

Minireview

The origin and evolution of lactation

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Abstract

The presence of mammary glands is the defining morphological feature of mammals. The recent assembly of the bovine genome and a report in *Genome Biology* that links the milk and lactation data of bovine and other mammalian genomes will help biologists investigate this economically and medically important feature.

The mammary gland has been a pivotal feature in the evolution and taxonomic classification of animal species, and it has even had a role in the acceptance of evolutionary theory. The presence and secretory capacity of the mammary gland provided the basis for the taxonomic grouping of species into the class Mammalia more than two centuries ago; and Darwin's explanation of how lactation may have evolved satisfied an early challenge to his theory of evolution by natural selection [1]. The challenge was that evolution of lactation was not feasible, because a neonate could not obtain a survival benefit from consuming the chance secretion of a rudimentary cutaneous gland. In response, Darwin hypothesized that mammary glands evolved from cutaneous glands that were contained within the brood pouches in which some fish and other marine species keep their eggs, and provided nourishment and thus a survival advantage to eggs of ancestral species. Two hundred years after Darwin's birth, the theory of evolution by natural selection remains a cornerstone of biology, as it has withstood this and other challenges. However, it is now clear that the mammary gland did not evolve from a brood pouch [1].

Milk nourishes the neonate and helps to establish immunological and endocrine competence in the offspring.

The nutrient composition of milk varies dramatically across species, and it can also be strongly influenced by the stage of lactation. For example, the fat content of milk may be as high as 60% in seals and negligible during early lactation in wallabies [2,3]. Furthermore, milk in the tamar wallaby (*Macropus eugenii*) changes from a very dilute secretion containing primarily carbohydrate during early lactation to a more energy-dense milk that contains substantial quantities of protein and fat during later phases of lactation. Thus, the details of lactation have evolved to meet the diverse reproductive and environmental demands of different species. About 10,000 years ago, the domestication of plant and animal species led to the Neolithic Revolution, with its changes in societal interactions and the evolution of civilization. Milk and dairy products were tightly coupled to this cultural evolution, and dairying (then and now) provides an important source of food and fiber throughout the world.

Sequencing and assembly of the bovine genome, establishment of mammary transcriptome and proteome libraries, the discovery of single nucleotide polymorphisms [4], and discoveries and developments to come, are providing important tools for agricultural scientists to investigate the

biology of lactation and to adopt genotype-based breeding schemes to select for desired traits. Moreover, comparative genomic studies enable evaluation of lactation across numerous and diverse mammalian species. Regardless of the perceived target species of this research, such knowledge improves our understanding of mammary gland biology and is applicable to normal and pathological states. Danielle Lemay and colleagues, in a recent report in *Genome Biology* [5], have taken this important step towards greater understanding through comparative genomics.

Evolution of lactation

Lactation appears to be an ancient reproductive feature that pre-dates the origin of mammals. A cogent theory for the evolution of the mammary gland and lactation has been provided by Olav Oftedal [1]. The features of current mammals were gradually accrued through radiations of synapsid ancestors, and the mammary gland is hypothesized to have evolved from apocrine-like glands associated with hair follicles (Figure 1). Oftedal suggests that these glands evolved from providing primarily moisture and antimicrobials to parchment-shelled eggs to the role of supplying nutrients for offspring. Fossil evidence indicates that some of the therapsids and the mammaliaformes, which were present during the Triassic period more than 200 million years ago, produced a nutrient-rich milk-like secretion.

The capacity to supply fluid and perhaps nutrients to eggs would be promoted and enhanced by incorporation of antimicrobials into the fluid. These may have been antimicrobials already produced in the skin, as in amphibian skin, and evolutionary pressure would probably have fostered the incorporation of molecules such as lysozyme and iron-binding proteins into the secretion, components that are prevalent in milk. The disaccharide lactose (galactose β 1-4 glucose) is contained in all milks, except for those of some marine mammals. Its synthesis is catalyzed in the mammary gland by lactose synthetase, an enzyme that is a complex of β 1-4-galactosyl transferase and the regulatory subunit α -lactalbumin. Because α -lactalbumin evolved from lysozyme before the division of amniotes into synapsids and sauropsids (see Figure 1), the capacity to produce lactose was an ancient trait that preceded its utility in milk synthesis. It is likely that early milks primarily contained antimicrobial oligosaccharides and the prevalence of lactose as a component of milk arose only when α -lactalbumin was produced in sufficient quantity.

With the synthesis of lactose, these modified secretions would have provided nutrients to the egg. The evolution of

the casein family of milk proteins in particular would provide calcium, phosphate and protein to hatchlings. Fossil records suggest that caseins were present during the Triassic, because the extensive bone and tooth development evident in the relevant species at stages before independent feeding would have required delivery of ample calcium. Given this evolutionary scenario, the composition of mammary secretions during early lactation in monotremes and marsupials is likely to be similar to that of the primitive milk of mammalian predecessors. The milk then converts to a more nutrient-rich source during later stages of lactation. The evolution of placenta-based reproduction displaced the function of milk as a source of water and nutrients for the egg, leading to secretion of a complex milk throughout lactation in eutherians (Figure 1).

