat pad as a dense mass, replacing the adipose tissue as it progresses. Lipids from the adipocytes are mobilized as the parenchymal structures grow into the fat pad. As the parenchymal mass gets larger, continued ductal elongation seems to occur by epithelial cell

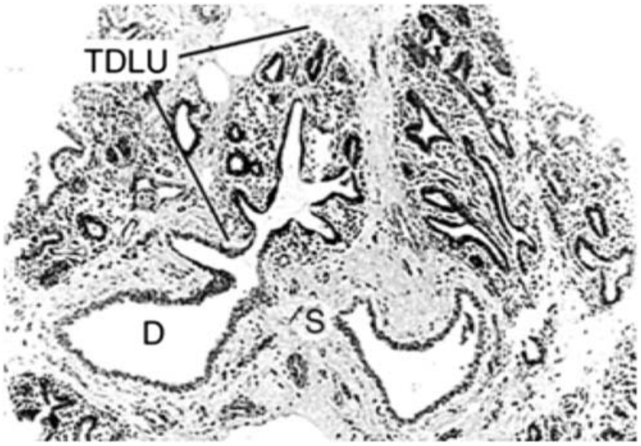

Fig. 3 Histological section of a structure similar to a terminal ductule lobular unit (TDLU). This tissue was collected by needle biopsy from a Holstein cow ~24 h after milking. This cow was about 15 months into her first lactation, not pregnant, and averaging approximately 13 kg of milk per day. An interlobular duct (D) has side branchings, one of which shows a TDLU in cross section with a cluster of small ductules branching from the central TDLU ductule. Note the distinct staining pattern of the "loose" intralobular connective tissue of the TDLU compared with the more fibrous connective tissue in the interlobular stroma (S). The presence of these immature structures in a lactating cow suggests that not all TDLUs may develop into milk-secreting lobuloalveolar units during late pregnancy or early lactation. Alternatively, additional TDLUs may develop during lactation, but not differentiate into milk-secreting lobuloalveolar units.

proliferation at the periphery of the growing terminal lobule structures. The interactions between epithelial cells and stromal tissue are central to mammary gland development and its regulation by hormones.

Hormones and Growth Factors

Mammogenic hormones establish the conditions for specific growth patterns in mammary tissue. For example, concurrently elevated blood concentrations of estrogen and progesterone observed in late gestation result in exponential parenchymal growth and in the formation of alveoli, whereas the cyclic changes of hormones associated with estrous cycles result primarily in duct elongation and some lobular tissue formation, but not in the formation of functional alveoli. Mammary development is usually driven by a complex of hormones acting in concert. The effects of many mammogenic hormones are thought to be mediated through stroma-derived growth factors, which act in a paracrine manner by eliciting mitogenic responses in the adjacent epithelial structures (Fig. 4C). Much of our current understanding of how mammogenic hormones and growth factors function has been derived from research in rodents. However, similarities have been noted in ruminants, and understanding of hormone action in rodents can help in understanding similar processes in ruminants.

Estrogen is an important mammogenic factor and removal of the ovaries before puberty reduces mammary gland development. Estrogen receptors appear in the gland around the time of puberty, coinciding with the period when the gland becomes exposed to cyclic elevations in the blood concentrations of estrogen. Estrogen acts on its receptors in the stromal tissue to stimulate production of growth factors, which in turn stimulate ductal development. Interestingly, the prepubertal bovine mammary gland seems to be responsive to estrogen, as well. This effect also is probably mediated through estrogen's effects on the mammary fat pad. The impact of mammogenic hormones on the heifer calf is an emerging area of research.

Progesterone is another ovarian steroid hormone that plays a key role in mammary development. While progesterone receptors have been difficult to identify in mammary fat pad, administration of progesterone can result in proliferation of stromal cells under some physiological conditions. The stimulatory effect of progesterone on DNA synthesis in ductal epithelium is probably mediated indirectly through its effects on stromal cells. The major mammogenic effect of progesterone is the stimulation of ductal side-branching or the formation of alveolar buds, which are the hallmarks of postpubertal mammary development. Estrogen stimulation of progesterone receptor expression in cells is required for this progesterone effect. Progesterone, therefore, has a major role in alveolar morphogenesis and a lesser role in ductal morphogenesis. During estrous cycles, duct elongation and expansion of the parenchymal tissue into the fat pad occur in limited bursts associated with the period of elevated estrogen. During the luteal phase of elevated progesterone in ruminants, relatively little further expansion occurs, but formation and maintenance of lobular structures may be stimulated by progesterone, with little ductal regression occurring between cycles.

