Chapter 1

Introductory Chapter: Insights into Lactation

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Additional information is available at the end of the chapter

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Lactation is a fascinating process that characterized all mammals. From primitive glands with no nipples—as in monotremes—to complex mammary glands, female mammals nourish their offspring with the perfect food. Each species has different nutritional requirements, and each mother secretes the correct concentration of macro and micronutrients. Fat, for instance, varies from 50% content as in gray seal [1] to 4% in cow milk [2]. In addition to nutrition, milk contains bioactive components that promote immunity such as immunoglobulin and lactoferrin [3, 4]. The importance of milk on the prevention of pathogens in the newborn has been known for a long time [5], yet as research progresses, new understanding arises. Recently, it was identified that human milk produces a large amount of oligosaccharides that are not digestible by the newborn. Researchers found that these short carbohydrates play an important role on the intestinal flora acting as prebiotic for beneficial bacteria and inhibiting the adhesion of pathogens on the intestinal epithelial [6–8]. Human milk is not the only one that produces prebiotic components. In cows, also have been identified a variety of oligosaccharides that promote a healthy microbiome [9]. All these recent studies highlight even more the impact of milk as a functional food.

The mammary gland develops through different phases: embryonic, pre- and post-puberal, and during pregnancy. An important feature in the mammary gland is that it undergoes different cycles of differentiation and regression throughout the adult female's life. Lactation is the final stage of reproduction; therefore, lactation regulation might differ according to the species' reproduction strategy. Female mammals can be classified as continuous or seasonal breeders. Concomitantly, seasonal breeder species can be divided into long and short day. The females on the first group present ovary activity in spring and summer, while are in anestrous in fall and winter (i.e., horses). On the contrary, in short-day breeders, reproduction takes place in fall and winter and ovary is inactive in spring and summer (i.e., sheep). In all seasonal breeders, regarding the reproduction strategy, the decreased light length produces the excitation of the superior cervical ganglion through the retina nerve, which unblocks the inhibition of the pineal gland. As a result, melatonin increases. Melatonin interacts with the gonadotropin-release hormone (GnRH) affecting the hypothalamus pineal ovary axis. The way melatonin influences GnRH is depending on the reproduction strategy: in short-day breeders, melatonin induces the synthesis of GnRH, and therefore, ovary cycles are produced; on the other hand, in long-day breeder, melatonin inhibits GnRH-inducing anestrous [10]. Sheep—which are short-day breeders—can be artificially manipulated to induce cycling out of season. Melatonin also affects mammary gland and lactation. Therefore, lactation in sheep lambing out of season could affect milk production. In Chapter 1, Dr. Molik describes the endocrine response associated with melatonin changes and the impact of the photoperiod on milk production in the sheep.

Another example of how reproduction strategy influences mammary gland development is observed in *Lagostomus maximus*. This rodent presents a pseudo-ovulation in mid-gestation. The changes in progesterone levels during pregnancy characterized the mammary gland development of this species. An interesting description of the mammary gland development and involution on the Vizcacha is described in Chapter 2 by Dr. Halperin et al.

