The evolution of genomic imprinting: Epigenetic control of mammary gland development and postnatal resource control

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Abstract
Genomic imprinting is an epigenetically regulated process leading to gene expression according to its parental origin. Imprinting is essential for prenatal growth and development, regulating nutritional resources to offspring, and contributing to a favored theory about the evolution of imprinting being due to a conflict between maternal and paternal genomes for the control of prenatal resources—the so-called kinship hypothesis. Genomic imprinting has been mainly studied during embryonic and placental development; however, maternal nutrient provisioning is not restricted to the prenatal period. In this context, the mammary gland acts at the maternal-offspring interface providing milk to the newborn. Maternal care including lactation supports the offspring, delivering nutrients and bioactive molecules protecting against infections and contributing to healthy organ development and immune maturation. The normal developmental cycle of the mammary gland—pregnancy, lactation, involution—is vital for this process, raising the question of whether genomic imprinting might also play a role in postnatal nutrient transfer by controlling mammary gland development. Characterizing the function and epigenetic regulation of imprinted genes in the mammary gland cycle may therefore provide novel insights into the evolution of imprinting since the offspring’s paternal genome is absent from the mammary gland, in addition to increasing our knowledge of postnatal nutrition and its relation to life-long health.

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1 INTRODUCTION

Genomic imprinting is a highly regulated epigenetic process which governs gene expression from one of the two chromosome homologues according to parent of origin (Ferguson-Smith, 2011). Some imprinted genes are expressed from the paternally inherited allele while others are expressed from that inherited from the mother (Bartolomei & Ferguson-Smith, 2011). Imprinting is highly conserved in mammals, and mouse studies have provided insights into the repertoire of developmental and physiological pathways regulated by imprinted genes (Cleaton, Edwards, & Ferguson-Smith, 2014). The genetic control of growth and nutrient acquisition in-utero is partly mediated by imprinted genes. The prevailing theory of imprinting evolution argues that it is the result of a conflict of interest between maternally and paternally derived genes in the conceptus based around resource control via the placenta (Coan, Burton, & Ferguson-Smith, 2005; Moore & Haig, 1991; Spencer & Clark, 2014). Traditionally, genomic imprinting has been mainly studied in the placenta, where paternally expressed genes generally promote growth and maternally expressed genes suppress growth.

However, similar to the placenta supporting growth and development of the offspring prenatally, the mammary gland nourishes the offspring postnatally, practically extending maternal provisioning to the neonate. From a functional perspective, we hypothesize that any organ that regulates growth via mother–offspring nutrient exchange would depend heavily on genomic imprinting, as has been proposed from marsupial studies where most nutrient transfer between mother and fetus occurs ex utero (Stringer, Pask, Shaw, & Renfree, 2014). Most studies on genomic imprinting have focused on prenatal development, but postnatal development is also critical in influencing adult health status (Martin-Gronert & Ozanne, 2012). This includes postnatal neurological development, namely growth and organization of the central nervous system, and other systems: gastrointestinal maturation and colonization of gut microbiota, renal blood flow, the visual system and more. Many of these developmental processes are influenced by nutrition during early postnatal life and have long-term effects. This suggests that imprinting is involved, as a major mechanism regulating growth and development, to influence phenotype and match the response of the offspring to the environment it is likely to experience later, hence presenting fitness advantage.

Maternal support of the mammalian newborn is characterized by extensive postnatal care including lactation, which enables nutrient transfer by the mammary gland delivering milk to the neonate. Human milk is a dynamic, complex fluid containing nutrients and bioactive factors needed for infant health and development. It contains bioactive molecules produced and secreted by the mammary epithelium, or by cells carried within the milk, that protect against infections and contribute to immune maturation, organ development, and microbial colonization (Ballard & Morrow, 2013). Growing evidence suggests that breastfeeding protects against obesity and diabetes later in life (Victora et al., 2016), but the molecular mechanisms underlying this remain unknown.

The mammary gland is composed of epithelial and mesenchymal cells, including adipocytes, fibroblasts, blood vessels and immune cells, together forming a branching ductal tree embedded in adipose tissue (Gjorevski & Nelson, 2011; Shackleton et al., 2006). Pregnancy is a major modulator of mammary gland activity, with the alveolar epithelium proliferating and differentiating to yield milk-producing alveoli. It was shown that this regenerative capacity is enabled by mammary stem cells (Rios, Fu, Lindeman, & Visvader, 2014). Oxytocin stimulation leads to myoepithelial cell contraction and flow of milk for the suckling offspring. Upon weaning, apoptosis removes up to 80% of the epithelium in a coordinated process called involution (Gjorevski & Nelson, 2011). The process reinitiates for the subsequent pregnancy. We speculate that the normal development and dynamic regulation of the particular cell types in the eutherian mammary gland before, during and after lactation involves epigenetic control and specifically imprinting. Recent data has identified an epigenetic memory between the first and second pregnancy. Specifically, DNA methylation changes in the mammary gland are retained at specific genes that are upregulated during pregnancy, possibly priming mammary gland function for subsequent pregnancies. (Santos, Dolzhenko, Hodges, Smith, & Hannon, 2015). Accumulating evidence suggests that during evolution, imprinting in the mammary gland might have contributed to the development of lactation as a fundamental mammalian reproductive strategy. Examples include insulin and IGF2 in marsupials, and Grb10 in mouse (Cowley et al., 2014; Stringer, Suzuki, Pask, Shaw, & Renfree, 2012). Other studies which have generated cell type-specific gene transcriptional catalogues of the mouse mammary gland have also identified several imprinted genes (Bach et al., 2017; Lim et al., 2010), supporting the notion that genomic imprinting plays a role in this tissue.

A predominant theory to explain the evolution of imprinting since the discovery of the first mammalian imprinted genes, has been the parental conflict or kinship theory (Haig & Westoby, 1991; Moore & Haig, 1991). This theory is based around divergent interests between genes of maternal and paternal origin in offspring acting to regulate nutritional resource control and offspring growth. Since the father's genome is not represented in the mammary gland, this
precludes it as a site of parental conflict over resource allocation to offspring. If imprinting was found to play an important role in the eutherian mammary gland, the finding might invoke a different evolutionary selection for the imprinted genes involved. Another model that has been proposed is the maternal-offspring co-adaptation theory for the evolution of imprinting. This alternative to the conflict/kinship hypothesis infers a role for imprinting as a mechanism to boost offspring fitness by increasing the genetic integration of co-adapted offspring and maternal traits (Wolf & Hager, 2006).

