Published in final edited form as:

Semin Cell Dev Biol. 2018 September ; 81: 141–148. doi:10.1016/j.semcdb.2017.10.012.

Milk Lipid Regulation at the Maternal-Offspring Interface

Dengbao Yang¹, HoangDinh Huynh¹, and Yihong Wan¹

¹Department of Pharmacology, The University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA

Abstract

Milk lipids provide a large proportion of energy, nutrients, essential fatty acids, and signaling molecules for the newborns, the synthesis of which is a tightly controlled process. Dysregulated milk lipid production and composition may be detrimental to the growth, development, health and survival of the newborns. Many genetically modified animal models have contributed to our understanding of milk lipid regulation in the lactating mammary gland. In this review, we discuss recent advances in our knowledge of the mechanisms that control milk lipid biosynthesis and secretion during lactation, and how maternal genetic and dietary defects impact milk lipid composition and consequently offspring traits.

Keywords

lactating mammary gland; milk lipid; genetic defect; high fat diet; inflammatory milk

1. Introduction

1.1 Lactation

Lactation is a highly energy- and nutrient-demanding physiological process that is crucial for the normal development of the newborn mammals. Mother's milk is the sole and ideal food for the newborn mammals before they are able to eat and digest solid food. It is widely regarded as nutritious and protective for the early postnatal development as it can provide not only nutrients but also immune-defensive factors [1–3]. Lipids are one of the main constituents of milk, which makes the lactating mammary gland one of the most active organs for lipid synthesis, transport and secretion in the body [4–7]. For example, the mammary glands of a lactating mouse synthesize and secrete approximate 32 g of milk lipids over a lactation period of 20 days, equivalent to its entire body weight [5]. In humans, a lactating mother can secrete nearly 6 kg of milk lipids during a typical six-month lactation period [4]. Thus, milk lipid is an important source of both calories and essential fatty acids for the newborns. In mice, nearly 80% of calories needed for development of the neonate is

Corresponding author: Yihong Wan (yihong.wan@utsouthwestern.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare that they have no financial conflict of interest.

provided by milk lipids [7]. Although there are some differences in the compositions of milk from different species, the main regulatory mechanisms of milk synthesis and secretion are largely conserved [8].

1.2 Mammary Gland and Milk Lipid Synthesis and Secretion

Mammary gland is responsible for milk production during lactation, which is a very dynamic tissue continually undergoing changes in structure and function [9–11]. The development of mammary gland has been well characterized into five stages: embryogenesis, pubertal development, and development in pregnancy, lactation and involution [9, 10]. During the transition from pregnancy to lactation, the mammary glands undergo a complex set of development under the coordinated control of many hormonal, metabolic and secretory pathways [7, 12, 13], and finally the functional lactating mammary gland is composed of a branching network of ducts formed of epithelial cells ending in extensive lobulo-alveolar clusters that is ready for milk synthesis and secretion. Immediately after parturition, the activity of lipid biosynthetic enzymes increases rapidly in mammary gland resulting in secretion of milk with about 30% lipid [7, 14–16]. Milk lipid synthesis and secretion requires the coordination of multiple biochemical and cellular events in the mammary epithelial cell (MEC) [10, 17, 18]. Milk lipids in the form of milk fat globules (MFG) are produced in the milk-secreting cells called alveoli [12]. Up to 98% of milk lipids are triacylglycerides (TAGs) predominantly composed of short and medium chain (C8–C12) fatty acids (FAs) [8], thus a constant supply of FAs for TAG synthesis in lactating mammary gland is necessary. Overall, there are three types of substrate sources that can be utilized for synthesizing milk TAG: dietary fat, FAs mobilized from adipose tissue stores, and lipids synthesized from *de novo* synthesis [7, 8, 19, 20]. FA composition and secretion rate of milk TAG can vary depending on maternal genetics and environmental factors such as dietary fat [8, 21, 22]. A network of genes that is involved in regulating mammary lipid synthesis and secretion has been revealed including a number of transcription factors such as sterol regulatory element-binding proteins (SREBPs), liver X receptors (LXRs), and peroxisome proliferator-activated receptors (PPARs) [13, 23]. To date, lactation defects in many transgenic (TG)/knockout (KO) mice have been analyzed, and some of them have been reviewed by McManaman and his colleagues [11]. These studies contribute greatly to our understanding of genetic control of mammary gland development and the regulation of milk lipid synthesis and secretion. These genes include but not limited to prolactin (PRL) or prolactin receptor (PRLR) [24, 25], oxytocin [26, 27], insulin-like growth factor 1 (IGF1) [28], diacylglycerol transferase 1 (DGAT1) [29, 30], tyrosine kinase Src [31], protein kinase N1 (PKN1) [32], xanthine oxidoreductase (XOR) [33, 34], butyrophilin subfamily 1 member a1 (BTN1A1) [35], cell death-inducing DNA fragmentation factor α -like effector A (CIDEA) [36], adipophilin (ADPH) [37–39], and microRNA-150 [40].

In this review, we will summarize the recent advances about the lipid regulation at the maternal-offspring interface during lactation. Specifically, we will focus on how maternal genetic modifications and dietary factors such as high-fat diet (HFD) affect milk lipid regulation, and their subsequent consequences on the offspring development. Several gene targets closely related to milk lipid regulation including SREBP-1, serine/threonine-specific

protein kinase B (Akt/PKB), thyroid hormone responsive spot 14 (S14), PPAR γ , very low-density lipoprotein receptor (VLDLR), and adiponectin are discussed.

2. Genetic Control of Milk Lipid Biosynthesis and Secretion during Lactation

2.1 SREBP-1

It has been well known that lipid synthesis in liver and adipose tissue is regulated by a family of membrane-bound transcription factors designated as SREBP-1 pathway [41–43]. SREBP-1 regulates the expression of many key genes necessary for fatty acid synthesis by binding to the sterol response element (SRE) in their promoters. The two isoforms, SREBP-1a and SREBP-1c, are generated from differential translation start sites in the SREBP-1 transcript [43]. SREBP-1a can activate genes in both cholesterol and FA synthesis pathways, and SREBP-1c primarily activates genes required for FA and TAG synthesis [42–44]. The mRNAs for SREBP-1a, SREBP-1c, and several downstream targets are upregulated dramatically in the mammary gland at the onset of lactation [23, 45], suggesting a possible role in milk lipid synthesis. SREBP-1c-null mice show only very minor deficiencies in lipid synthesis during lactation, possibly due to the compensatory upregulation of SREBP-1a expression [45]. To test this possibility, complete loss of SREBP-dependent genes was achieved by deletion of SREBP cleavage-activating protein (SCAP) specifically in the MECs [45]. SCAP is both an escort for SREBPs and a sensor of sterols [42, 44, 46]. Disruption of SCAP severely decreased pup growth rate, but the pups did not die [45]. Consistent with the reduced mRNA expression of fatty acid synthase (FASN), insulin-induced gene 1 (INSIG1), mitochondrial citrate transporter (SLC25A1), and stearoyl-CoA desaturase 2 (SCD2) in SCAP KO mice, the proportion of *de novo* synthesized FAs in the milk decreased by 25%, suggesting that SREBP-dependent pathway is necessary for optimal lipogenesis in the lactating mammary gland. An *in vitro* study found that overexpression of SREBP-1 promoted *de novo* FA synthesis and TAG accumulation in goat MECs [47], further confirming the role of SREBP-1 pathway in milk lipid synthesis. In addition, SREBP-1 is involved in the regulation of bovine mammary lipid synthesis during diet-induced milk fat depression [48]. It should be noted that FA synthesis in the mammary gland may differ from that in liver and adipose tissue, as mammary alveolar cells contain thioesterase II, a special enzyme that terminates FA synthesis after the addition of 8–16 carbons [49]. Saturated FAs with 6–14 carbons are the major product of *de novo* FA synthesis in lactating mammary gland [50]. Longer chain FAs in milk are shown to originate from the diet or from mobilization of adipose tissue TAGs [51]. Polymorphisms in genes in the SREBP-1 signaling pathway and SCD are associated with altered milk FA composition [52, 53]. SREBP-1c is a known target of LXRs; and the activation of SREBP-1c by LXRs is accompanied by an increase in FA synthesis [54–56]. LXRs are members of the nuclear hormone receptor (NHR) superfamily that are bound and activated by oxysterols. One study in bovine MECs showed that activation of LXRs can enhance *de novo* FA synthesis [57]. Another one in goat MECs suggested that LXR α promotes the synthesis of monounsaturated FAs via the control of SCD1 in an SREBP-1-dependent manner [58]. In summary, genes in the LXR-SREBP-1 pathway play an important role in the regulation of milk lipid synthesis.