Synergy between estrogen and progesterone is observed during pregnancy when both hormones are present in blood at high concentrations. Elevated blood concentrations of estrogen and of progesterone together establish the conditions required for the exponential cell growth that occurs during pregnancy. Lobuloalveolar development represents the greatest increase in mammary gland tissue mass during pregnancy. In the cow, progesterone is elevated throughout gestation, while estrogen concentrations

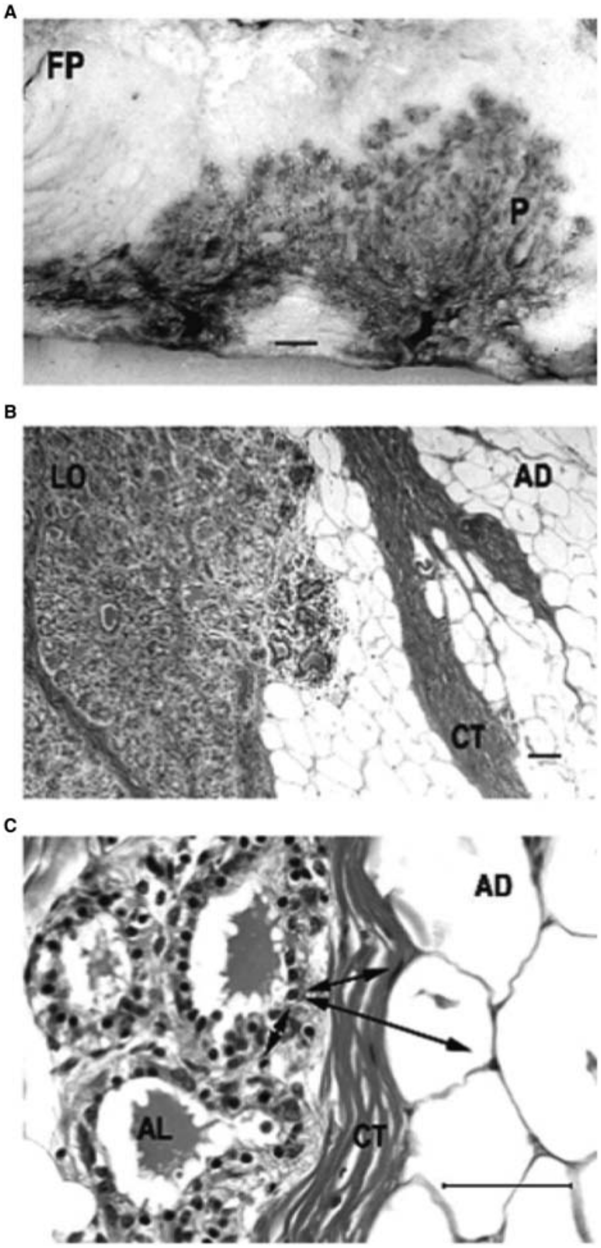

Fig. 4 Gross and histological structure of the fat pad and parenchymal tissue in the developing mammary gland (A) Cross section through fore and rear quarters of a postpubertal beef heifer. Note the branching and elongation of parenchyma (P; ducts, lobules, and associated connective tissue) into the mammary fat pad (FP), and the gland cisterns at the base of the parenchymal tissue. Scale = 1 cm (B) Low-magnification histological section of developing mammary gland (gilt during early pregnancy) illustrating fibrous connective tissue (CT) sheaths that form a meshwork interspersed among the adipocytes (AD). Note the development of lobules (LO) associated with the connective tissue sheaths. Scale = 50 μm (C) High-magnification histological section of developing mammary gland (gilt during early pregnancy) illustrating the structural relationship among alveoli (AL), fibrous connective tissue (CT), and adipocytes (AD). The *double-headed arrow* represents cross talk of paracrine factors between epithelial cells, cells in connective tissue, and adipocytes. Scale = 50 μm.

increase gradually and are particularly elevated during the later phase of gestation, coinciding with the period of greatest increase in mammary tissue mass.