Here, we focus on a vital and established biological process from a novel perspective, providing a different view to the evolution of genomic imprinting, and its relevance to reproductive physiology, integrating multiple disciplines and systems including organ development, and cellular and tissue physiology. Our perspective highlights the mammary gland as the postnatal analogue of the placenta in terms of imprinting control with implications for healthy development of mammalian offspring.

2 | THE ROLES OF IMPRIMTED GENES

Genomic imprinting, a major epigenetic process specific to mammals leading to parental-specific and monoallelic gene expression, has been extensively studied in the last few decades. About 150 imprinted genes have been identified and validated in the mouse and most of them are arranged in clusters of different sizes containing between 2 and 15 genes (Figure 1) (Barlow, 2011; Bartolomei & Ferguson-Smith, 2011). The monoallelic expression of imprinted genes is associated with the dosage sensitivity of many of them, and in several cases, their functions have been identified as a consequence of disruption in their dosage (Cleaton et al., 2014).

Imprinted genes are well known for having critical roles in many different biological processes, including growth, development, and placentation. Several human syndromes have been associated with alteration in genomic imprinting, including the neurodevelopmental syndromes Prader-Willi and Angelman (Horsthemke & Buiting, 2006), the outgrowth disorder Beckwith-Wiedemann syndrome (Weksberg, Shen, Fei, Song, & Squire, 1993), pseudohyoparathyroidism type 1a and 1b (Liu et al., 2000), transient neonatal diabetes (Mackay et al., 2008), and the growth restriction syndrome Silver-Russell (Abu-Amero et al., 2008). Additionally, many imprinted genes affect metabolism and are associated with adult obesity or leanness.

One of the key roles for imprinted genes is in prenatal growth control. For example, Insulin-like growth factor 2 (Igf2) affects nutrient transport across the feto-placental interface and placental and fetal growth (Constância et al., 2002). The gene Achaete-scute complex homolog 2 (Ascl2) is essential for trophoblast development, epidermal

**FIGURE 1**  Schematic representation of genomic imprinting. Paternal chromosome is blue, maternal is pink. The unmethylated regulatory regions are represented as white circles, and methylation as dark gray circles. The Dlk1-Dio3 imprinted domain is shown as an example, it is comprised of Meg3 and multiple small-noncoding RNA that are expressed from the maternally inherited chromosome, and three protein-coding genes, Dlk1, Rtl1, and Dio3 that are expressed from the paternal chromosome. Arrows indicate the direction of transcription.
development, myogenesis, and intestinal stem cell development (Bogutz et al., 2018) and paternally expressed gene 10 (Peg10) and Peg 11 are essential regulators of mid-gestation placental function (Ito et al., 2015; Sekita et al., 2008). Peg3 is expressed in the placenta and in maternal brain and in one study has been found to affect maternal care and the pre- and postnatal growth of pups (Curley, Barton, Surani, & Keverne, 2004); however, a more recent study did not reproduce this result and concluded that Peg3 does not influence these parameters (Denizot et al., 2016). Solute carrier family 22 member 2 (Slc22a2) encodes transporters which regulate transplacental solute exchange (Jonker, Wagenaar, van Eijl, & Schinkel, 2003). Concordant with the behavior of these aforementioned genes in prenatal growth, intrauterine growth restriction has been associated with expression alteration in various other imprinted genes such as Phlda2, Dlk1, Cdkn1c, Igf2r, Snrpn, Ube3a, and Gnasxd (Cleaton et al., 2014; Ishida & Moore, 2013).

A recurrent theme in the postnatal function of imprinted genes is the regulation of metabolism from early neonatal stages to adulthood in multiple tissue and pathways. Disruption in imprinted gene expression has been linked to perinatal lethality, for example, in the case of Gnasxl (Fernández-Rebollo et al., 2012). In early postnatal stages, perturbed DLK1 and Dio3 levels have been associated with nonshivering thermogenesis in brown adipose tissue, essential to prevent hypothermia (Hernandez, Garcia, & Obregon, 2007), and other imprinted genes such as Gnas, Gnasxl, Ndn, and Dio3 are involved brown adipose tissue metabolism (Peters, 2014). In the adult, several mouse mutant studies associate increased or reduced imprinted gene expression with adult obesity and the metabolic syndrome; examples include Gnas, Mest, Peg3, Ndn, Igf2, and Dlk1 (Chen et al., 2005, 2012; Peters, 2014).

Many imprinted genes are expressed in the brain regulate neurological functions including neurogenesis, sleep, memory and learning, and social behavior (Tucci et al., 2019). In addition, imprinted genes in the brain regulate maternal care for example, Peg3, Peg1/Mest and Magel2 (Lefebvre et al., 1998; Schaller et al., 2010), and in particular feeding and suckling in neonates for example, Peg3, Dlk1, Gnasxl and Magel2 (Teixeira da Rocha et al., 2009; Peters, 2014).

3 | CURRENT THEORIES OF THE EVOLUTION OF GENOMIC IMPRINTING

The underlying reasons for the emergence of genomic imprinting in mammals remain unknown, however, as these genes are monoallelically expressed they should stipulate an advantage to sustain this mechanism. There are two main theories attempting to address the evolutionary origin of this monoallelic gene expression pattern: The kinship theory and the maternal-offspring co-adaptation theory (Haig, 2000; Wolf & Hager, 2006). The kinship theory (also known as the parental-conflict hypothesis) suggests that a conflict of interest exists between the maternal and paternal genes in the offspring around the acquisition of resources specifically at the stages when the offspring is dependent on maternal resources for its growth. Simply, the kinship theory is taking into account the fact that a single mother can have multiple offspring from different fathers, while all the offspring are related in the same manner to the mother. From the paternal genetic perspective, the goal is to ensure the fitness and survival of his offspring, even if it will exhaust maternal resources. Maternally expressed genes, according to this hypothesis, have evolved to optimize resources in order to provide for additional offspring in the future. This theory is supported by the fact that usually paternal genes promote growth whereas maternal genes suppress growth.