2.2 Akt

We have already known that SREBP-1 is an important regulator of secretory activation with regard to lipid biosynthesis. Recently this process has been suggested to be influenced by Akt [59–61], which is known to be activated by a wide variety of stimuli and can mediate many cellular and physiological processes through phosphorylation of numerous substrates [62]. Akt is expressed during mammary gland development, and its expression is upregulated during pregnancy and lactation and is decreased at the onset of involution [5, 63]. The roles of Akt in regulating lactation process have been examined using mouse genetic models [5, 64, 65]. Overexpression of constitutively activated Akt in the mammary glands of Akt TG mice results in delayed involution and onset of apoptosis [64]. Further analysis shows that Akt overexpression also results in precocious lipid droplet formation in MECs, as well as excess lipid synthesis causing the secretion of milk with significantly higher lipid content [5], suggesting that Akt upregulation may help meet the increased lipid biosynthetic demand during pregnancy and lactation, but Akt must be downregulated in order for a timely mammary gland involution to occur. Consistent with these *in vivo* observations, *in vitro* result shows that overexpression of recombinant human active Akt in mammary epithelial cell line CIT3 leads to an increase in glucose transport and lipid biosynthesis, further confirming the role of Akt in the developmental regulation of milk lipid metabolism in lactating mammary gland [5]. Indeed, a lactation defect is observed in the Akt TG mice, because the body weight of the pups in the litter is decreased by 50% over the first 9 days of lactation. The retarded growth of pups nursed by TG mothers may result from the inability of the pups to acquire sufficient quantities of milk by suckling, possibly due to the high viscosity of the milk [5]. In addition, Akt may also contribute to the regulation of milk secretion by modifying the formation and accumulation of cytoplasmic lipid droplets in MECs [5]. In a later study, the question whether Akt and which Akt isoform is required for these processes is answered by Akt KO mouse model. The results show that loss of Akt-1 but not Akt-2 specifically causes defects in glucose uptake and lipid synthesis in the lactating mammary gland, which is severe enough to lead to growth defects and pup mortality due to the insufficient quantities of milk [65]. Further deletion of one allele of Akt-2 in Akt-1-KO mice results in a more severe lactation defect (i.e. decreased milk production) due to the loss of terminal differentiation in the mammary gland during late pregnancy [66]. Decreased lactation capacity is also observed in insulin receptor substrate (IRS) null mice, and this might be associated with reduced insulin-dependent phosphorylation of mammary Akt [60]. Overall all these studies highlight that Akt is required for lactating mice to synthesize and secrete milk.

2.3 S14

S14 was first discovered in 1981 while screening rat hepatic proteins regulated by thyroid hormone [67]. S14 is highly expressed in lipogenic tissues including liver, adipose tissue and lactating mammary gland and associated with lipogenesis [68–71]. The roles of S14 in *de novo* lipogenesis have been reported as inhibition in liver and activation in lactating mammary gland, because S14 deletion increases hepatic *de novo* lipogenesis [72] but decreases the lipogenesis in lactating mammary gland [73]. The difference observed in these two tissues may be due to the coexpression of a paralogous S14 related gene (S14R or MIG12) in liver but not in lactating mammary gland as S14 and S14R can form

heterodimers that are determined to be inhibitory in lipogenesis through reducing acetyl-CoA carboxylase (ACC) polymerization and activity [73–76]. The absence of S14R in lactating mammary gland facilitates researchers to elucidate the lipogenic roles of S14 in this tissue. Transcriptional analyses show that S14 mRNA is upregulated by about two-fold at the onset of lactation [23]. Deletion of S14 in the lactating mammary gland reduces *de novo* lipid synthesis, and the milk from S14-null mother shows a 33% reduction in TAG levels distinguished by lower levels of medium-chain fatty acids (MCFAs) [73, 77]. Similar to the findings from the SREBP-1 and Akt study, S14 KO mice show a lactation defect reflected by a retarded pup growth due to the reduced TAG content in milk. The lactation defect can be rescued by provision of a HFD to the lactating dam [77]. TG mice overexpressing S14 in MECs increase the amount of MCFAs without altering the total milk fat or influencing the growth of the offspring [77]. Further analysis shows that a molecular function of S14 in MECs is to enhance FASN catalysis during lactation when optimal milk MCFA production is needed [77]. S14 is also involved in milk fat production in dairy cows [48, 78]. Together, these findings support that S14 is required for the *de novo* lipid synthesis in the lactating mammary gland. Studies have suggested that S14 can be regulated at the transcriptional level by SREBP-1c, LXRs and other transcription factors involved in FA synthesis [45, 71, 79–81]. In addition, S14 expression is noted to be elevated in the mammary glands of Akt1 TG mice, which exhibit precocious lipid synthesis, suggesting the possible interaction between S14 and Akt in this process [23]. Considering the widespread contributions of S14 to obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD) [71, 82], and the complex interactions of S14 with other factors, more studies will be required to address its function in the future.

3. Genetic and Dietary Regulation of Milk Composition and Neonatal Inflammation

Mother's milk represents a unique metabolic entity that exerts direct consequences on the developing newborns, whose digestive and immune systems are still immature. Several studies in our lab have demonstrated that maternal genetic defects including PPAR γ , VLDLR, and adiponectin, as well as maternal dietary defects such as high fat diet, can affect the composition of milk so that it triggers systemic inflammation and related disorders in the nursing offspring, which we have termed as “inflammatory milk” or “toxic milk” [83–87].

3.1 PPAR γ

PPAR γ is a member of a subfamily of the NRs that is known to promote adipogenesis and lipogenesis [88, 89]. It is also a well-known target with great specificity for PPAR agonist thiazolidinediones (TZDs), a class of drugs for the treatment of insulin resistance and type II diabetes [90]. In addition, it modulates lipid homeostasis and inflammatory responses [91–97]. The roles of PPAR γ signaling in milk lipid metabolism have been revealed in several studies [98, 99], as many genes involved in milk lipid synthesis and secretion in ruminants MECs are regulated by PPAR γ . Furthermore, trans-10, cis 12-conjugated linoleic acid-induced milk fat depression is associated with inhibition of PPAR γ signaling and inflammation in murine mammary gland [100]. Germline deletion of PPAR γ in mice leads to embryonic lethality [101]. Conditional KO of PPAR γ specifically in hematopoietic and

endothelial cells using Tie2cre mice results in increased lipid accumulation and elevated expression of lipid oxidation enzymes including 12-lipoxygenase (12-LO) and microsomal epoxide hydrolase (EPHX1) in the lactating mammary gland [83]. Consequently, the milk from these PPAR γ -deficient mothers may have higher levels of oxidized free fatty acids (FFAs), which may be the major inflammatory lipids. Ingestion of this inflammatory milk causes a systemic inflammatory and toxic response in the nursing neonates that is manifested as skin inflammation, fur loss/alopecia, growth retardation, anemia, and lipid accumulation in multiple tissues such as skin and liver. However, overexpression of an active form of PPAR γ in the MECs did not result in any defect in mammary gland development [102], suggesting that possibly PPAR γ in hematopoietic and endothelial cells, rather than MECs, plays a critical role in the lactating mammary gland. Interestingly, hair follicle stem cell-specific PPAR γ deletion causes scarring alopecia [103]. In summary, maternal PPAR γ is pivotal for maintaining the quality of milk and protecting the nursing newborns by suppressing the production of inflammatory lipids. These findings reveal a novel role for PPAR γ in the postnatal maternal–offspring interaction via the mammary gland, and further support the idea that milk lipids provide not only calories, but also signaling molecules that regulate the development of the newborns.