Growth hormone (somatotropin) administration to cattle is known to stimulate milk production during lactation. This effect is in part indirect in that growth hormone stimulates secretion of insulin-like growth factor-I (IGF-I) from the liver, which in turn mediates many of the galactopoietic effects of growth hormone during lactation. Growth hormone also acts as a mammogenic hormone and can stimulate mammary growth at all stages of development. Growth hormone may act on ruminant mammary tissue by stimulating stromal production of IGF-I, which is mitogenic for mammary epithelial cells. The highest level of IGF-I expression in mammary tissue occurs in the fat pad and is greatest during the prepubertal allometric growth phase and during late pregnancy. Mammary expression of IGF-I is regulated by growth hormone, estrogen, and positive feedback stimulation from proliferating epithelial cells.

Prolactin is often associated with initiation of lactation and galactopoiesis, but it also has mammogenic effects. Prolactin receptors are present in the fat pad of some species, as well as in the epithelium. Prolactin may act on both epithelial and stromal components of the growing mammary tissue. Inhibition of prolactin secretion inhibits mammary gland development in pregnant goats, pigs, and other species. Blood concentrations of prolactin are normally low during pregnancy. Mammary development during pregnancy may not be limited by the normal blood concentrations of prolactin.

Placental lactogens are secreted from the placenta and they may have prolactin- or growth hormone-like activities, depending upon the species. In pregnant goats, placental lactogen in the maternal blood is closely correlated with the number of fetuses present. This graded concentration of placental lactogen, in combination with other mammogenic hormones, may regulate the extent of mammary development during late pregnancy. In the dairy cow, there is a relationship between placental mass and subsequent milk production. However, the concentration of placental lactogen in the maternal blood of the dairy cow is low, and the effect of placental mass may result from other placental hormones, including estrogen.

Other hormones are also required for mammary growth, including glucocorticoids, thyroid hormones, and insulin. Severely diabetic mice given estrogen and progesterone will develop extensive lobuloalveolar structures. Nevertheless, insulin synergizes with estrogen and progesterone to increase mammary development. Normal blood concentrations of insulin are probably not limiting for normal mammary development.

In addition to the IGFs, other growth factors have positive or negative effects on mammary gland development. Local mammary production of transforming growth factor-β (TGF-β) inhibits mammary growth, during the prepubertal period and between estrous cycles. Epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) stimulate mammary cell proliferation. Both EGF and TGF-α bind to the EGF receptor. The mammogenic action of estrogen and progesterone occurs in part by decreasing local production of the inhibitory TGF-β, while increasing local production of TGF-α and the levels of EGF receptor in the epithelium. Stromal EGF receptors are also necessary for normal ductal growth. Several additional growth factors produced by stromal cells are known epithelial cell mitogens and may be involved in mediating the effects of mammogenic hormones.

Mammary epithelial structures are often seen growing into a lipid-rich environment of the fat pad. Cytosolic triacylglycerols (TAG) are stored in mammary cells and this will depend on the individual fatty acid structure such as the chain length, degree of saturation, and number and orientation of FA double bonds. Fatty acids, particularly unsaturated fatty acids, stimulate mammary epithelial cell growth and can substantially enhance the in vitro effects of other growth factors such as IGF-I and EGF. Mammary stromal cells are also involved in dissolving the connective tissue collagen, and hence the epithelial structures can continue to grow. Several proteases involved in tissue remodeling and growth of parenchymal tissue are derived from stromal tissue. Extracellular matrix components, which are important for mammary tissue growth and function, are produced by both epithelial cells and stromal cells.

Pre-weaning Nutrition Impact on Mammary Gland Development

The annual costs for raising heifers is estimated at approximately 20% of the overall dairy farm expenses. Therefore, an important goal is for heifers to reach puberty as early as possible, without causing excess fat accumulation. The plane of nutrition in pre-wean animals is a very important on-farm management tool that can have a deep impact on mammary gland development and consequently affect the performance in the first lactation. In fact, by increasing 1 kg/d in pre-wean average daily gain, heifers can increase up to 1000 kg or more in milk yield.