Alternatively, the maternal-offspring coadaptation theory argues that imprinted genes evolved to act co-adaptively and optimize both the offspring’s development and maternal provisioning. The theory claims that exclusive expression of maternal genes is facilitated by natural selection, boosting the adaptive integration of the offspring and maternal genomes and subsequently contributing to higher offspring fitness. The maternal-offspring coadaptation theory is supported by the fact that cross-fostered mice pups receive more provisioning from foster mothers of their own maternal strain irrespective of their father’s strain (Hager & Johnstone, 2003). This hypothesis is consistent with the pleiotropic effects of many imprinted genes. For example, Peg3 has been suggested to be involved in maternal care, maternal nutrition provision and placental nutrient functions (Curley et al., 2004), but in the offspring, it acts in the hypothalamus to regulate attachment to the teat and suckling (Champagne, Curley, Swaney, Hasen, & Keverne, 2010). Dlk1 is secreted by the conceptus into the maternal circulation and controls nutrient partitioning in mother, a benefit that allows effective glucose metabolism across the placenta to the conceptus and lipid metabolism provision for mother (Cleaton et al., 2016).
FUNCTIONAL COMPARISON BETWEEN THE PLACENTA AND THE MAMMARY GLAND

We support the idea first proposed for marsupial mammals (Stringer et al., 2014), that the mammary gland represents the functional equivalent of the placenta in the postnatal stage of eutherian mammals. Both these organs support the normal growth and development of the offspring. The placenta is an extremely specialized organ supporting the fetal normal growth and development during pregnancy (Gude, Roberts, Kalionis, & King, 2004). The mammary gland is the organ that provides milk to the offspring postnatally. The milk is produced and secreted by the mammary epithelium, and contains a plethora of molecules with diverse functions, cells, and exosomes (Manca et al., 2018).

Both organs, though they function at different stages, share several common functions, and here we summarize the similarities between the placenta and the mammary gland (Figure 2).

4.1 | Nutritional support

The placenta, acts to provide nutrients and oxygen to the fetus. Maternal blood contacts directly with placental trophoblast cells and enables constant supply of nutrients to the developing embryo. This interaction takes place in the intervillous space, which is the site where the maternal basal plate exchanges nutrients with the fetal blood vessels, at the terminal regions of the chorionic villi (Gude et al., 2004). The placenta acts to provide oxygen, carbohydrates (mainly glucose which is the primary source of energy for the fetus), amino acids for protein synthesis, lipids (including free fatty acids, triglycerides, phospholipids, cholesterol), and more. Water transfer occurs through hydrostatic and osmotic pressure, and vitamins and minerals pass both passively and actively, like iron which dissociates from transferrin at the placental interface (Sibley et al., 2002; Štulc, 1997).

The mammary gland is an extraordinarily adaptive organ, which evolved over 300 million years ago to provide nutrition to the neonate (Visvader & Stingl, 2014). It is capable of rapid complex development to produce milk during lactation, and remodeling and apoptosis upon cessation of this process (Macias & Hinck, 2012; Watson, 2006). The milk is uniquely suited to the offspring, both in the composition of its nutrients as well as nonnutritive bioactive factors, which together supporting survival and healthy development (Ballard & Morrow, 2013). The composition of the milk is very plastic, and changes over time to match the needs and age of the offspring in its mineral and fat content (Vaughan, Weber, & Kemberling, 1979). The milk composition is remarkably conserved across populations, despite variation in genetics and maternal nutritional status. It contains water, proteins, lipids, vitamins and minerals, amino acids, oligosaccharides and the disaccharide lactose. Additionally, there are numerous growth factors which contribute to intestinal maturation, for example EGF, neuronal growth factors (BDNF, GDF, CNTF), Insulin like growth factors IGF-I and IGF-II and vascular system growth factors like VEGF. Together, these macronutrients, micronutrients and growth factors contribute to the development and healthy thriving of the offspring.

4.2 | Immunity

The placenta functions as a barrier between the mother and the fetus, capable of responding to pathogens (Mor & Cardenas, 2011). It can act to protect the fetus against infections and maternal diseases, although some viruses such as HIV, CMV, rubella, and others can be transmitted across the placenta. Furthermore, the placenta embodies an immune
function, containing active lymphocytes, Hofbauer cells, neutrophils, natural killer cells, and T-cells (Hurtado et al., 2010). Maternal antibodies, mainly immunoglobulin G (IgG), cross the placenta by pinocytosis (Gude et al., 2004; Palmeira, Quinello, Silveira-Lessa, Zago, & Carneiro-Sampaio, 2012), depending on gestational age, IgG subclass, and maternal levels of that particular immunoglobulin. Evidently, the newborn’s repertoire of IgG antibodies correlate with maternal ones (Palmeira et al., 2012). The placental transfer of immunoglobulins to the fetus is an adaptive mechanism that confers short-term passive immunity.

Similarly, milk protects against infection and inflammation assisting and benefiting the offspring’s immune maturation and ensuring its survival (Ballard & Morrow, 2013). Indeed, the first bioactive proteins identified in the milk were immunoglobulins; transfer of immunity from mother to offspring has been described early in the 20th century (Witebsky, Anderson, & Heide, 1942). Milk composition changes during the lactation period and the first fluid produced by the mammary gland after delivery, the colostrum is exceptionally rich in immunologic factors. Both the colostrum and the mature milk contain immunoglobulins (Ig) which belong predominantly to the IgA class, but IgM and IgG are also found in low levels, providing immune protection to the infant (Van De Perre, 2003). The milk also contains maternal cells like macrophages, leukocytes, T-cells, and multipotent mesenchymal milk stem cells (Hassiotou et al., 2012; Patki, Kadam, Chandra, & Bhonde, 2010). Cytokines and chemokines also are able to cross the intestinal barrier of the neonate and influence immune activity, providing an additional layer of communication between mother and offspring (Gersting, Kotto-Kome, Du, Christensen, & Calhoun, 2003). Additionally, passive immune protecting factors including lysozymes and bile salt stimulating lipase provide the innate immune system (Hennet & Borsig, 2016).

4.3 | Endocrine signaling

The placenta releases hormones into both the maternal and fetal circulations to affect and maintain pregnancy, communicating bi-directionally in a highly orchestrated manner to govern the normal growth and function of the placenta and ensuring the healthy growth of the fetus. The conceptus influences the provision of maternal resources via the endocrine signals that regulate maternal metabolism (Murphy, Smith, Giles, & Clifton, 2006). For example, the imprinted gene product DLK1 is an endocrine signaling molecule that functions in this way. It is produced by the fetus and then transported to the maternal circulation where it functions to partition maternal metabolism. In the absence of fetal DLK1, the maternal metabolic response to pregnancy is impaired resulting in compromised lipid metabolism possibly due to impaired growth hormone (GH) release (Cleaton et al., 2016).