3.2 VLDLR

VLDLR is a member of the low-density lipoprotein receptor (LDLR) family. It is highly expressed in tissues with active TAG metabolism such as adipose tissue, heart, and skeletal muscle, but absent from the liver [104, 105]. VLDLR is known to regulate TAG metabolism via mediating the uptake of its ligand very low-density lipoprotein (VLDL) by peripheral tissues [106, 107]. It also modulates brain development by forming a heterodimer with ApoER2 [108]. Activation of VLDLR by its ligand Reelin (Reln) triggers downstream signaling events that modulate neuronal functions [108, 109]. In addition, VLDLR has protective roles against obesity, insulin resistance and inflammation [110, 111]. Maternal VLDLR deletion in mice causes the production of defective milk containing diminished levels of platelet-activating factor acetylhydrolase (PAFAH) [85]. Detailed analysis shows that VLDLR deletion significantly impairs the expression of phospholipase A2 group 7 (PLA2G7) in macrophages, leading to decreased PAFAH secretion in milk. Platelet-activating factors (PAFs) represent a class of potent pro-inflammatory lipids that are present in neonates whose immune system is not fully developed, and is elevated in infants suffering inflammatory disorders such as necrotizing enterocolitis [3, 112]. Previous studies show that milk contains the secreted form of PAF degradation enzyme PAFAH, which may be critical to suppress the proinflammatory activity of PAF in the nursing neonates [112–114]. Ingestion of the PAFAH-deficient milk from VLDLR KO mother leads to PAF accumulation in the nursing pups [85]. As a consequence, the nursing neonates suffer from alopecia, anemia, growth retardation, and systemic inflammation. Oral PAFAH supplementation to the pups can rescue the neonatal toxicity. Therefore, we have identified a novel anti-inflammatory role of VLDLR in promoting macrophage PAFAH secretion, and demonstrate its physiological significance in ensuring milk PAFAH levels and protecting the nursing newborns from systemic inflammation.

Provocatively, our recent study reveals that maternal toxic milk can exert long-term impact on the offspring to adulthood. The abnormal milk from VLDLR KO mice blunts the differentiation of the bone-resorbing cell type osteoclast and consequently causes osteopetrosis in the offspring up to 3 month of age [87]. Our detailed pharmacological and genetic rescue experiments reveal that these milk defects are largely due to an excessive activity of mammalian target of rapamycin (mTOR) signaling in the adipocytes, which can be reversed by maternal rapamycin treatment during lactation [87]. Moreover, we find that these milk defects are also contributed by an increased expression of the rate-limiting enzyme in the cholesterol biosynthetic pathway 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), and consequently elevated levels of cholesterol precursors in the milk [87]. Together, these findings further uncover the cellular, molecular and biochemical mechanisms for how maternal VLDLR ensures milk quality and protects the offspring from both immediate and long-term abnormalities.

3.3 Adiponectin

Adiponectin is an adipokine playing important roles in lipid and glucose metabolism [115–117]. Increasing evidence suggests that altered adiponectin levels are associated with inflammatory disorders, which can further exacerbate the metabolic syndrome [118]. Our recent study suggests that adiponectin is also essential for the normal development and function of lactating mammary gland. Interestingly, both too much adiponectin as in the TG mice and too little adiponectin as in the KO mice cause inflammatory milk secretion and neonatal inflammation but with different developmental and metabolic defects in the lactating mammary glands [86]. The glands from adiponectin KO mice exhibit an early involution due to more apoptosis and less ductal/alveolar structures; whereas the glands from adiponectin TG mice display a reduced alveolar expansion with more adipocytes during pregnancy and lactation. Consequently, these developmental defects both lead to inefficient lactation and reduced milk production evidenced by lower body weight in the pups nursed by adiponectin KO and TG dams. In addition, milk quality is compromised by both maternal adiponectin deletion and overexpression. Ingestion of these toxic milk leads to systemic inflammation in the pups, manifested as transient fur loss [86]. Adiponectin deficiency triggers leukocyte infiltration and production of proinflammatory cytokines in the lactating mammary gland. Moreover, the expression of several enzymes that produce proinflammatory lipids such as prostaglandin and leukotriene, including cyclooxygenase 2 (COX2), arachidonate 5-lipoxygenase (ALOX5) and Ephx1, is higher in adiponectin KO glands. Consistent with these observations, the levels of oxidized FAs are increased in the skin of the pups nursed by adiponectin KO dams. In contrast, adiponectin overexpression increases lipid accumulation in the lactating mammary gland, resulting in excessive long-chain saturated fatty acids (LcS-FAs) in milk. Inflammatory lipids can affect immune cells and immunity through various mechanisms. One major understanding on how LcS-FAs and lipids cause inflammation is through the activation of toll-like receptors (TLRs) [119–121]. Interestingly, in both cases, the inflammation and alopecia in the pups can be rescued by TLR2/4 deletion because TLR2/4 double KO pups are resistant. These results indicate that both increased abundance in LcS-FA and increased sensitivity to LcS-FA due to elevated inflammatory cytokines can trigger a systemic inflammation in the offspring via TLR2/4-dependent signaling. Our findings reveal adiponectin as a dosage-dependent regulator of

lactation homeostasis and milk quality that critically control inflammation in the nursing neonates. Furthermore, these results suggest that inflammatory infantile disorders may result from maternal adiponectin dysregulation that can be treated by TLR2/4 inhibition. Maternal adiponectin is also a key genetic program that controls the normal development of mammary gland as well as metabolic and immune homeostasis during lactation to ensure normal milk production and their composition and prevent neonatal inflammation.

3.4 Western High Fat Diet

Consumption of a western HFD is highly associated with the current epidemic of metabolic disorders such as obesity and diabetes. It is increasingly recognized that peripheral as well as central activation of inflammatory pathway related to consumption of HFD is linked to these metabolic disorders [118, 122–124]. Western HFD not only causes metabolic consequences to adult individuals consuming it, but maternal consumption of western HFD during sensitive prenatal and postnatal development (e.g. pregnancy and lactation) can exert long-lasting consequences on the offspring both peripherally or centrally causing various metabolic disorders [125–128]. In addition to the in utero effects during pregnancy, this kind of early life programming can also be mediated through milk during lactation. Our recent study reveals that maternal HFD consumption in mice causes the production of milk that contains not only higher fat content but also excessive LcS-FAs [84]. Studies have showed that LcS-FAs (C16:0 and C18:0) but not unsaturated FAs or medium/short-chain FAs (C8:0–C12:0) can specifically activate proinflammatory pathway via TLRs [119, 129–131]. The pups that ingest this inflammatory milk from HFD mother exhibit an increased body weight, and show ceramide accumulation and systemic inflammation, manifested as alopecia [84]. Similar as the findings from adiponectin study [86], the neonatal toxicity in this case also requires TLRs, because genetic TLR2/4 deletion or pharmacological TLR4 inhibition in the pups confers resistance. In summary, maternal western HFD feeding causes the secretion of inflammatory milk that contains excessive LcS-FAs, which activate the TLRs signaling pathway to elevate the levels of ceramide as well as proinflammatory cytokines and enzymes, consequently triggering neonatal toxicity. These findings unravel maternal HFD-induced inflammatory milk secretion as a novel aspect of the metabolic syndrome at the maternal-offspring interface. Furthermore, studies show that maternal consumption of western HFD can also exert other long-lasting consequences on the offspring such as neurodevelopmental disorders [132–134], disrupted gut microbiota [134, 135], liver diseases [136–139], impaired islet vascularization [140], and atherosclerosis development [141].