One plausible nutritional strategy to improve mammary gland growth and development in pre-wean animals is the modulation of fat and protein content in the milk replacer together with an elevated nutrient intake. This is why nutrient density and quantity of milk replacer offered to young animals is pivotal for their future performance. In the past 5 years, studies have demonstrated positive effects on mammary gland growth and development when animals are fed a higher plane of nutrition (above 1 kg/d/animal) compared to a restricted intake of milk replacer (around 0.5 kg/d/animal).

Changes in the concentration of these nutrients in milk replacers and the amount of milk replacer offered can alter tissue growth and development, in part through alterations at the transcriptome level in tissues primarily related to growth (e.g., adipose and skeletal muscle) and/or metabolism (e.g., liver). Nutrition can influence pre-weaning mammary gland allometric growth with heifers fed on a high plane of nutrition achieving greater mammary gland growth rate by 2 months of age. Such response allows for greater physiological development relative to animals that receive milk replacers with less nutrients density.

On an "accelerated early nutrition" feeding strategy, pre-wean animals can be fed around 1.1 kg/d/animal with milk replacers containing up to 30% crude protein and from 15% to 20% fat. With this higher plane of nutrition pre-weaning, parenchyma and mammary fat pad development also is enhanced. Furthermore, at 28.9% of crude protein and 26.2% fat in milk replacers offered at a ratio of 1.1 kg/d/animal, heifer calves improve body weight gain, and frame size without deleterious effects on mammary parenchyma composition.

Another possibility to improve mammary gland growth is by feeding animals with 1.1 kg/d/animal of milk replacers containing 28.9% of crude protein and 26.2% of fat together with an estrogen implant. This management leads to heavier mammary gland weights that can translate into enhanced mammogenic responses.

It is clear that early-life nutrition is pivotal for mammary gland growth and development as increasing feeding rates during that stage affects the morphology of myoepithelial cells in the mammary epithelium. Recent evidence suggests a role for other types of cells (i.e., immune cells), in the penetration of the mammary parenchyma into the fat pad during early life development of the bovine mammary gland. This growth and development is not only controlled by local tissue but a coordinated network system of other tissue types such as those related to the immune system.

Phases of Mammary Development

Fetal Development

Mammary development begins when the animal is a fetus. The first discernible group of embryonic ectodermal cells that is destined to form the mammary gland is called the mammary band, which runs on either side of the trunk of the fetus from the upper limb to the lower limb. The mammary band appears in the bovine embryo at about 32 days after conception. Mammary bands undergo several further stages of development, ultimately giving rise to the mammary buds. In the bovine species, there are two discrete mammary buds on each side of the embryo’s ventral midline in the inguinal region. These give rise to the fore and rear quarters. Mammary buds form early in the second month after conception. The mammary bud stage marks the beginning of differential development patterns of male and female glands. The mammary bud stage is followed by teat development. At the same time, mammary bud cells are invaginating into the surrounding mesenchyme, resulting in formation of a solid core of ectodermal cells, called the primary sprout. The primary sprout ultimately gives rise to the teat and gland cisterns. The mammary fat pad also begins to develop at this time. Limited branching of the primary sprout occurs as the ectodermal cells continue to divide and grow into the surrounding mesenchyme, resulting in cords of epithelial cells called secondary and tertiary sprouts. During secondary sprout formation, the rapidly expanding core of epithelial cells of the primary sprout leads to the formation of a lumen by a process called canalization.

Most major prenatal developmental changes of the gland occur by midgestation. By the time the calf is born, teats are well developed; secondary sprouts are canalized, but still have the solid core of cells at the end; growth of the sprouts is limited to the area around the gland cistern; median suspensory ligament formed; and mammary connective tissue, fat pad, blood vessels, and lymph vessels have formed. There is no development of mammary secretory or glandular structures during the fetal stage of development. In the calf, the mammary fat pad makes up the majority of the udder’s mass.

Postnatal Development

In the neonatal ruminant, the parenchymal tissue of each gland, or udder quarter, includes a single primary duct, which branches to form several secondary and tertiary ducts. At the ends of the secondary and tertiary ducts are clusters of ductules, which will give rise to the TDLU-like structures after puberty.

Growth of mammary parenchyma of the heifer calf occurs at the same rate as general body growth (isometric growth) for the first 2–3 months after birth. Mammary parenchyma then begins growing faster than the body (allometric growth) until about 9 months of age or a short time beyond puberty, after which mammary growth returns to an isometric rate. The major increase in total udder size during the prepubertal period results from continued growth of the fat pad.