Various endocrine, paracrine and autocrine factors are produced by the placenta, including estrogen, progesterone, growth factors (EGF, IGF-I and –II, and others), glucocorticoids which are required for organ maturation and fetal growth. Generally, hormones produced by the placenta influence maternal metabolism, nutrient intake and blood flow necessary to promote placental development and growth.

The mammary gland is also a tissue that is subject to extensive endocrine signaling; it responds to many signaling molecules including estrogen, progesterone, prolactin, and glucocorticoids necessary for its development during gestation and lactation (Brisken & O’Malley, 2010). Some cell populations in the mammary luminal epithelium are defined by the existence of hormone receptors on their surface. During puberty, the ductal morphogenesis process is partially induced by GH, insulin-like growth factor (IGF1), and estrogen. In the mature mammary gland, the virgin state is constantly influenced by oscillating progesterone, and upon pregnancy, alveologenesis is induced by prolactin together with progesterone. Prolactin continues to be crucial throughout the lactogenesis stage (Macias & Hinck, 2012).

Milk itself also contains a plethora of hormones. Milk calcitonin and its precursor function in the development of enteric neurons (Koldovsky, 1994). Similarly, somatostatin regulates gastric epithelial growth in the offspring. Metabolic hormones are also major components of the milk; these include adiponectin, which can cross the intestinal barrier and modify infant metabolism, leptin which affects appetite and with ghrelin regulates energy stores, erythropoietin (Epo) responsible for increasing red blood cells in the infant (Ballard & Morrow, 2013), and insulin which can interact with intestinal mucosa and promote gut maturation (Savino & Liguori, 2008; Shehadeh et al., 2003).

4.4 | Thermal regulation

The placenta together with the maternal environment provides thermal regulation to the fetus in order that it maintains a relatively constant body temperature for a successful pregnancy and optimal function of metabolic pathways. In many
mammals, fetal temperature typically exceeds maternal temperature by 0.5–1°C. Its own metabolism in utero generates heat which is released to the maternal environment mostly moving to the placenta. The placenta in turn serves as a heat exchanger, used to transfer heat energy from the fetus to the mother (Schröder & Power, 1997). Studies have shown the presence of inhibitors of nonshivering thermogenesis in the placenta such as prostaglandins and adenosine (Schröder & Power, 1997). Additionally, it has been found that thermal stress affects placental size and subsequently fetal growth (Wells, 2002).

The milk fat content contributes to the development of adipose tissue in the neonate and subsequent thermal regulation, but there are other factors promoting thermal regulation in the offspring as well. In milk, irisin or FNDC5, a myokine secreted in response to activation of peroxisome proliferator-activated receptor γ (PPARγ) co-activator-1α (PGC-1α), functions as a facilitator of adipose browning, and thermogenesis. Brown adipose tissue is especially abundant in young offspring, generating large amounts of heat due to the presence of a unique uncoupling protein 1 (UCP1) supporting them against hypothermia and premature death (Aydin, Kuloglu, & Aydin, 2013; Boström et al., 2012). Fibroblast growth factor (FGF21), a hormonal factor is present in rodent and human milk and has a powerful effect in the neonate where it induces brown adipose tissue thermogenesis (Gavaldá-Navarro et al., 2015). Milk also contains small RNA molecules such as microRNAs (miRNAs) (Manca et al., 2018), one of these miRNAs, miRNA-155, is present in large amounts in cow’s milk (Melnik, John, & Schmitz, 2013) and targets the adipogenic transcription factor CCAAT/ enhancer-binding protein β (C/EBPβ) promoting lipid and energy storage. Other breast milk specific lipids such as alkylglycerol-type (AKG-type) function in the maintenance of beige adipose tissue in the infant (Yu et al., 2019).

4.5 | Circadian rhythm

Physiological rhythms entrained by the circadian clock are present in all organs. In mammals they are driven by the suprachiasmatic nucleus in the hypothalamus which is the central regulator of endocrine, autonomic and behavioral cues to control 24 hour clock. In the placenta, all canonical circadian genes are expressed, and Bmal1, Per1, and Per2 display circadian variation with peaks in the active phase (Ratajczak, Herzog, & Muglia, 2010; Waddell, Wharfe, Crew, & Mark, 2012; Wharfe, Mark, & Waddell, 2011), suggesting that this may affect downstream genes that mediate metabolism and other processes. Studies have shown that the neurohormone melatonin, can limit the adverse effect of undernutrition on placental and fetal growth (Richter, Hansell, Raut, & Giussani, 2009). Glucocorticoids, also transmitting circadian information from mother to placenta and fetus show zone dependent and rhythmic expression in the placenta (Waddell et al., 2012); however, further studies are necessary to decipher the regulation and consequences of the placental circadian clock.

Breast milk also provides a clock to the neonate who is born without circadian rhythm and sleeps at random times. The content of breast milk changes throughout the day; for example, melatonin is present in a rhythmic manner being undetectable during daytime and dramatically increasing in the evening, peaking at night followed by a decrease in its levels towards the morning. This might contribute time of the day information to the breast-fed infant and mimics melatonin levels in maternal blood (Illnerová, Buresová, & Presl, 1993). Milk amino acids display a periodic pattern and it has been shown that the circadian rhythm of tryptophan in milk affects the rhythm of 6-sulfatoxymelatonin and sleep in newborn (Cubero et al., 2005). Methionine also has been shown to exhibit rhythmic variation. Milk nucleotides have rhythmicity as well, particularly 5’AMP, 5’UMP, and 5’GMP which show increased concentration at night (Sánchez et al., 2009). Fat concentrations show circadian variation, and breast milk tends to be fattier in the evening (Moran-Lev et al., 2015). It is very likely that more components of the milk also have rhythmic pattern, to suit perfectly the needs of the neonate and help its adaptation to the new environment.

5 | Maternal Support and Lactation

Maternal support of the mammalian newborn is characterized by extensive postnatal care including lactation which enables nutrient transfer by the mammary gland delivering milk to the neonate. Human milk is a dynamic, complex fluid containing nutrients and bioactive factors needed for infant health and development. It contains thousands of bioactive molecules produced and secreted both by the mammary epithelium and by cells carried within the milk. These protect against infections and contribute to immune maturation, organ development, and microbial colonization (Ballard & Morrow, 2013). Examples include lipids, immunoglobulins, cytokines, growth factors, metabolic hormones,
and oligosaccharides that promote thriving of beneficial gut microbiota and vitamins (Gura, 2014). Recent studies have shown that breast milk contains other components which impact the breastfed infant including miRNAs (Kosaka, Izumi, Sekine, & Ochiya, 2010) possibly in exosomes (Munch, Harris, Mohammad, Benham, & Pejerrey, 2013; Zhou et al., 2012), stem cells, and other progenitor cell types, endothelial cells, and leukocytes which are mostly studied due to their protective properties and ability to infiltrate the infant's tissues (Hassiotou et al., 2013).