4. Conclusions and Perspectives

Milk quality impacts the health of the offspring, as it not only regulates their postnatal development, but also influences their propensity to develop chronic diseases in adulthood. Therefore, the understanding of the genetic and biochemical mechanisms that ensure proper milk composition will provide new insights for human physiology and diseases [142]. Latest research uncover that maternal genetic or dietary defects can lead to dysregulated lipid metabolism in the mammary gland during lactation and the secretion of toxic milk with abnormal milk lipid composition that causes various disorders in nursing newborns. Thus, toxic milk will greatly compromise the health of both breast-fed infants and consumers of

dairy products. As such, milk defects may represent previously unrecognized etiology for mysterious infantile diseases. Future studies are required to further elucidate the genetic, dietary and environmental factors that affect the ability of the mother to produce sufficient milk with appropriate compositions. In addition, studies are needed to explore the mechanisms, such as via epigenetic regulation, for how defects in maternal milk composition exert long-term consequences in the offspring and make them more vulnerable to various chronic diseases. Finally, an equally important question is how offspring genetic defects may render them incompatible with normal breast milk and generate inflammatory disorders. To that end, we have identified mitochondria complex I as a key factor in the offspring that is required for the postnatal metabolic adaptation to milk consumption [143]. These findings suggest a mother-infant co-evolution in which the offspring adapts its genetic makeup to match the mother's milk composition and vice versa. Ultimately, elucidation of the mechanisms by which mother's milk nourishes and protects the newborns is fundamentally important in order to design better infant formula and novel diagnostic/therapeutic strategies for infantile and chronic diseases.

Acknowledgments

We thank all the researchers whose work have contributed to our understanding of milk lipid regulation but could not be cited here due to space limitation. Y.W. is Lawrence Raisz Professor in Bone Cell Metabolism and a Virginia Murchison Linthicum Scholar in Medical Research. This work was in part supported by March of Dimes (#6-FY13-137, Y.W.), The Welch Foundation (I-1751, Y.W.), NIH (R01DK089113, Y.W.), CPRIT (RP130145, Y.W.), DOD (W81XWH-13-1-0318, Y.W.) and UTSW Endowed Scholar Startup Fund (Y.W.).

Abbreviations

ACC	acetyl-CoA carboxylase
ADPH	adipophilin
Akt/PKB	protein kinase B
ALOX5	arachidonate 5-lipoxygenase
BTN1A1	butyrophilin subfamily 1 member a1
CIDEA	cell death-inducing DNA fragmentation factor α -like effector A
COX2	cyclooxygenase 2
DGAT1	diacylglycerol transferase 1
EPHX1	microsomal epoxide hydrolase
FA	fatty acid
FASN	fatty acid synthase
FFA	free fatty acids
HFD	high-fat diet
HMGCR	3-hydroxy-3-methylglutaryl coenzyme A reductase

IGF1	insulin-like growth factor 1
INSIG1	insulin-induced gene 1
IRS	insulin receptor substrate
KO	knockout
LcS-FA	long-chain saturated fatty acids
LDLR	low-density lipoprotein receptor
LXR	liver X receptor
MCFA	medium-chain fatty acid
MEC	mammary epithelial cell
MFG	milk fat globule
mTOR	mammalian target of rapamycin
NAFLD	nonalcoholic fatty liver disease
NHR	nuclear hormone receptor
PAF	platelet-activating factor
PAFAH	platelet-activating factor acetylhydrolase
PKN1	protein kinase N1
PLA2G7	phospholipase A2 group 7
PPAR	peroxisome proliferator-activated receptor
PRL	prolactin
PRLR	prolactin receptor
RELN	Reelin
S14	thyroid hormone responsive spot 14
S14R	S14 related gene
SCAP	SREBP cleavage-activating protein
SCD	stearoyl-CoA desaturase
SLC25A1	mitochondrial citrate transporter
SRE	sterol response element
SREBP	sterol regulatory element-binding protein
TAG	triacylglyceride

TG	transgenic
TLR	toll-like receptor
TZD	Thiazolidinedione
VLDL	very low-density lipoprotein
VLDLR	very low-density lipoprotein receptor
XOR	xanthine oxidoreductase
12-LO	12-lipoxygenase

References

1. Neville M. Lactation and its hormonal control. In: Neill JD, editor Knobil and Neill's Physiology of Reproduction. 3rd. Academic Press; San Diego: 2006. 2993–3054.
2. McClellan HL, Miller SJ, Hartmann PE. Evolution of lactation: nutrition v. protection with special reference to five mammalian species. *Nutr Res Rev*. 2008; 21(2):97–116. [PubMed: 19087365]
3. Walker A. Breast milk as the gold standard for protective nutrients. *J Pediatr*. 2010; 156(2):S3–S7. [PubMed: 20105662]
4. Allen JC, Keller RP, Archer PC, Neville MC. Studies in human lactation: milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr*. 1991; 54(1):69–80. [PubMed: 2058590]
5. Schwertfeger KL, McManaman JL, Palmer CA, Neville MC, Anderson SM. Expression of constitutively activated Akt in the mammary gland leads to excess lipid synthesis during pregnancy and lactation. *J Lipid Res*. 2003; 44(6):1100–1112. [PubMed: 12700340]
6. McManaman JL. Lipid Transport in the Lactating Mammary Gland. *J Mammary Gland Biol Neoplasia*. 2014; 19(1):35–42. [PubMed: 24567110]
7. Rudolph MC, Neville MC, Anderson SM. Lipid Synthesis in Lactation: Diet and the Fatty Acid Switch. *J Mammary Gland Biol Neoplasia*. 2007; 12(4):269–281. [PubMed: 18027074]
8. Neville MC, Picciano MF. Regulation of milk lipid secretion and composition. *Annu Rev Nutr*. 1997; 17(1):159–184. [PubMed: 9240924]
9. Richert MM, Schwertfeger KL, Ryder JW, Anderson SM. An atlas of mouse mammary gland development. *J Mammary Gland Biol Neoplasia*. 2000; 5(2):227–241. [PubMed: 11149575]
10. Neville MC. Anatomy and Physiology of Lactation. *Pediatr Clin North Am*. 2001; 48(1):13–34. [PubMed: 11236721]
11. Palmer CA, Neville MC, Anderson SM, McManaman JL. Analysis of Lactation Defects in Transgenic Mice. *J Mammary Gland Biol Neoplasia*. 2006; 11(3):269–282. [PubMed: 17136614]
12. McManaman JL, Neville MC. Mammary physiology and milk secretion. *Adv Drug Deliv Rev*. 2003; 55(5):629–641. [PubMed: 12706546]
13. Bionaz M, Looor JJ. Gene networks driving bovine milk fat synthesis during the lactation cycle. *BMC Genomics*. 2008; 9(1):366. [PubMed: 18671863]
14. Vernon B, Flint D. Control of fatty acid synthesis in lactation. *Proc Nutr Soc*. 1983; 42(2):315–331. [PubMed: 6351088]
15. Rudolph MC, McManaman JL, Hunter L, Phang T, Neville MC. Functional development of the mammary gland: Use of expression profiling and trajectory clustering to reveal changes in gene expression during pregnancy, lactation, and involution. *J Mammary Gland Biol Neoplasia*. 2003; 8(3):287–307. [PubMed: 14973374]
16. Anderson SM, Rudolph MC, McManaman JL, Neville MC. Key stages in mammary gland development. Secretory activation in the mammary gland: it's not just about milk protein synthesis! *Breast Cancer Res*. 2007; 9(1):204. [PubMed: 17338830]

