Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Milk lipid regulation at the maternal-offspring interface

Dengbao Yang, HoangDinh Huynh, Yihong Wan*

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

ARTICLE INFO

Article history:
Received 8 August 2017
Accepted 12 October 2017
Available online xxx

Keywords:
Lactating mammary gland
Milk lipid
Genetic defect
High fat diet
Inflammatory milk

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.

Contents

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.

* Corresponding author.
E-mail address: yihong.wan@utsouthwestern.edu (Y. Wan).

https://doi.org/10.1016/j.semcdb.2017.10.012
1084-9521/

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 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 secretary 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 synthesised 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), PPARγ, 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* synthesised 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

Please cite this article in press as: D. Yang, et al., Milk lipid regulation at the maternal-offspring interface, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.012