Milk also enhances the survival of offspring by satisfying other needs, for example, by promoting immunological competence and endocrine maturation in the neonate [6,7]. In this regard, milk seems to provide for the immediate and long-term needs of the offspring. These needs can be highly species-specific. There are also behavioral and 'psychological' aspects of suckling and nurturing between mother (dam) and offspring that produce bonds that promote neonate survival. This is an aspect of lactation that is independent of the chemical and physical characteristics of milk.

Systemic and local control of mammary function

Mammary gland development and function is subject to systemic and local control. In placental mammals, our understanding of this regulation has been advanced by decades of scientific inquiry, using physiological, molecular and genomic tools. In these mammals, development of the mammary gland during gestation generates abundant alveolar secretory cells. Differentiation of the secretory cells and the onset of copious milk synthesis and secretion are regulated to coincide with parturition. The combined effects of positive endocrine stimulators (prolactin, insulin, glucocorticoids, growth hormone and estradiol) are kept in check by the overriding negative influence of progesterone [8]. The decline in progesterone at parturition largely determines the onset of copious milk secretion, but regulation in marsupials differs from that in eutherians. The reproductive cycle in marsupials is characterized by a short gestation and a long lactation, during which the female will nurse offspring of different ages. Lactation in the tammar wallaby has been studied and, consistent with the marsupial reproductive strategy, is found to be insensitive to inhibition by progesterone [2,9]. The tammar wallaby offspring (joey) is born in an immature state at 26 days gestation. At birth it remains attached to the nipple for a