17. Mather IH, Keenan T. Origin and secretion of milk lipids. *J Mammary Gland Biol Neoplasia*. 1998; 3(3):259–273. [PubMed: 10819513]
18. McManaman JL, Palmer CA, Anderson S, Schwertfeger K, Neville MC. Regulation of Milk Lipid Formation and Secretion in the Mouse Mammary Gland. In: Pickering LK, Morrow AL, Ruiz-Palacios GM, Schanler RJ, editors *Protecting Infants through Human Milk: Advancing the Scientific Evidence*. Springer; US, Boston, MA: 2004. 263–279.
19. Jensen D, Bessesen D, Etienne J, Eckel R, Neville M. Distribution and source of lipoprotein lipase in mouse mammary gland. *J Lipid Res*. 1991; 32(5):733–742. [PubMed: 2072037]
20. Clegg RA, Barber MC, Pooley L, Ernens I, Larondelle Y, Travers MT. Milk fat synthesis and secretion: molecular and cellular aspects. *Livest Prod Sci*. 2001; 70(1):3–14.
21. Insull W Jr, Hirsch J, James T, Ahrens E Jr. The fatty acids of human milk. II. Alterations produced by manipulation of caloric balance and exchange of dietary fats. *J Clin Invest*. 1959; 38(2):443–450. [PubMed: 13631077]
22. Jensen RG. The lipids in human milk. *Prog Lipid Res*. 1996; 35(1):53–92. [PubMed: 9039426]
23. Rudolph MC, McManaman JL, Phang T, Russel T, Kominsky DM, Serkova N. Metabolic regulation in the lactating mammary gland: A lipid synthesizing machine. *Physiol Genomics*. 2007; 28(3):323–336. [PubMed: 17105756]
24. Ormandy CJ, Camus A, Barra J, Damotte D, Lucas B, Buteau H, Edery M, Brousse N, Babinet C, Binart N. Null mutation of the prolactin receptor gene produces multiple reproductive defects in the mouse. *Genes Dev*. 1997; 11(2):167–178. [PubMed: 9009200]
25. Rudolph MC, Russell TD, Webb P, Neville MC, Anderson SM. Prolactin-mediated regulation of lipid biosynthesis genes in vivo in the lactating mammary epithelial cell. *Am J Physiol Endocrinol Metab*. 2011; 300(6):E1059–E1068. [PubMed: 21467304]
26. Ho MY, Murphy D. A bovine oxytocin transgene in mice: expression in the female reproductive organs and regulation during pregnancy, parturition and lactation. *Mol Cell Endocrinol*. 1997; 136(1):15–21. [PubMed: 9510063]
27. Wagner KU, Young WS, Liu X, Ginns EI, Li M, Furth PA, Hennighausen L. Oxytocin and milk removal are required for post-partum mammary gland development. *Genes Funct*. 1997; 1(4):233–244. [PubMed: 9678900]
28. Hadsell DL, Torres DT, Lawrence NA, George J, Parlow AF, Lee AV, Fiorotto ML. Overexpression of des (1–3) insulin-like growth factor 1 in the mammary glands of transgenic mice delays the loss of milk production with prolonged lactation. *Biol Reprod*. 2005; 73(6):1116–1125. [PubMed: 16079306]
29. Smith SJ, Cases S, Jensen DR, Chen HC, Sande E, Tow B, Sanan DA, Raber J, Eckel RH, Farese RV. Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking Dgat. *Nat Genet*. 2000; 25(1):87–90. [PubMed: 10802663]
30. Cases S, Zhou P, Shillingford JM, Wiseman BS, Fish JD, Angle CS, Hennighausen L, Werb Z, Farese RV. Development of the mammary gland requires DGAT1 expression in stromal and epithelial tissues. *Development*. 2004; 131(13):3047–3055. [PubMed: 15163627]
31. Watkin H, Richert MM, Lewis A, Terrell K, McManaman JP, Anderson SM. Lactation failure in Src knockout mice is due to impaired secretory activation. *BMC Dev Biol*. 2008; 8(1):6. [PubMed: 18215306]
32. Fischer A, Stuckas H, Gluth M, Russell TD, Rudolph MC, Beeman NE, Bachmann S, Umemura S, Ohashi Y, Neville MC. Impaired tight junction sealing and precocious involution in mammary glands of PKN1 transgenic mice. *J Cell Sci*. 2007; 120(13):2272–2283. [PubMed: 17591691]
33. McManaman J, Palmer C, Wright R, Neville M. Functional regulation of xanthine oxidoreductase expression and localization in the mouse mammary gland: evidence of a role in lipid secretion. *J Physiol*. 2002; 545(2):567–579. [PubMed: 12456835]
34. Vorbach C, Scriven A, Capecchi MR. The housekeeping gene xanthine oxidoreductase is necessary for milk fat droplet enveloping and secretion: gene sharing in the lactating mammary gland. *Genes Dev*. 2002; 16(24):3223–3235. [PubMed: 12502743]
35. Ogg SL, Weldon AK, Dobbie L, Smith AJH, Mather IH. Expression of butyrophilin (Btln1a1) in lactating mammary gland is essential for the regulated secretion of milk-lipid droplets. *Proc Natl Acad Sci U S A*. 2004; 101(27):10084–10089. [PubMed: 15226505]

36. Wang W, Lv N, Zhang S, Shui G, Qian H, Zhang J, Chen Y, Ye J, Xie Y, Shen Y. Cidea is an essential transcriptional coactivator regulating mammary gland secretion of milk lipids. *Nat Med*. 2012; 18(2):235–243. [PubMed: 22245780]
37. Russell TD, Palmer CA, Orlicky DJ, Bales ES, Chang BH, Chan L, McManaman JL. Mammary glands of adipophilin-null mice produce an amino-terminally truncated form of adipophilin that mediates milk lipid droplet formation and secretion. *J Lipid Res*. 2008; 49(1):206–216. [PubMed: 17921437]
38. Chong BM, Reigan P, Mayle-Combs KD, Orlicky DJ, McManaman JL. Determinants of adipophilin function in milk lipid formation and secretion. *Trends Endocrinol Metab*. 2011; 22(6): 211–217. [PubMed: 21592818]
39. Russell TD, Schaack J, Orlicky DJ, Palmer C, Chang BHJ, Chan L, McManaman JL. Adipophilin regulates maturation of cytoplasmic lipid droplets and alveolae in differentiating mammary glands. *J Cell Sci*. 2011; 124(19):3247–3253. [PubMed: 21878492]
40. Heinz RE, Rudolph MC, Ramanathan P, Spoelstra NS, Butterfield KT, Webb PG, Babbs BL, Gao H, Chen S, Gordon MA. Constitutive expression of microRNA-150 in mammary epithelium suppresses secretory activation and impairs de novo lipogenesis. *Development*. 2016; 143(22): 4236–4248. [PubMed: 27729410]
41. Eberlé D, Hegarty B, Bossard P, Ferré P, Foufelle F. SREBP transcription factors: master regulators of lipid homeostasis. *Biochimie*. 2004; 86(11):839–848. [PubMed: 15589694]
42. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest*. 2002; 109(9):1125–1131. [PubMed: 11994399]
43. Shimomura I, Shimano H, Horton JD, Goldstein JL, Brown MS. Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. *J Clin Invest*. 1997; 99(5):838–845. [PubMed: 9062340]
44. Engelking LJ, Cantoria MJ, Xu Y, Liang G. Developmental and extrahepatic physiological functions of SREBP pathway genes in mice. *Semin Cell Dev Biol*. 2017.
45. Rudolph MC, Monks J, Burns V, Phistry M, Mariani R, Foote MR, Bauman DE, Anderson SM, Neville MC. Sterol regulatory element binding protein and dietary lipid regulation of fatty acid synthesis in the mammary epithelium. *Am J Physiol Endocrinol Metab*. 2010; 299(6):E918–E927. [PubMed: 20739508]
46. Ye J, DeBose-Boyd RA. Regulation of cholesterol and fatty acid synthesis. *Cold Spring Harb Perspect Biol*. 2011; 3(7):a004754. [PubMed: 21504873]
47. Xu HF, Luo J, Zhao WS, Yang YC, Tian HB, Shi HB, Bionaz M. Overexpression of SREBP1 (sterol regulatory element binding protein 1) promotes de novo fatty acid synthesis and triacylglycerol accumulation in goat mammary epithelial cells. *J Dairy Sci*. 2016; 99(1):783–795. [PubMed: 26601584]
48. Harvatine KJ, Bauman DE. SREBP1 and thyroid hormone responsive Spot 14 (S14) are involved in the regulation of bovine mammary lipid synthesis during diet-induced milk fat depression and treatment with CLA. *J Nutr*. 2006; 136(10):2468–2474. [PubMed: 16988111]
49. Libertini LJ, Smith S. Purification and properties of a thioesterase from lactating rat mammary gland which modifies the product specificity of fatty acid synthetase. *J Biol Chem*. 1978; 253(5): 1393–1401. [PubMed: 627544]
50. Smith S, Dils R. Factors affecting the chain length of fatty acids synthesised by lactating-rabbit mammary glands. *Biochim Biophys Acta Lipids Lipid Metab*. 1966; 116(1):23–40.
51. Smith S. Mechanism of Chain Length Determination in Biosynthesis of Milk Fatty Acids. *J Dairy Sci*. 1980; 63(2):337–352. [PubMed: 6102100]
52. Rincon G, Islas-Trejo A, Castillo AR, Bauman DE, German BJ, Medrano JF. Polymorphisms in genes in the SREBP1 signalling pathway and SCD are associated with milk fatty acid composition in Holstein cattle. *J Dairy Res*. 2012; 79(1):66–75. [PubMed: 22114848]
53. Nafikov RA, Schoonmaker JP, Korn KT, Noack K, Garrick DJ, Koehler KJ, Minick-Bormann J, Reecy JM, Spurlock DE, Beitz DC. Sterol regulatory element binding transcription factor 1 (SREBF1) polymorphism and milk fatty acid composition. *J Dairy Sci*. 2013; 96(4):2605–2616. [PubMed: 23403193]

54. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JMA, Shimomura I, Shan B, Brown MS, Goldstein JL, Mangelsdorf DJ. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXR α and LXR β . *Genes Dev.* 2000; 14(22):2819–2830. [PubMed: 11090130]
55. Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ. Role of LXRs in control of lipogenesis. *Genes Dev.* 2000; 14(22):2831–2838. [PubMed: 11090131]
56. Chen G, Liang G, Ou J, Goldstein JL, Brown MS. Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver. *Proc Natl Acad Sci U S A.* 2004; 101(31):11245–11250. [PubMed: 15266058]
57. McFadden JW, Corl BA. Activation of liver X receptor (LXR) enhances de novo fatty acid synthesis in bovine mammary epithelial cells. *J Dairy Sci.* 2010; 93(10):4651–4658. [PubMed: 20854999]
58. Yao DW, Luo J, He QY, Xu HF, Li J, Shi HB, Wang H, Chen Z, Looor JJ. Liver X receptor α promotes the synthesis of monounsaturated fatty acids in goat mammary epithelial cells via the control of stearoyl-coenzyme A desaturase 1 in an SREBP-1-dependent manner. *J Dairy Sci.* 2016; 99(8):6391–6402. [PubMed: 27209141]
59. Porstmann T, Griffiths B, Yuen-Li C, Delpuech O, Griffiths JR, Downward J, Schulze A. PKB/Akt induces transcription of enzymes involved in cholesterol and fatty acid biosynthesis via activation of SREBP. *Oncogene.* 2005; 24(43):6465–6481. [PubMed: 16007182]
60. Hadsell DL, Olea W, Lawrence N, George J, Torres D, Kadowaki T, Lee AV. Decreased lactation capacity and altered milk composition in insulin receptor substrate null mice is associated with decreased maternal body mass and reduced insulin-dependent phosphorylation of mammary Akt. *J Endocrinol.* 2007; 194(2):327–336. [PubMed: 17641282]
61. Yecies JL, Zhang HH, Menon S, Liu S, Yecies D, Lipovsky AI, Gorgun C, Kwiatkowski DJ, Hotamisligil GS, Lee CH, Manning BD. Akt stimulates hepatic SREBP1c and lipogenesis through parallel mTORC1-dependent and independent pathways. *Cell Metab.* 2011; 14(1):21–32. [PubMed: 21723501]
62. Yang ZZ, Tschopp O, Baudry A, Duemmler B, Hynx D, Hemmings BA. Physiological functions of protein kinase B/Akt. *Biochem Soc Trans.* 2004; 32(Pt 2):350–354. [PubMed: 15046607]
63. Chodosh LA, Gardner HP, Rajan JV, Stairs DB, Marquis ST, Leder PA. Protein Kinase Expression during Murine Mammary Development. *Dev Biol.* 2000; 219(2):259–276. [PubMed: 10694421]
64. Schwertfeger KL, Richert MM, Anderson SM. Mammary gland involution is delayed by activated Akt in transgenic mice. *Mol Endocrinol.* 2001; 15(6):867–881. [PubMed: 11376107]
65. Boxer RB, Stairs DB, Dugan KD, Notarfrancesco KL, Portocarrero CP, Keister BA, Belka GK, Cho H, Rathmell JC, Thompson CB. Isoform-specific requirement for Akt1 in the developmental regulation of cellular metabolism during lactation. *Cell Metab.* 2006; 4(6):475–490. [PubMed: 17141631]
66. Chen CC, Boxer RB, Stairs DB, Portocarrero CP, Horton RH, Alvarez JV, Birnbaum MJ, Chodosh LA. Akt is required for Stat5 activation and mammary differentiation. *Breast Cancer Res.* 2010; 12(5):R72. [PubMed: 20849614]
67. Seelig S, Liaw C, Towle HC, Oppenheimer JH. Thyroid hormone attenuates and augments hepatic gene expression at a pretranslational level. *Proc Natl Acad Sci U S A.* 1981; 78(8):4733–4737. [PubMed: 6946422]
68. Jump DB, Oppenheimer JH. High basal expression and 3, 5, 3'-triiodothyronine regulation of messenger ribonucleic acid S14 in lipogenic tissues. *Endocrinology.* 1985; 117(6):2259–2266. [PubMed: 4065033]
69. Brown SB, Maloney M, Kinlaw WB. "Spot 14" protein functions at the pretranslational level in the regulation of hepatic metabolism by thyroid hormone and glucose. *J Biol Chem.* 1997; 272(4):2163–2166. [PubMed: 8999918]
70. Kinlaw WB, Church JL, Harmon J, Mariash CN. Direct evidence for a role of the "spot 14" protein in the regulation of lipid synthesis. *J Biol Chem.* 1995; 270(28):16615–16618. [PubMed: 7622469]