Breastfeeding improves the survival, and development of the infant. However, the health and economic costs of sub-optimal breastfeeding are largely unrecognized. According to recent estimates, increasing breastfeeding to near universal levels could prevent 823,000 annual deaths in children under 5 years and 20,000 annual deaths from breast cancer (Victora et al., 2016). Children who are breastfed for longer periods have lower infectious morbidity and mortality, than those who are breastfed for shorter periods, or not breastfed. Growing evidence suggests that breastfeeding protects against obesity and diabetes later in life (Victora et al., 2016). Breastfeeding also benefits mothers by preventing breast cancer, and reducing risk of diabetes and ovarian cancer by 30% (Victora et al., 2016).

6 | MAMMARY GLAND DEVELOPMENT ENABLES ITS SUPPORT IN NUTRITIONAL RESOURCING

The mammary gland is composed of epithelial and mesenchymal cells, including adipocytes, fibroblasts, blood vessels, and immune cells which together form a branching ductal tree embedded in adipose tissue (Gjorevski & Nelson, 2011; Shackleton et al., 2006). The development of the mammary gland occurs over the lifetime of an individual and each step is regulated temporally and by hormonal constraint. Many signal pathways are deployed over multiples stages of its normal development indicating a highly regulated sophisticated dynamic cyclical system that uniquely integrates a wide range of molecular, cellular, and physiological processes. Pregnancy is a major modulator of mammary gland activity, with the alveolar epithelium proliferating and differentiating to yield milk-producing alveoli primarily under the control of progesterone and prolactin. Interstitial adipocytes disappear as the proliferating epithelial cells occupy the available interductal space while at the same time increasing angiogenesis which gives rise to capillaries surrounding the alveoli (Macias & Hinck, 2012). It was recently shown that this regenerative capacity is enabled by mammary stem cells (Rios et al., 2014). Oxytocin stimulation leads to myoepithelial cell contraction and flow of milk for the sucking offspring. Upon weaning, apoptosis removes up to 80% of the epithelium, concomitantly with alveolar cell detachment and accumulation of shed cells in the lumen, this occurs in a two-phase process called involution. The entire developmental cycle is shown in Figure 3 (Gjorevski & Nelson, 2011). The process reinitiates for the subsequent pregnancy. The normal development and dynamic regulation of the particular cell types in the mammary gland before, during, and after lactation suggests that epigenetic control and specifically imprinting may be implicated.

7 | EVIDENCE FOR EPIGENETIC REGULATION OF MAMMARY GLAND DEVELOPMENT

In recent years several studies have explored whether epigenetic regulation is important for mammary gland development (Dravis et al., 2018; Pal et al., 2013; Santos et al., 2015). These reports are not necessarily related to imprinting, which is a special case of epigenetic regulation, but imply that the plasticity of this tissue and the rapid changes occurring during its development including cell differentiation and tissue remodeling suggest that its temporal regulation might integrate previously undescribed epigenetic controls to establish, maintain, and reverse cellular functions. There are multiple levels of epigenetic regulation including DNA methylation and histone tail modifications which contribute to chromatin topological states that, along with transcription factors, regulate genome function. Several groups have obtained data using methods like ATAC-Seq, or ChIP-Seq, that interrogate chromatin states and some of them correlate chromatin accessibility to gene expression. Most commonly this is conducted in the context of breast cancer and tumorigenesis hence little is understood about the dynamic epigenetic landscape of the normal mammary cycle. Cancer-associated epigenetic changes can be influenced by many factors including age, environment, and disease; hence, comparison between studies must take into account these differences.

Several reports have shown the importance of epigenetic regulatory mechanisms for normal mammary gland development. Dnmt1 is indispensable for mammary stem cell (MaSC) maintenance (Pathania et al., 2015). The key H3K27 methyltransferase, Ezh2, is required for normal mammary gland development and its absence results in reduced
accumulating evidence suggests not only that epigenetic regulation plays a role in mammary gland development, but also that a specific type of such epigenetic regulation—genomic imprinting in the mammary gland—might have contributed to the evolution of lactation development as a mammalian fundamental reproductive strategy. This is important for evolutionary theories of imprinting since the paternal genome makes no contribution to the development of the mother's mammary gland and hence an evolutionary role for imprinting in mammary development would be inconsistent with the kinship theory for the evolution of imprinting proposed by Haig and colleagues.

In marsupials, a smaller subset of genes is imprinted compared to eutherian mammals, pregnancy is shorter, and the major provision of nutrition is supplied through suckling, with the mammary gland delivering milk to the altricial neonate. Renfree and coauthors identified the specific imprinting of insulin (Ins2 in mice) and IGF2 in this tissue...
During postnatal stages, maternal provision continues and is known to be crucial for short and long-term health and disease susceptibility hence investigating imprinting in the mammary gland has the potential to provide useful insights because of its predominant role in nutritional support of its altricial neonate (Stringer et al., 2014). They have proposed that imprinting in the marsupial mammary gland parallels eutherian placenta imprinting. To test this idea, it is important to determine whether there is an important role for imprinting in the eutherian mammary gland; however, such imprinting studies have been limited. Grb10 has been shown to be maternally expressed and paternally repressed in murine mammary glands. It is expressed from the maternal allele in mouse mammary glands, and has been found to be involved in controlling supply/demand in postnatal stages (Cowley et al., 2014). A cell type-specific gene expression catalogue of the mouse mammary gland has also identified enrichment in several expressed imprinted genes in MaSC, including Meg3, Peg3, and Nmat (Lim et al., 2010). Another study which explored the role of DNA methylation in pregnancy and aging found high expression of Igf2r in luminal progenitors in virgin females, and Rian in luminal progenitors of pregnant females (Huh et al., 2015).

We conducted a systematic review of imprinted gene expression in mammary cells in other published datasets. We determined that Gnas, Grb10, Snrpn, Rasgrf1 were all expressed in different stages of mammary gland development (Fu et al., 2015), and a single-cell RNA sequencing study of mammary epithelial cell dynamics identified expression of Gnas, Rasgrf1, H13, and Ube3a (Bach et al., 2017). A summary of the expression of imprinted genes in the mammary gland along with a diagrammatic representation of these cell types is shown in Figure 4a,b.