Individual differences in udder shape and size are observed at birth; however, palpation of the gland from birth to 6 months of age is a poor predictor of the potential for future milk production of the mature animal. Correlations between mammary DNA and subsequent milk production are low in young heifers. Nevertheless, the prepubertal period marks an important phase for mammary gland development and subsequent milk production. Nutrition and growth rate of prepubertal heifers can significantly affect mammary development during this phase and may affect milk yield once the heifer begins lactation. Underfeeding during the prepubertal period decreases subsequent milk yield. The effect of feeding for high growth rates in prepubertal heifers, but not postpubertal heifers, may have a negative impact on mammary gland development and subsequent lactation. However, some recent studies have not reported negative effects of feeding for high growth rates; probably because modern heifers can sustain higher growth rate without getting fat. Prepubertal nutrition may also affect the response of the developing mammary gland to mammogenic hormones. The mechanism by which prepubertal feeding may affect subsequent milk yield remains an active area of investigation.

Growth hormone concentrations in the blood of prepubertal heifers on restricted intake (slower growth rates) are increased compared with heifers having *ad libitum* access to feed. Mammary parenchymal tissue mass is positively correlated with growth hormone levels and negatively correlated with mammary adipose tissue. This is consistent with the high level of IGF-I expression in mammary tissue during the prepubertal allometric growth phase, as noted above. Growth hormone administration during the prepubertal period increases mammary parenchyma and decreases extraparenchymal tissue compared with controls, but does not seem to increase milk yield during the first lactation in heifers. The limited increase in mammary development in the prepubertal period may be overshadowed by the exponential growth occurring during late pregnancy.

After puberty, the gland is exposed to cyclic changes in ovarian steroid hormones. In postpubertal ruminants, mammary development occurs in bursts of duct elongation and development (Fig. 4A), and development of the TDLU. The postestrus decline in parenchymal tissue is irregular. There is a linear relationship between increased udder weight and increasing age of the heifer up to about 30 months. This is partly due to increased body weight and partly due to accumulation of udder fat as heifers put on body conditioning with advancing age.

Pregnancy

Once the animal becomes pregnant, development of the mammary gland accelerates at an exponential rate. This means that mammary growth is greatest during the later stages of pregnancy, coinciding with the most rapid period of fetal growth. Extensive lobuloalveolar development occurs only during pregnancy. This period is important in determining the number of secretory cells in the lactating gland and the subsequent production of milk. Correlations between total DNA in a lactating gland and milk yield range between 0.50 and 0.85, depending on the species and other factors. High body growth rate does not affect mammary gland development during pregnancy.

Lactation

Mammary cell numbers continue to increase after parturition. The impact of postpartum mammary growth on milk production can be substantial in litter-bearing species such as the rat and pig, where total mammary DNA can increase by over 100% during lactation depending upon litter size. In contrast, postpartum cell proliferation in dairy ruminants is thought to occur only in the early postpartum period. Mammary DNA in lactating goats increases by about 25% during the first 3 weeks of lactation. Because milk production does not peak until about 8 weeks of lactation in goats, the postpartum increase in mammary cell numbers is thought to contribute only a portion of the ascending phase of the lactation curve, with increased milk synthesis per cell being the major contributor. In cows, mammary DNA increases by 65% between 10 days prepartum and 10 days postpartum, although how much of this increase occurred prepartum versus postpartum is unclear. Other researches have reported, as for goats, that the increase in milk production in early lactation is due an increase in secretory activity and the decline in milk yield with advancing lactation is due to a decrease in cell number.

Mammary Gland Involution

The dairy cow requires a nonlactating period prior to an impending parturition in order to optimize milk production in the subsequent lactation. This period is called the dry period and it includes the period between cessation of milk removal at dry-off and the initiation of milking at the subsequent calving. If the dry period is less than 40 days, then milk yield in the next lactation is typically decreased. Physiology of the mammary gland during the dry period differs markedly from that during lactation. The dry period can be divided into three phases: active involution, steady-state involution (mid-dry period), and redevelopment and colostrogenesis. Active involution begins with cessation of periodic milk removal, either by drying off the cow or by weaning the young. It is the phase when the mammary gland makes the transition from a lactating to a nonlactating state and it marks the final phase of a lactation cycle.