71. Wu J, Wang C, Li S, Li S, Wang W, Li J, Chi Y, Yang H, Kong X, Zhou Y. Thyroid Hormone-Responsive SPOT 14 Homolog Promotes Hepatic Lipogenesis, and Its Expression Is Regulated By Liver X Receptor a Through a Sterol Regulatory Element-Binding Protein 1c-Dependent Mechanism in Mice. *Hepatology*. 2013; 58(2):617–628. [PubMed: 23348573]
72. Zhu Q, Mariash A, Margosian MR, Gopinath S, Fareed MT, Anderson GW, Mariash CN. Spot 14 gene deletion increases hepatic de novo lipogenesis. *Endocrinology*. 2001; 142(10):4363–4370. [PubMed: 11564699]
73. Zhu Q, Anderson GW, Mucha GT, Parks EJ, Metkowski JK, Mariash CN. The Spot 14 protein is required for de novolipid synthesis in the lactating mammary gland. *Endocrinology*. 2005; 146(8): 3343–3350. [PubMed: 15890771]
74. Kim CW, Moon YA, Park SW, Cheng D, Kwon HJ, Horton JD. Induced polymerization of mammalian acetyl-CoA carboxylase by MIG12 provides a tertiary level of regulation of fatty acid synthesis. *Proc Natl Acad Sci U S A*. 2010; 107(21):9626–9631. [PubMed: 20457939]
75. Aipoalani DL, O'callaghan BL, Mashek DG, Mariash CN, Towle HC. Overlapping roles of the glucose-responsive genes, S14 and S14R, in hepatic lipogenesis. *Endocrinology*. 2010; 151(5): 2071–2077. [PubMed: 20233797]
76. Colbert CL, Kim CW, Moon YA, Henry L, Palnitkar M, McKean WB, Fitzgerald K, Deisenhofer J, Horton JD, Kwon HJ. Crystal structure of Spot 14, a modulator of fatty acid synthesis. *Proc Natl Acad Sci U S A*. 2010; 107(44):18820–18825. [PubMed: 20952656]
77. Rudolph MC, Wellberg EA, Lewis AS, Terrell KL, Merz AL, Maluf NK, Serkova NJ, Anderson SM. Thyroid hormone responsive protein Spot14 enhances catalysis of fatty acid synthase in lactating mammary epithelium. *J Lipid Res*. 2014; 55(6):1052–1065. [PubMed: 24771867]
78. Bauman DE, Harvatine KJ, Lock AL. Nutrigenomics, rumen-derived bioactive fatty acids, and the regulation of milk fat synthesis. *Annu Rev Nutr*. 2011; 31:299–319. [PubMed: 21568706]
79. Horton JD, Shah NA, Warrington JA, Anderson NN, Park SW, Brown MS, Goldstein JL. Combined analysis of oligonucleotide microarray data from transgenic and knockout mice identifies direct SREBP target genes. *Proc Natl Acad Sci U S A*. 2003; 100(21):12027–12032. [PubMed: 14512514]
80. Mater MK, Thelen AP, Pan DA, Jump DB. Sterol response element-binding protein 1c (SREBP1c) is involved in the polyunsaturated fatty acid suppression of hepatic S14 gene transcription. *J Biol Chem*. 1999; 274(46):32725–32732. [PubMed: 10551830]
81. Shimomura I, Shimano H, Korn BS, Bashmakov Y, Horton JD. Nuclear sterol regulatory element-binding proteins activate genes responsible for the entire program of unsaturated fatty acid biosynthesis in transgenic mouse liver. *J Biol Chem*. 1998; 273(52):35299–35306. [PubMed: 9857071]
82. Anderson GW, Zhu Q, Metkowski J, Stack MJ, Gopinath S, Mariash CN. The Thrsp null mouse (Thrsptm1cnm) and diet-induced obesity. *Mol Cell Endocrinol*. 2009; 302(1):99–107. [PubMed: 19356628]
83. Wan Y, Saghatelian A, Chong LW, Zhang CL, Cravatt BF, Evans RM. Maternal PPAR γ protects nursing neonates by suppressing the production of inflammatory milk. *Genes Dev*. 2007; 21(15): 1895–1908. [PubMed: 17652179]
84. Du Y, Yang M, Lee S, Behrendt CL, Hooper LV, Saghatelian A, Wan Y. Maternal western diet causes inflammatory milk and TLR2/4-dependent neonatal toxicity. *Genes Dev*. 2012; 26(12): 1306–1311. [PubMed: 22713870]
85. Du Y, Yang M, Wei W, Huynh HD, Herz J, Saghatelian A, Wan Y. Macrophage VLDL receptor promotes PAFAH secretion in mother's milk and suppresses systemic inflammation in nursing neonates. *Nat Commun*. 2012; 3:1008. [PubMed: 22910354]
86. Jin Z, Du Y, Schwaib AG, Asterholm IW, Scherer PE, Saghatelian A, Wan Y. Maternal Adiponectin Controls Milk Composition to Prevent Neonatal Inflammation. *Endocrinology*. 2015; 156(4):1504–1513. [PubMed: 25590242]
87. Huynh H, Wei W, Wan Y. mTOR Inhibition Subdues Milk Disorder Caused by Maternal VLDLR Loss. *Cell Rep*. 2017; 19(10):2014–2025. [PubMed: 28591574]
88. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPAR γ 2, a lipid-activated transcription factor. *Cell*. 1994; 79(7):1147–1156. [PubMed: 8001151]

89. Tontonoz P, Nagy L, Alvarez JGA, Thomazy VA, Evans RM. PPAR γ Promotes Monocyte/Macrophage Differentiation and Uptake of Oxidized LDL. *Cell*. 1998; 93(2):241–252. [PubMed: 9568716]
90. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*. 1996; 45(12):1661–1669. [PubMed: 8922349]
91. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature*. 1998; 391(6662):82–86. [PubMed: 9422509]
92. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature*. 1998; 391(6662):79–82. [PubMed: 9422508]
93. Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR-[gamma] dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. *Nat Med*. 2001; 7(1):48–52. [PubMed: 11135615]
94. Daynes RA, Jones DC. Emerging roles of PPARs in inflammation and immunity. *Nat Rev Immunol*. 2002; 2(10):748–759. [PubMed: 12360213]
95. Harmon GS, Lam MT, Glass CK. PPARs and lipid ligands in inflammation and metabolism. *Chem Rev*. 2011; 111(10):6321–6340. [PubMed: 21988241]
96. Wahli W, Michalik L. PPARs at the crossroads of lipid signaling and inflammation. *Trends Endocrinol Metab*. 2012; 23(7):351–363. [PubMed: 22704720]
97. Cariou B, Charbonnel B, Staels B. Thiazolidinediones and PPAR γ agonists: time for a reassessment. *Trends Endocrinol Metab*. 2012; 23(5):205–215. [PubMed: 22513163]
98. Kadegowda AKG, Bionaz M, Piperova LS, Erdman RA, Loor JJ. Peroxisome proliferator-activated receptor- γ activation and long-chain fatty acids alter lipogenic gene networks in bovine mammary epithelial cells to various extents. *J Dairy Sci*. 2009; 92(9):4276–4289. [PubMed: 19700688]
99. Shi H, Luo J, Zhu J, Li J, Sun Y, Lin X, Zhang L, Yao D, Shi H. PPAR γ regulates genes involved in triacylglycerol synthesis and secretion in mammary gland epithelial cells of dairy goats. *PPAR Res*. 2013; 2013:310948. [PubMed: 23710163]
100. Kadegowda AK, Khan MJ, Piperova LS, Teter BB, Rodriguez-Zas SL, Erdman RA, Loor JJ. Trans-10, cis 12-Conjugated Linoleic Acid-Induced Milk Fat Depression Is Associated with Inhibition of PPAR Signaling and Inflammation in Murine Mammary Tissue. *J Lipids*. 2013; 2013:890343. [PubMed: 23762566]
101. Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans RM. PPAR γ Is Required for Placental, Cardiac, and Adipose Tissue Development. *Mol Cell*. 1999; 4(4):585–595. [PubMed: 10549290]
102. Saez E, Rosenfeld J, Livolsi A, Olson P, Lombardo E, Nelson M, Banayo E, Cardiff RD, Izpisua-Belmonte JC, Evans RM. PPAR γ signaling exacerbates mammary gland tumor development. *Genes Dev*. 2004; 18(5):528–540. [PubMed: 15037548]
103. Karnik P, Tekeste Z, McCormick TS, Gilliam AC, Price VH, Cooper KD, Mirmirani P. Hair Follicle Stem Cell-Specific PPAR γ Deletion Causes Scarring Alopecia. *J Invest Dermatol*. 2009; 129(5):1243–1257. [PubMed: 19052558]
104. Oka K, Ishimura Oka K, Chu MJ, Sullivan M, Krushkal J, Li WH, Chan L. Mouse very-low-density-lipoprotein receptor (VLDLR) cDNA cloning, tissue-specific expression and evolutionary relationship with the low-density-lipoprotein receptor. *Eur J Biochem*. 1994; 224(3):975–982. [PubMed: 7925422]
105. Webb JC, Patel DD, Jones MD, Knight BL, Soutar AK. Characterization and tissue-specific expression of the human ‘very low density lipoprotein (VLDL) receptor’ mRNA. *Hum Mol Genet*. 1994; 3(4):531–537. [PubMed: 8069294]
106. Tacke PJ, Hofker MH, Havekes LM, van Dijk KW. Living up to a name: the role of the VLDL receptor in lipid metabolism. *Curr Opin Lipidol*. 2001; 12(3):275–279. [PubMed: 11353330]
107. Takahashi S, Sakai J, Fujino T, Hattori H, Zenimaru Y, Suzuki J, Miyamori I, Yamamoto TT. The very low-density lipoprotein (VLDL) receptor: characterization and functions as a peripheral lipoprotein receptor. *J Atheroscler Thromb*. 2004; 11(4):200–208. [PubMed: 15356379]
108. Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, Hammer RE, Richardson JA, Herz J. Reeler/Disabled-like disruption of neuronal migration in knockout mice