Deletion of the paternally expressed imprinted gene, Peg3, results in impairment of milk let-down in nursing mothers but is also essential in the offspring for this process; findings which together support the maternal-offspring coadaptation theory of imprinting (Frey & Kim, 2015). However, another study found no lactation deficiencies (Denizot et al., 2016), possibly due differences in the position of the deletion, the genetic background of the mouse models used, or the methodologies applied. Interestingly, a more recent study shows that oxytocin receptor is regulated by Peg3 (Frey et al., 2018), suggesting that Peg3 can influence milk production as a secondary effect by influencing expression of the oxytocin receptor. Igf2, another imprinted gene expressed from the paternal allele, mediates prolactin-induced morphogenesis in the mammary gland (Brisken et al., 2002), and has been shown to be produced specifically by hormone-receptor positive cells in early pregnancy (De Silva, Kunasegaran, Ghosh, & Pietersen, 2015). Recently, it has been reported that paternally expressed Mest is involved in mammary gland maturation; specifically, its expression is increased during gestation contributing to the formation and proliferation of alveoli (Yonekura et al., 2019). The epithelium is not the only site for imprinted gene expression since a study found differential allelic expression of GNAS in human mammary adipose tissue samples (Klenke, Siffert, & Frey, 2011).

It has been shown that there is considerable deregulation of genomic imprinting, particularly downregulation, in breast cancer samples (Goovaerts et al., 2018), but it is not yet clear whether these effects are driving tumorigenesis or are secondary consequences. Given that some imprinted genes such as Igf2 function as mitogens, and others such as Cdkn1c are tumor suppressors, it is likely that loss of normal imprinting has functional implications for breast cancer.

In 2017, an RNA sequencing study in various tissues concluded that imprinting does not play a role in lactation, due to only minor difference in imprinting being detected between virgin and lactating mammary glands (Andergassen et al., 2017). However, it is possible that this study, which pooled all the mammary cell types together, did not have the sensitivity to address this in full.

Altogether, the evidence summarized in Figure 4(b), indicates that a more thorough systematic approach is necessary to fully understand the significance and the physiological role of imprinted genes in the mammary gland and in postnatal provisioning.

9 | CONCLUSION

Extensive studies have highlighted the importance of genomic imprinting in many different contexts and tissues. However, most of the research has been focused on the prenatal stages and the contribution to growth and development. During postnatal stages, maternal provision continues and is known to be crucial for short and long-term health and disease susceptibility hence investigating imprinting in the mammary gland has the potential to provide useful insights into the evolution and function of this process. We look at genomic imprinting from a more holistic point of view, taking into account not only an individual organ, stage or process, but a more general and integrating consideration of the system. In this case, our perspective includes parent and offspring, combined with biological insight from the organs playing an important role in this bidirectional relationship.
We support the idea that the mammary gland together with the milk represents the postnatal equivalent of the placenta, and provide evidence supporting their functional similarities, not only in their nutritional role but also in delivering immune protection, circadian rhythm, thermal regulation, and endocrine function. This idea fits with the

**FIGURE 4**  (a) A schematic representation of the various cell types comprising the adult mammary gland. (b) Table showing the currently available data on imprinted gene expression in mammary gland cells, allelic expression in the mammary gland if available and the relevant reference. Background color represents the corresponding cell type in (a). White background represents information which does not refer to a single cell type.

We support the idea that the mammary gland together with the milk represents the postnatal equivalent of the placenta, and provide evidence supporting their functional similarities, not only in their nutritional role but also in delivering immune protection, circadian rhythm, thermal regulation, and endocrine function. This idea fits with the
maternal-coadaptation theory of genomic imprinting, as the milk provides many factors helping with the adaptation of the offspring to the new environment ex utero.

From the evolutionary point of view, multiple maternal organs take part in this adaptation, affecting mammary gland function and milk production. Of those, the brain is important, sending signals to the mammary gland, and also acting as a site for genomic imprinting. The imprinted gene \textit{Grb10}, supports this notion, controlling supply of nutrients from the mother, but in turn transmitting the demand of the offspring to its mother. Importantly, since the father's genome is not represented in the mammary gland, this precludes it as a site of parental conflict over resource allocation. If imprinting is found to be important in this eutherian tissue, this would not fit well with the existing hypotheses. It is possible that imprinting in the mammary gland is important as an epigenetic mechanism to control gene dosage and different selective pressures have acted at different times over evolution to confer imprinting.

The normal developmental cycle of the mammary gland is vital for this process, raising the question of whether genomic imprinting might also play a role in postnatal nutrient transfer by controlling mammary gland development. So far, we found multiple imprinted genes expressed in mammary cell types, but more data is required to determine the functional significance of these genes to the physiology of the mammary gland and lactation.

Although mammary gland research is highly driven by breast cancer, we could find supporting evidence for the existence of epigenetic regulation in the differentiation dynamics of the normal mammary gland, and data showing expression of imprinted genes. Intriguingly, perturbation of epigenetic mechanisms can lead to the onset of disease, but further studies in a normal environment are necessary to fully understand such mechanisms and their functions.

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CONFLICT OF INTEREST
The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS
\textbf{Geula Hanin}: Conceptualization-equal; data curation-lead; formal analysis-lead; funding acquisition-supporting; validation-equal; visualization-lead; and writing-original draft-lead. \textbf{Anne Ferguson-Smith}: Conceptualization-equal; formal analysis-supporting; funding acquisition-lead; validation-equal; visualization-supporting; writing-review and editing-lead.