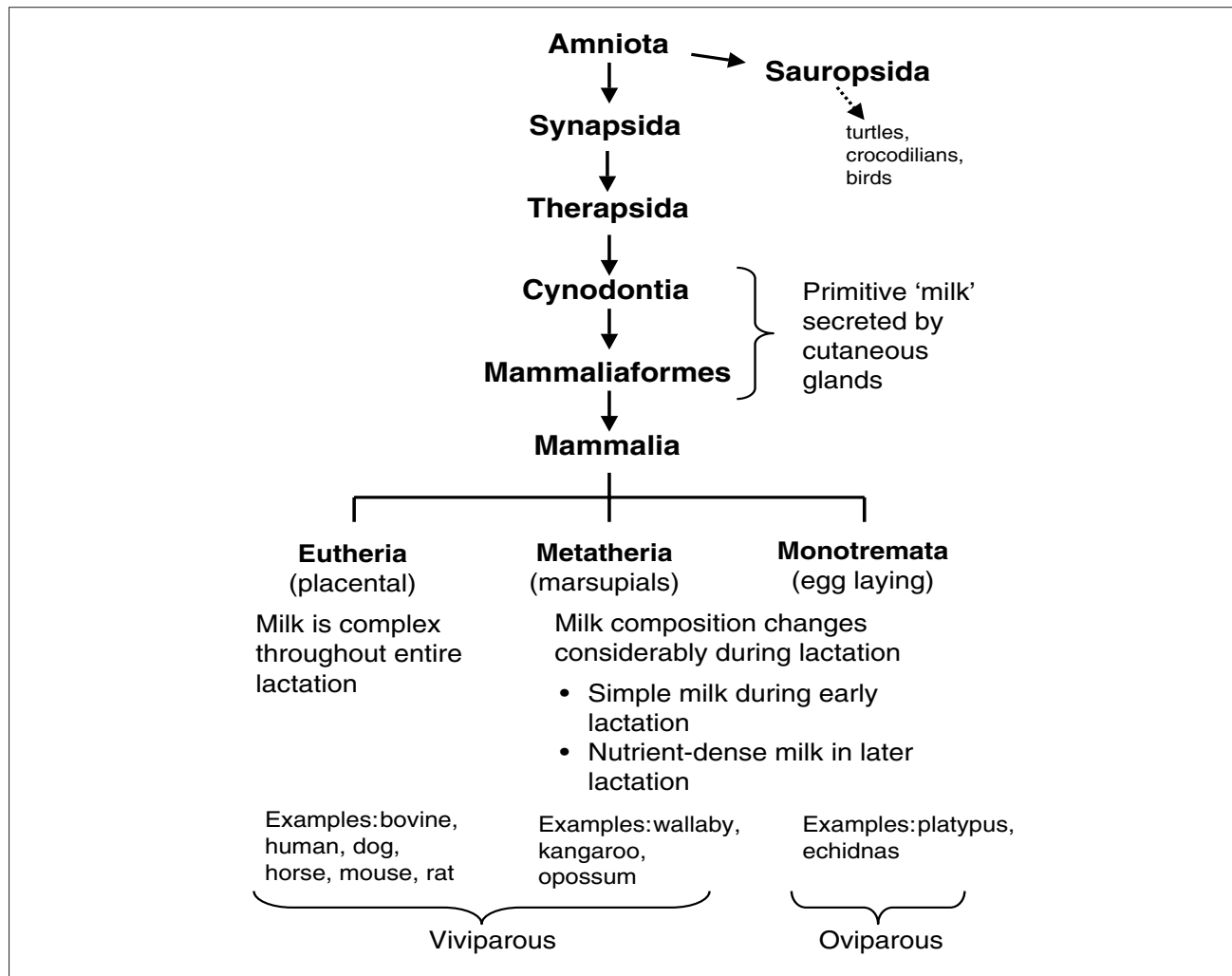


Figure 1
Simplified representation of evolution of extant Mammalia and lactation.

period, during which it obtains a dilute, carbohydrate-rich milk. However, the composition of the milk changes significantly during lactation to meet the demands of the developing joey. Moreover, the tammar has asynchronous concurrent lactation, during which the dam provides milk of differing composition from adjacent glands to feed two offspring of different ages and nutritional needs. This provides an example of local regulation of lactation.

Another clear example of local regulation is provided by lactation in the Cape fur seal (*Arctocephalus pusillus pusillus*), which is characterized by short suckling periods (2-3 days) on shore and lengthy foraging periods (about 20 days) at sea, during which maternal nutrient stores are replenished. In most eutherian species, milk secretion decreases in the absence of suckling, and this is accompanied by an increase

in apoptosis and mammary involution, seemingly promoted by feedback inhibition from components of the unused milk. Lactation in the Cape seal has uncoupled the apoptotic response from decreased milk synthesis, so that the mammary gland simply shuts down during the long foraging periods and resumes secretion when suckling is resumed. The local factor recently implicated in this process is the milk protein α -lactalbumin. The α -lactalbumin in this group of seals (the otariid pinnipeds) apparently cannot promote apoptosis (or lactose synthesis) [10].

Features of milk and mammary genes (the ‘lactome’)

Lemay *et al.* [5] used the *Bos taurus* genome sequence (draft 3.1, August 2006) and expression libraries derived from tissue obtained during various stages of mammary development

and lactation status to identify unique milk proteins and mammary-related proteins. With the exception of four milk-protein gene clusters (casein genes, immunoglobulin genes, fibrinogen genes and genes encoding proteins of the milk fat globule), they found that milk-protein genes do not cluster with each other, but rather tend to cluster with other lactation genes. They also did not cluster by developmental stage or gene duplication, suggesting that these genes clustered to facilitate coordinate gene expression.

The bovine genome was compared with six other mammalian genomes: human, dog, mouse and rat (eutherians), opossum (marsupial) and platypus (monotreme). In general, milk and mammary genes were more conserved and seemed to evolve more slowly than others in the bovine genome, despite selective breeding for milk production. This supports the hypothesis that lactation has evolved to minimize the energy cost to the dam while maximizing survival of the neonate, thus promoting survival of the maternal-offspring pair. The most divergent proteins in the lactome were those with nutritional or immunological attributes, suggesting continuing selection of these genes to meet nutritional and pathogen challenges that are incurred by diverse environments and reproductive strategies. The most conserved genes were those for proteins of the milk fat globule membrane, confirming the essentiality of this mechanism for milk-fat secretion and indicating that the diversity in milk fat may be due to altered efficiency in secretion, not to inherent changes in the secretory process. Diversity in milk composition could not be explained by diversity of the encoded milk proteins; and although gene duplication may contribute to species variation, this is not a major determinant. Thus, other regulatory mechanisms must be involved. For example, on the basis of analysis of the opossum genome, Mikkelsen *et al.* [11] concluded that most of the genomic diversity between marsupials and placental mammals comes from non-coding sequences. These, or other factors that regulate the partitioning of nutrients, the interaction between mammary gland and supporting organs, or mammary gland metabolism, may be primary determinants of milk composition.

Expansion of comparative studies to include additional non-placental species and inclusion of non-coding regions of the genome is certain to provide additional insight into the regulation of mammary gland function and milk composition. For example, a systematic study of the role of microRNAs in mammary development and lactation is likely to be a fruitful area of investigation. Because no single species can provide an ample and sufficient model for the physiology of another, and because the potential gain in knowledge from comparative studies is great, the research

community should not be species-centric. Continued research in mammary gland biology that incorporates comparative genomic and physiological studies of animals with varied and extreme adaptations to lactation will be necessary to provide insights into the development and regulation of mammary gland function, as well as the probable evolution of these processes.

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