- lacking the VLDL receptor and ApoE receptor 2. *Cell*. 1999; 97(6):689–701. [PubMed: 10380922]
109. D'Arcangelo G, Homayouni R, Keshvara L, Rice DS, Sheldon M, Curran T. Reelin is a ligand for lipoprotein receptors. *Neuron*. 1999; 24(2):471–479. [PubMed: 10571240]
 110. Goudriaan JR, Tacke PJ, Dahlmans VE, Gijbels MJ, van Dijk KW, Havekes LM, Jong MC. Protection from obesity in mice lacking the VLDL receptor. *Arterioscler Thromb Vasc Biol*. 2001; 21(9):1488–1493. [PubMed: 11557677]
 111. Nguyen A, Tao H, Mettrione M, Hajri T. Very low density lipoprotein receptor (VLDLR) expression is a determinant factor in adipose tissue inflammation and adipocyte-macrophage interaction. *J Biol Chem*. 2014; 289(3):1688–1703. [PubMed: 24293365]
 112. Caplan MS, Sun XM, Hsueh W, Hageman JR. Role of platelet activating factor and tumor necrosis factor- α in neonatal necrotizing enterocolitis. *J Pediatr*. 1990; 116(6):960–964. [PubMed: 2348301]
 113. Furukawa M, Narahara H, Yasuda K, Johnston JM. Presence of platelet-activating factor-acetylhydrolase in milk. *J Lipid Res*. 1993; 34(9):1603–1609. [PubMed: 8228643]
 114. Moya FR, Eguchi H, Zhao B, Furukawa M, Sfeir S, Osorio M, Ogawa Y, Johnston JM. Platelet-activating factor acetylhydrolase in term and preterm human milk: a preliminary report. *J Pediatr Gastroenterol Nutr*. 1994; 19(2):236–239. [PubMed: 7815247]
 115. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem*. 1995; 270(45):26746–26749. [PubMed: 7592907]
 116. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab*. 2002; 13(2):84–89. [PubMed: 11854024]
 117. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011; 11(2):85–97. [PubMed: 21252989]
 118. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444(7121):860–867. [PubMed: 17167474]
 119. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest*. 2006; 116(11):3015–3025. [PubMed: 17053832]
 120. Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. *Eur J Pharmacol*. 2011; 668(Suppl 1):S50–S58. [PubMed: 21816146]
 121. Huang S, Rutkowski JM, Snodgrass RG, Ono-Moore KD, Schneider DA, Newman JW, Adams SH, Hwang DH. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. *J Lipid Res*. 2012; 53(9):2002–2013. [PubMed: 22766885]
 122. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao X, Sarruf DA, Izgur V, Maravilla KR. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012; 122(1):153–162. [PubMed: 22201683]
 123. Jais A, Brüning JC. Hypothalamic inflammation in obesity and metabolic disease. *J Clin Invest*. 2017; 127(1):24–32. [PubMed: 28045396]
 124. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Invest*. 2017; 127(1):1–4. [PubMed: 28045402]
 125. Srinivasan M, Patel MS. Metabolic programming in the immediate postnatal period. *Trends Endocrinol Metab*. 2008; 19(4):146–152. [PubMed: 18329279]
 126. Bouret S, Simerly R. Developmental programming of hypothalamic feeding circuits. *Clin Genet*. 2006; 70(4):295–301. [PubMed: 16965320]
 127. Vogt MC, Paeger L, Hess S, Steculorum SM, Awazawa M, Hampel B, Neupert S, Nicholls HT, Mauer J, Hausen AC. Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high-fat feeding. *Cell*. 2014; 156(3):495–509. [PubMed: 24462248]
 128. Dearden L, Ozanne SE. Early life origins of metabolic disease: Developmental programming of hypothalamic pathways controlling energy homeostasis. *Front Neuroendocrinol*. 2015; 39:3–16. [PubMed: 26296796]
 129. Hommelberg PP, Plat J, Langen RC, Schols AM, Mensink RP. Fatty acid-induced NF- κ B activation and insulin resistance in skeletal muscle are chain length dependent. *Am J Physiol Endocrinol Metab*. 2009; 296(1):E114–E120. [PubMed: 18957619]

130. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem.* 2001; 276(20):16683–16689. [PubMed: 11278967]
131. Lee JY, Ye J, Gao Z, Youn HS, Lee WH, Zhao L, Sizemore N, Hwang DH. Reciprocal modulation of Toll-like receptor-4 signaling pathways involving MyD88 and phosphatidylinositol 3-kinase/AKT by saturated and polyunsaturated fatty acids. *J Biol Chem.* 2003; 278(39):37041–37051. [PubMed: 12865424]
132. Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K. Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. *Neurochem Int.* 2010; 57(3):235–247. [PubMed: 20538025]
133. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ. Early Life Programming and Neurodevelopmental Disorders. *Biol Psychiatry.* 2010; 68(4):314–319. [PubMed: 20674602]
134. Val-Laillet D, Besson M, Guérin S, Coquery N, Randuineau G, Kanzari A, Quesnel H, Bonhomme N, Bolhuis JE, Kemp B. A maternal Western diet during gestation and lactation modifies offspring's microbiota activity, blood lipid levels, cognitive responses, and hippocampal neurogenesis in Yucatan pigs. *FASEB J.* 2017; 31(5):2037–2049. [PubMed: 28167496]
135. Steegenga WT, Mischke M, Lute C, Boekschoten MV, Lendvai A, Pruis MG, Verkade HJ, de Heijning BJ, Boekhorst J, Timmerman HM. Maternal exposure to a Western-style diet causes differences in intestinal microbiota composition and gene expression of suckling mouse pups. *Mol Nutr Food Res.* 2017; 61(1):1600141.
136. Bruce KD, Cagampang FR, Argenton M, Zhang J, Ethirajan PL, Burdge GC, Bateman AC, Clough GF, Poston L, Hanson MA. Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. *Hepatology.* 2009; 50(6):1796–1808. [PubMed: 19816994]
137. McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, Grove KL. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. *J Clin Invest.* 2009; 119(2):323–335. [PubMed: 19147984]
138. Pruis M, Lendvai A, Bloks V, Zwier M, Baller J, Bruin A, Groen A, Plösch T. Maternal western diet primes non-alcoholic fatty liver disease in adult mouse offspring. *Acta Physiol.* 2014; 210(1):215–227.
139. Zhang X, Strakovsky R, Zhou D, Zhang Y, Pan Y. A maternal high-fat diet represses the expression of antioxidant defense genes and induces the cellular senescence pathway in the liver of male offspring rats. *J Nutr.* 2011; 141(7):1254–1259. [PubMed: 21562236]
140. Pound LD, Comstock SM, Grove KL. Consumption of a Western-style diet during pregnancy impairs offspring islet vascularization in a Japanese macaque model. *Am J Physiol Endocrinol Metab.* 2014; 307(1):E115–E123. [PubMed: 24844258]
141. Wakana N, Irie D, Kikai M, Terada K, Yamamoto K, Kawahito H, Kato T, Ogata T, Ueyama T, Matoba S. Maternal high-fat diet exaggerates atherosclerosis in adult offspring by augmenting periaortic adipose tissue-specific proinflammatory response. *Arterioscler Thromb Vasc Biol.* 2015; 35(3):558–569. [PubMed: 25593133]
142. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, Eidelman AI. Breastfeeding and the use of human milk. *Pediatrics.* 2005; 115(2):496–506. [PubMed: 15687461]
143. Jin Z, Wei W, Yang M, Du Y, Wan Y. Mitochondrial Complex I Activity Suppresses Inflammation and Enhances Bone Resorption by Shifting Macrophage-Osteoclast Polarization. *Cell Metab.* 2014; 20(3):483–498. [PubMed: 25130399]