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REFERENCES
Abu-Amero, S., Monk, D., Frost, J., Preece, M., Stanier, P., & Moore, G. E. (2008). The genetic aetiology of Silver-Russell syndrome. \textit{Journal of Medical Genetics}, 45(4), 193–199. \text{https://doi.org/10.1136/jmg.2007.053017}
Andergassen, D., Dotter, C. P., Wenzel, D., Sigl, V., Bammer, P. C., Muckenhuber, M., ... Hudson, Q. J. (2017). Mapping the mouse allelome reveals tissue-specific regulation of allelic expression. \textit{eLife}, 6(Xci), 1–29. \text{https://doi.org/10.7554/eLife.25125}
Aydin, S., Kuloglu, T., & Aydin, S. (2013). Copeptin, adropin and irisin concentrations in breast milk and plasma of healthy women and those with gestational diabetes mellitus. \textit{Peptides}, 47, 66–70. \text{https://doi.org/10.1016/j.peptides.2013.07.001}
Bach, K., Pensa, S., Grzelak, M., Hadfield, J., Adams, D. J., Marioni, J. C., & Khaled, W. T. (2017). Differentiation dynamics of mammary epithelial cells revealed by single-cell RNA sequencing. \textit{Nature Communications}, 8(1), 2128. \text{https://doi.org/10.1038/s41467-017-02001-5}
Ballard, O., & Morrow, A. L. (2013). Human milk composition. Nutrients and bioactive factors. \textit{Pediatric Clinics of North America}, 60(1), 49–74. \text{https://doi.org/10.1016/j.pcl.2012.10.002}
Barlow, D. P. (2011). Genomic imprinting: a mammalian epigenetic discovery model. \textit{Annual Review of Genetics}, 45(1), 379–403. \text{https://doi.org/10.1146/annurev-genet-110410-132459}
Bartolomei, M. S., & Ferguson-Smith, A. C. (2011). Mammalian genomic imprinting. *Cold Spring Harbor Perspectives in Biology*, 3(7), 1–17. https://doi.org/10.1101/cshperspect.a002592

Bogutz, A. B., Oh-McGinnis, R., Jacob, K. J., Ho-Lau, R., Gu, T., Gertenstein, M., ... Lefebvre, L. (2018). Transcription factor ASCL2 is required for development of the glycogen trophoblast cell lineage. *PLoS Genetics*, 14(8), 1–26. https://doi.org/10.1371/journal.pgen.1007587

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., ... Spiegelman, B. M. (2012). A PGC1α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, 481(7382), 463–468. https://doi.org/10.1038/nature10777

Brisken, C., Ayyannan, A., Nguyen, C., Heineman, A., Reinhardt, F., Jan, T., ... Weinberg, R. A. (2002). IGF-2 is a mediator of prolactin-induced morphogenesis in the breast. *Developmental Cell*, 3(6), 877–887. https://doi.org/10.1016/S1534-5807(02)00365-9

Brisken, C., & O’Malley, B. (2010). Hormone action in the mammary gland. *Cold Spring Harbor Perspectives in Biology*, 2(12), 1–15. https://doi.org/10.1101/cshperspect.a003178

Champagne, F. A., Curley, J. P., Swaney, W. T., Hasen, N. S., & Keverne, E. B. (2009). Paternal influence on female behavior: The role of Peg3 in exploration, olfaction, and neuroendocrine regulation of maternal behavior of female mice. *Behavioral Neuroscience*, 123(3), 469–480. https://doi.org/10.1037/a0015060

Chen, M., Berger, A., Kablan, A., Zhang, J., Gavrilova, O., & Weinstein, L. S. (2012). Gsα deficiency in the paraventricular nucleus of the hypothalamus partially contributes to obesity associated with Gsα mutations. *Endocrinology*, 153(9), 4256–4265. https://doi.org/10.1210/en.2012-1113

Chen, M., Gavrilova, O., Liu, J., Xie, T., Deng, C., Nguyen, A. T., ... Weinstein, L. S. (2005). Alternative Gnas gene products have opposite effects on glucose and lipid metabolism. *Proceedings of the National Academy of Sciences of the United States of America*, 102(20), 7386–7391. https://doi.org/10.1073/pnas.0408268102

Cleaton, M. A. M., Dent, C. L., Howard, M., Corish, J. A., Gutteridge, I., Sovio, U., ... Keverne, E. B. (2004). Coadaptation in mother and infant regulated by a paternally expressed imprinted gene. *PLoS Genetics*, 1(5), e12. https://doi.org/10.1371/journal.pgen.0010034

Coan, P. M., Burton, G. J., & Ferguson-Smith, A. C. (2005). Imprinted genes in the placenta—a review. *Placenta*, 26(Suppl.), 10–20. https://doi.org/10.1016/j.placenta.2004.12.009

Constâncio, M., Hemberger, M., Hughes, J., Dean, W., Ferguson-Smith, A., Fundele, R., ... Keverne, E. B. (2002). Placental-specific IGF-II is a major modulator of placental and fetal growth. *Nature*, 417(6892), 945–948. https://doi.org/10.1038/nature00819

Cowley, M., Garfield, A. S., Madon-Simon, M., Charalambous, M., Clarkson, R. W., Smalley, M. J., ... Ward, A. (2014). Developmental programming mediated by complementary roles of imprinted Grb10 in mother and pup. *PLoS Biology*, 12(2), e1001799. https://doi.org/10.1371/journal.pbio.1001799

Cubero, J., Valero, V., Sánchez, J., Rivero, M., Parvez, H., Rodríguez, A. B., & Barriga Ibarra, C. (2005). The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. *Neuroendocrinology Letters*, 26(6), 657–661.

Curley, J. P., Barton, S., Surani, A., & Keverne, E. B. (2004). Cocauditation in mother and infant regulated by a paternally expressed imprinted gene. *Proceedings of the Royal Society B: Biological Sciences*, 271(1545), 1303–1309. https://doi.org/10.1098/rspb.2004.2725

De Silva, D., Kunasegaran, K., Ghosh, S., & Pietersen, A. M. (2015). Transcripdmote analysis of the hormone-sensing cells in mammary epithelial reveals dynamic changes in early pregnancy. *BMC Developmental Biology*, 15(1), 1–14. https://doi.org/10.1186/s12861-015-0058-9

Denizot, A. L., Besson, V., Correra, R. M., Mazzola, A., Lopes, I., Courbard, J. R., ... Sasoon, D. A. (2016). A novel mutant allele of Pw1/Peg3 does not affect maternal behavior or nursing behavior. *PLoS Genetics*, 12(5), 1–20. https://doi.org/10.1371/journal.pgen.1006053

Dravis, C., Chung, C. Y., Lytle, N. K., Herrera-Valdez, J., Luna, G., Trejo, C. L., ... Wahl, G. M. (2018). Epigenetic and transcriptomic profiling of mammary gland development and tumor models disclose regulators of cell state plasticity. *Cancer Cell*, 34(3), 466–482.e6. https://doi.org/10.1016/j.ccell.2018.08.001

Ferguson-Smith, A. C. (2011). Genomic imprinting: The emergence of an epigenetic paradigm. *Nature Reviews Genetics*, 12(8), 565–575. https://doi.org/10.1038/nrg3032

Fernández-Rebollo, E., Maeda, A., Reyes, M., Turan, S., Fröhlich, L. F., Plagge, A., ... Bastephe, M. (2012). Loss of XLsα (extra-large α) imprinting results in early postnatal hypoglycemia and lethality in a mouse model of pseudohyoparathyroidism Ib. *Proceedings of the National Academy of Sciences*, 109(17), 6638–6643. https://doi.org/10.1073/pnas.1117608109