Numerous factors interact at the onset and maintaining of lactation. There is a consensus of the main lactogenic hormones that regulate milk synthesis and secretion, but as research advances, we are getting a better understanding on the fine balance among the systemic hormones and the local regulatory factors. Milk secretion is trigger at parturition when progesterone falls and glucocorticoid, prolactin, and growth hormone (GH) rise [4]. The association among these hormones and lactation has been known for many years. Probably, one of the earlier evidence that progesterone inhibits lactation was back in 1925, when Hammond described that milk secretion in rabbits was the consequence of corpora lutea involution [11]. Prolactin is needed to maintain milk secretion in most mammals. However, in ruminants, the predominant lactogenic hormone is considered to be GH [12]. A synthetic GH was widely used in dairy industry to increase milk yield in the 1980s when a recombinant GH was commercially available [13]. At a molecular level, lactogenic hormones activate gene expression through JAK2/STAT5. Briefly, once the hormones bind the cell surface receptors, JAK2 proteins phosphorylate and consequently induce the phosphorylation of STAT5. Then, the phosphorylated dimer STAT5 translocates to the nucleus and induces transcription of target milk protein genes. For a review, see Ref. [14]. Milk is synthesized and secreted into the mammary alveoli lumen. When milk let-down stimulus is triggered, oxytocin is released from the pituitary gland and binds to its receptor on the myoepithelial cells; as a consequence, milk is ejected. Oxytocin structure and function have been described in the 1950s. Vincent du Vigneaud received a Nobel Prized in 1955 for his work on the oxytocin [15]. Maintaining of lactation requires the periodic removal of milk. Systemic endocrine factors and autocrine mechanisms act concomitantly to control mammary gland function. Once milking is discontinuous, the mammary gland undergoes to a series of involution process that drive it from a secretory phase to an inactive organ. Involution is divided into two stages. The first stage is regulated by local factors, which outweigh the positives stimulus exerted by the lactogenic hormones. To exemplify the importance of this concept, interrupting milking in a single gland in the cow, triggers the involution process only on that quarter, while the other three lands maintain milk production. During the second involution stage, apoptosis of epithelial cells and tissue remodeling occurs. In Chapter 3 of the present book, Dr. Kordon and Dr. Coso describe in detail the cell signaling associated with mammary gland involution and cancer.

Authors explain the role of STAT3 and leukemia inhibitory factor (LIF) on mammary cell death and show that the effect of stretching mammary epithelial cells in culture—as happen in vivo by milk accumulation—induces both LIF expression and STAT3 phosphorylation. Also, it discussed the role of the extracellular matrix in the involution process.

Local mechanisms not only regulate milk yield but also control milk composition. A beautiful example of local regulation in milk composition is observed in the Tammar Wallaby. When the immature joey is born, it crawls to the mother's pouch and attaches to the nipple. As the youth growths and its nutritional requirement change, milk composition is adapted to the new demand. However, it could occur that the female gives birth to a second joey, while the oldest one is still lactating. On this occasion, entirely different composition of milk would be produced in each mammary gland. This is called asynchronous concurrent lactation and is regulated by local factors. For an extensive review, see Ref. [16].

The development of new molecular tools—such as new-generation sequencing and RNA sequencing—revealed remarkable information that challenges our knowledge. In 1998, Fire and Mello received a Nobel Prize for their discovery of small RNA (miRNA) that control proteins synthesis post-transcriptional in Caenorhabditis [17]. By 2001, it was shown that these miRNAs far from being specific in worms were small molecules that regulate gene expression in eukaryote. Since then, thousands of miRNAs have been identified in different organs and specifically in the mammary gland and even in milk secretion. In mammary gland, miRNAs modulate development and regression. Several miRNAs are secreted in milk inside vesicles that give them protection from the low gastric pH. It was postulated that milk miRNAs could regulate gene expression in the newborn. Still it is controversial, and further research is needed to indicate if milk miRNAs are biological active ones there are absorbed [18, 19]. In Chapter 4, Dr. Duy and Dr. Ibeagha-Awemu describe in detail the state-of-the-art on noncoding RNA in the ruminant mammary gland.

Our knowledge on mammary gland physiology has increased considerably in the last decades. This book offers to the readers an update on research in four important areas: influence of melatonin in lactation, mammary gland development, signaling process in the mammary gland involution, and the role of miRNAs in mammary gland physiology. The study of comparative physiology lactation contributes to understanding biological process than could be present in all species but less evident in some and provides a wider understanding of the lactation process. The discovery of miRNAs definitely opens a new era in the study of gene expression. All these studies—plus the new molecular technology available—have increased and certainly will increase even more, our knowledge in the mammary gland and lactation, a captivating physiology process.