Mammary gland involution is initiated when milk is no longer removed from the gland. Mammary involution in a species like the mouse is characterized by a rapid loss of tissue function, cell death, and degeneration of alveolar structure resulting from loss of epithelial cells. The number of cells in the gland at any given time is a function of the balance between cell division and apoptosis (programmed cell death or cell suicide). Although, loss of mammary cells by apoptosis also occurs in the mammary tissue of cows, the total number of cells does not decrease indicating that lost cells are replaced. In contrast to the involuting mouse mammary gland the bovine mammary requires 3 or 4 weeks to be completed. Accordingly, resuming milking after a week of milk stasis will re-initiate lactation with minimal losses in milk production in cows. General structural integrity of lobular units in the tissue seems to be retained throughout involution. Redevelopment of the mammary gland in cows during the dry period, as defined by an increase in cell division, begins 5–6 weeks prior to calving. Interestingly, some evidence indicates that apoptosis is actually increased in very early lactation, perhaps as a means of eliminating dysfunctional cells in the tissue.

Systemic and locally produced IGF-I play important roles in the survival of mammary epithelial cells. Activity of IGF-I in tissues is modulated by local production of IGF binding proteins (IGFBPs), a family of proteins that may inhibit or enhance IGF activity depending on a number of factors. Research in rodents and sows indicates that specific IGFBPs produced by mammary tissue during early involution are involved in inhibiting IGF-mediated cell survival. This may be part of the mechanism for increased apoptotic cell death during involution. Some IGFBPs may have a similar function in cattle and sheep.

Histological and ultrastructural changes associated with involution begin within 48 h after cessation of milk removal in bovine mammary tissue. The most apparent change is the formation of large stasis vacuoles in the epithelial cells (Fig. 5B), formed largely as a result of intracellular accumulation of milk fat droplets and secretory vesicles. These vacuoles persist for at least 2 weeks of involution, but typically are absent by the fourth week. Alveolar lumenal area declines during this period, while interalveolar stromal area increases (Fig. 5C).

A substantial reduction in fluid volume in the gland occurs between days 3 and 7 after drying-off. Fluid volume continues to decrease through about 4 weeks of involution. Concentrations of milk proteins, fat, and lactose decline during the initial 1–2 weeks of the dry period. Concentrations of several protective factors, such as lactoferrin and leukocytes, increase during early involution. The protective factors are important for the gland's resistance to intramammary infection.

The length of the steady-state period depends on the total length of the dry period. If active involution takes about 3–4 weeks to complete in the dairy cow and the redevelopment stage takes about 3–4 weeks, then the gland spends little time in the steady-state