Frey, W. D., & Kim, J. (2015). Tissue-specific contributions of paternally expressed gene 3 in lactation and maternal care of *Mus musculus*. *PLoS One*, 10(12), 1–16. https://doi.org/10.1371/journal.pone.0144459

Frey, W. D., Sharma, K., Cain, T. L., Nishimori, K., Teruyama, R., & Kim, J. (2018). Oxytocin receptor is regulated by Peg3. *PLoS One*, 13(8), 1–12 https://doi.org/10.1371/journal.pone.0202476

Fu, N. Y., Rios, A. C., Pal, B., Soetanto, R., Lun, A. T. L., Liu, K., ... Visvader, J. E. (2015). EGF-mediated induction of Mcl-1 at the switch to lactation is essential for alveolar cell survival. *Nature Cell Biology*, 17(4), 365–375. https://doi.org/10.1038/ncb3117

Gavalda-Navarro, A., Honduares, E., Giralt, M., Mampel, T., Iglesias, R., & Villarroya, F. (2015). Fibroblast growth factor 21 in breast milk controls neonatal intestine function. *Scientific Reports*, 5, 1–13. https://doi.org/10.1038/srep13717

Gersting, J. A., Kotto-Kome, C. A., Du, Y., Christensen, R. D., & Callhoun, D. A. (2003). Bioavailability of granulocyte colony-stimulating factor administered enterally to suckling mice. *Pharmacological Research*, 48(6), 643–647. https://doi.org/10.1016/S1043-6618(03)00249-4
Stringer, J. M., Pask, A. J., Shaw, G., & Renfree, M. B. (2014). Post-natal imprinting: Evidence from marsupials. *Heredity, 113*(2), 145–155. https://doi.org/10.1038/hdy.2014.10

Stringer, J. M., Suzuki, S., Pask, A. J., Shaw, G., & Renfree, M. B. (2012). Selected imprinting of INS in the marsupial. *Epigenetics & Chromatin, 5*(1), 14. https://doi.org/10.1186/1756-8935-5-14

Štulc, J. (1997). Placental transfer of inorganic ions and water. *Physiological Reviews, 77*, 805–836. Retrieved from https://www.physiology.org/doi/abs/10.1152/physrev.1997.77.3.805

Teixeira da Rocha, S., Charalambous, M., Lin, S. P., Gutteridge, I., Ito, Y., Gray, D., ... Ferguson-Smith, A. C. (2009). Gene dosage effects of the imprinted delta-like homologue 1 (Dlk1/Pref1) in development: Implications for the evolution of imprinting. *PLoS Genetics, 5*(2), e1000392. https://doi.org/10.1371/journal.pgen.1000392

Tucci, V., Isles, A. R., Kelsey, G., Ferguson-Smith, A. C., Bartolomei, M. S., Benvenisty, N., ... Wilkins, J. (2019, February 21). Genomic imprinting and physiological processes in mammals. *Cell, 176*(5), 952–965. https://doi.org/10.1016/j.cell.2019.01.043

Van De Perre, P. (2003). Transfer of antibody via mother’s milk. *Vaccine, 21*(24), 3374–3376. https://doi.org/10.1016/S0264-410X(03)00336-0

Victora, C. G., Bahl, R., Barros, A. J. D., França, G. V. A., Horton, S., Krasevec, J., ... Richter, L. (2016). Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. *The Lancet, 387*(10017), 475–490. https://doi.org/10.1016/S0140-6736(15)01024-7

Visvader, J. E., & Stingl, J. (2014). Mammary stem cells and the differentiation hierarchy: Current status and perspectives. *Genes & Development, 28*(11), 1143–1158. https://doi.org/10.1101/gad.242511.114.targeted

Waddell, B. J., Wharfe, M. D., Crew, R. C., & Mark, P. J. (2012). A rhythmic placenta? Circadian variation, clock genes and placental function. *Placenta, 33*(7), 533–539. https://doi.org/10.1016/j.placenta.2012.03.008

Watson, C. J. (2006). Key stages in mammary gland development: Apoptosis and tissue remodelling that convert the mammary gland from milk factory to a quiescent organ. *Breast Cancer Research, 8*(2), 1–5. https://doi.org/10.1186/bcr1401

Weksberg, R., Shen, D. R., Fei, Y. L., Song, Q. L., & Squire, J. (1993). Disruption of insulin-like growth factor 2 imprinting in Beckwith-Wiedemann syndrome. *Nature Genetics, 5*(2), 143–150.

Wells, J. C. K. (2002). Thermal environment and human birth weight. *Journal of Theoretical Biology, 214*(3), 413–425. https://doi.org/10.1006/jtbi.2001.2465

Wharfe, M. D., Mark, P. J., & Waddell, B. J. (2011). Circadian variation in placental and hepatic clock genes in rat pregnancy. *Endocrinology, 152*(9), 3552–3560. https://doi.org/10.1210/en.2011-0081

Witebsky, E., Anderson, G. W., & Heide, A. (1942). Demonstration of Rh antibody in breast milk. *Proceedings of the Society for Experimental Biology and Medicine, 49*(2), 179–183. https://doi.org/10.3181/00379727-49-13506

Wolf, J. B., & Hager, R. (2006). A maternal-offspring coadaptation theory for the evolution of genomic imprinting. *PLoS Biology, 4*(12), 2238–2243. https://doi.org/10.1371/journal.pbio.0040380

Yonekura, S., Ohata, M., Tsuchiya, M., Tokita, H., Mizusawa, M., & Tokutake, Y. (2019). Peg1/Mest, an imprinted gene, is involved in mammary gland maturation. *Journal of Cellular Physiology, 234*(2), 1080–1087. https://doi.org/10.1002/jcp.27219

Yu, H., Dilbaz, S., Coßmann, J., Hoang, A. C., Diedrich, V., Herwig, A., ... Röszer, T. (2019). Breast milk alkylglycerols sustain beige adipocytes through adipose tissue macrophages. *Journal of Clinical Investigation, 129*(6), 2485–2499. https://doi.org/10.1172/JCI125646

Zhou, Q., Li, M., Wang, X., Li, Q., Wang, T., Zhu, Q., ... Li, X. (2012). Immune-related MicroRNAs are abundant in breast milk exosomes. *International Journal of Biological Sciences, 8*(1), 118–123.

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