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References

[1] Baker JR. Grey seal (*Halichoerus grypus*) milk composition and its variation over lactation. British Veterinary Journal. 1990;**146**(3):233–238

[2] Akers RM. Functional development of the mammary gland. In: Lactation and the Mammary Gland. Chapter 3. Wiley-Blackwell; Hoboken, New Jersey, United States, 2002. pp. 66–87. ISBN: 978-0-8138-2992-0

[3] Ribeiro ST, Vainstein MH, Ulhoa CJ. Free secretory component and lactoferrin of human milk inhibit the adhesion of enterotoxigenic *Escherichia coli*. Journal of Medical Microbiology. 1995;**42**(1):3–9

[4] Neville MC. Lactation and its hormonal control. Chapter 57. In: Physiology of Reproduction. 3rd ed. Knobil and Neill's. Academic Pres, Elsevier; Cambridge, Massachusetts, United States; 2006. pp. 2983-3036. eBook ISBN: 9780080535272

[5] Mccarthy EF, Mcdougall EI. Absorption of immune globulin by the young lamb after ingestion of colostrum. Nature. 1949;**164**(4165):354

[6] Manthey CF, Autran CA, Eckmann L, Bode LJ. Human milk oligosaccharides protect against enteropathogenic Escherichia coli attachment in vitro and EPEC colonization in suckling mice. J Pediatr Gastroenterol Nutr. 2014;**58**(2):165–168

[7] Boudry G, Hamilton MK, Chichlowski M, Wickramasinghe S, Barile D, Kalanetra KM, Mills DA, Raybould HE. Bovine milk oligosaccharides decrease gut permeability and improve inflammation and microbial dysbiosis in diet-induced obese mice. Journal of Dairy Science. 2017;**100**:2471–2481. pii: S0022-0302(17)30072-3. DOI: 10.3168/jds.2016-11890

[8] Lammerts van Bueren A, Mulder M, Leeuwen SV, Dijkhuizen L. Prebiotic galactooligosaccharides activate mucin and pectic galactan utilization pathways in the human gut symbiont *Bacteroides thetaiotaomicron*. Scientific Reports. 2017;**7**:40478.

[9] Mehra R, Barile D, Marotta M, Lebrilla CB, Chu C, German JB. Novel high-molecular weight fucosylated milk oligosaccharides identified in dairy streams. PLoS One. 2014;**9**(5):e96040

[10] Ginther OJ. In Reproductive Biology of the Mare: Basic and Applied Aspects published by Equiservices; 1981. 413p. DOI: http://dx.doi.org/10.1016/S0737-0806(81)80003-2

[11] Hammond J and Marshall FHA. Reproduction in the Rabbit. Edinburgh: Oliver and Boyd; 1925. 210p

[12] Peel CJ, Fronk TJ, Bauman DE, Gorewit RC. Effect of exogenous growth hormone in early and late lactation on lactational performance of dairy cows. Journal of Dairy Science. 1983;**66**(4):776–782

[13] Bauman DE, Eppard PJ, DeGeeter MJ, Lanza GM. Responses of high-producing dairy cows to long-term treatment with pituitary somatotropin and recombinant somatotropin. Journal of Dairy Science. 1985;**68**(6):1352–1362

[14] Watson CJ, Burdon TG. Prolactin signal transduction mechanisms in the mammary gland: The role of the Jak/Stat pathway. Reviews of Reproduction. 1996;**1**:1–5. Review

[15] du Vigneaud V. Oxytocin, the principal oxytocic hormone of the posterior pituitary gland: Its isolation, structure, and synthesis. Experientia. 1955;**10**(Suppl 2):9–26

[16] Brennan AJ, Sharp JA, Lefevre C, Topcic D, Auguste A, Digby M, Nicholas KR. The tammar wallaby and fur seal: Models to examine local control of lactation. Journal of Dairy Science. 2007;**90**(Suppl 1):E66–E75

[17] Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature. 1998; **391**(6669):806–811

[18] Melnik BC, Kakulas F, Geddes DT, Hartmann PE, John SM, Carrera-Bastos P, Cordain L, Schmitz G. Milk miRNAs: Simple nutrients or systemic functional regulators?. Nutrition & Metabolism (London). 2016;**13**:42

[19] Auerbach A, Vyas G, Li A, Halushka M, Witwer K. Uptake of dietary milk miRNAs by adult humans: A validation study. F1000Research. 2016;**721**:1–14. DOI: 10.12688/f1000research.8548.1