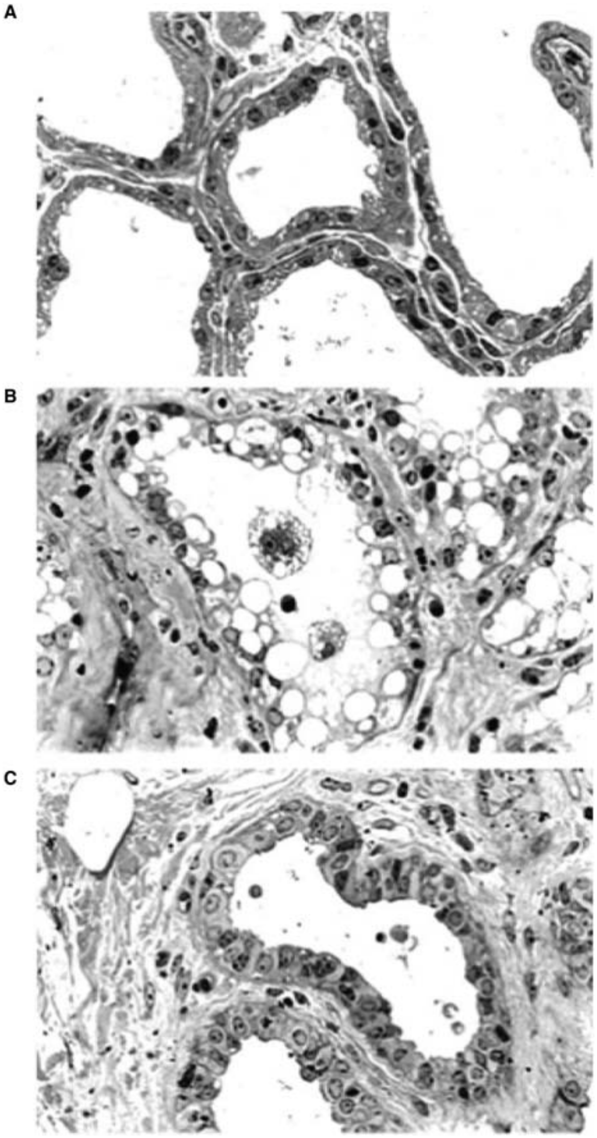

Fig. 5 Histological structure of bovine mammary gland tissue during involution (A) Alveoli of a lactating mammary gland with large lumens. Minimal stromal tissue is present in the lactating tissue (B) Mammary tissue 4 days after drying-off. Alveolar epithelial cells contain large vacuoles. Interalveolar connective tissue is increased compared with lactating tissue. Note leukocytes in the alveolar lumen; leukocyte concentration is increased in mammary secretions during involution (C) Mammary tissue 21 days after drying-off. Vacuoles are no longer present. Extensive interalveolar connective tissue is present. Integrity of epithelial structures remains intact with a single layer of cells.

involution phase during the recommended 45- to 60-day dry period. Synthesis of DNA in mammary tissue begins as much as 35 days prepartum in the pregnant dry cow. This marks the phase of the dry period when the gland begins the transition from the nonlactating state to the lactating state. Selective transport of IgG_1 is a major activity of epithelial cells during the last 2–3 weeks prior to parturition and is one of the hallmarks of colostrum formation. Concentrations of major milk components begin to increase from about 2 weeks prepartum, and then increase markedly from 3 to 5 days prepartum leading up to the subsequent initiation of lactation.

Reflection on the Current Knowledge on Mammary Development and Lactation

Recent research demonstrates that feeding a higher plane of nutrition with increased nutrient density in early life, increases mammary fat pad weights and size of mammary parenchyma. These changes are reflected later in the animal's performance.

We have a good understanding, as detailed above, on the hormones and growth factors that govern the mammary growth. The development of multiple assays to measure concentrations of mammogenic, lactogenic and galactopoietic hormones coupled with a wide variety of growth factors in blood, milk and tissues, has helped to explain mammary cell proliferation and regulation of function in different production environments, different nutritional regimens, different genetics and different physiological stages.

The advent of high-throughput technologies in molecular biology together with advances in computer sciences and informatics have made possible new strategies in molecular biology that enable collection and analysis of data related to complex interactions at the mammary gland level. These technologies can be used to analyze and integrate information from mammary gland-related processes from different angles such as genomics (DNA level), transcriptomics (RNA level), proteomics (protein level), lipidomics (lipid level) and other related fields (e.g., metabolomics and other -omics). A weakness of this approach to date is that the data are often produced from few animals and/or cell and tissues cultures. There needs to be caution when extrapolating the newer findings into the complexities that high-yielding animals encounter in commercial farms.

Conclusion

Mammary gland development and lactation may occur multiple times in a mammal's life. Development of mammary gland epithelial structures relies on the presence of a mammary fat pad and other stromal components of the tissue. Many mammogenic hormones function through their effects on stromal tissue, leading to the secretion of growth factors that control epithelial development. Development of lobular epithelial structures in the gland begins after puberty in response to cyclic changes in ovarian steroid hormones. Exponential growth of lobular structures and development of alveoli within the lobules occur during pregnancy in response to high blood concentrations of estrogen and progesterone.

Further mammary gland growth after parturition is limited in dairy ruminants, although production of milk continues to increase up to peak lactation. When milk removal is stopped at the end of lactation, the mammary gland undergoes a process of involution, which returns the tissue to a nonlactating state that will get prepared for the next cycle of mammary growth, lactation, and regression. A greater understanding of the growth regulatory factors at each phase of development, as well as an understanding of the relationship among the developmental phases, is essential for enhancing mammary gland growth.

See Also: Mammary Gland: Anatomy; Mammary Gland: Gene Networks Controlling Development and Involution

Further Reading

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