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Role of Liver X Receptor in Mastitis Therapy and Regulation of Milk Fat Synthesis

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Abstract

Mastitis is important disease that causes huge economic losses in the dairy industry. In recent years, antibiotic therapy has become the primary treatment for mastitis, however, due to drug residue in milk and food safety factors, we lack safe and effective drugs for treating mastitis. Therefore, new targets and drugs are urgently needed to control mastitis. LXRα, one of the main members of the nuclear receptor superfamily, is reported to play important roles in metabolism, infection and immunity. Activation of LXRα could inhibit LPS-induced mastitis. Furthermore, LXRα is reported to enhance milk fat production, thus, LXRα may serve as a new target for mastitis therapy and regulation of milk fat synthesis. This review summarizes the effects of LXRα in regulating milk fat synthesis and treatment of mastitis and highlights the potential agonists involved in both issues.

Keywords LXRα · Mastitis · Milk fat

Abbreviation

LXR	liver X receptor
LPS	lipopolysaccharide
TLR4	toll-like receptor 4
NF-κB	nuclear transcription factor κB
TNF-α	necrosis factor-α
IL	interleukin
ABCG1	Adenosine triphosphate binds to the box subfamily G1 antibody
SREBP1	sterol regulatory element binding proteins 1c
PPARγ	peroxisome proliferator activated receptor γ
FASN	fatty synthase
PRRs	pattern recognition receptors
PAMPs	pathogen-associated molecular patterns
LBP	LPS-binding protein
MD-2	myeloid differentiation protein-2
CD14	leukocyte differentiation antigen
MyD88	myeloid differentiation protein antigen
MAPK	mitogenactivated protein kinase
IRF3	interferon regulating factor 3
IFN	interferon
ABCA1	ATP-binding cassette transporter A1
ApoA1	apolipoprotein A1
HDL	high density lipoprotein
PEG2	prostaglandin
SSa	saikosaponina A
RXR	retinoid x receptor
PLD	platycodin D
C3G	cyaniding-3-o-β-glucoside
MFGM	milk fat globule membrane
ACC	Acetyl-CoA carboxylase
FAS	fatty acid synthase
NME-UV	bovine mammary epithelial cells

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Introduction

Mastitis is an inflammatory disease of the host's mammary gland tissues, which causes enormous economic losses, including those associated with decreased milk production, discarded milk, pharmacologic expenses, and increased cull rates [1]. This disease is also a significant welfare issue [2]. The incidence of clinical mastitis was estimated to range between 16 and 48 cases per 100 cows. The prevalence of subclinical mastitis was reported to be 20 to 80% globally [3], and the cost of clinical mastitis ranges from $ 16.43 to $ 572.19

per cow [4]. Mastitis deteriorates productivity of cows and impairs their health conditions as well. Based on the clinical symptoms, mastitis can be divided into clinical and subclinical mastitis. Gram-negative bacteria, such as *Escherichia coli*, often cause clinical mastitis [5]. LPS, the main component of gram-negative bacteria outer membrane, often causes severe inflammatory responses in mammary glands by activating the TLR4 signaling pathway [6, 7]. Upon activating TLR4, TLR4 translocates to the lipid rafts-, which are specialized cholesterol and glycosphingolipid-rich membrane microdomains-, inducing NF-κB signaling pathways expression and leading to produce large amounts of inflammatory cytokines, such as TNF-α, and IL-1β [8]. In other words, understanding the regulation of the inflammatory response in mastitis may shed light on new approaches that can be developed to treat this disease.

Liver X receptors (LXRs), including LXRα and LXRβ, are members of the nuclear receptor superfamily, consisting of various sub-families. LXRα exists in three variants originating from alternative promoter usage and mRNA splicing: LXRα1, LXRα2, and LXRα3 [9, 10]. Both LXRα and LXRβ are extensively expressed in several areas of the body, including the lung, liver, brain, and mammary glands [11–14]. LXRs, ligand-dependent transcription factors, are essential in regulating inflammatory signaling [15–17]. Our results revealed that activation of LXRα by T0901318 suppressed mastitis in mice [18], suggesting a new clinical approach to managing this disease.

Milk fat is a main ingredient of milk, containing approximately 400 different fatty acids, and is considered to be the major energy source in milk [19]. Milk fat regulation is influenced by many factors, such as genes, the environment, dietary structure, feed nutrition, and management. LXRs involved in milk fat synthesis have also been reported [20, 21]. Studies have shown that T0901317, an LXRα agonist, induces ABCG1 and SREBP1 expression in mammary gland epithelial cells [22, 23]. PPARγ belongs to another nuclear receptor which, similarly to LXRs, is participates in the regulation of milk fat synthesis (Fig. 1) [24, 25]. Thus, activating LXRs to accelerate milk fat metabolism may be a potential method of increasing milk fat and quality in the dairy-farming industry.

This review focuses on our current understanding of the role LXRs play in biology and pharmacology as well as the links between LXRs and mastitis and fat milk synthesis. In addition, LXRs agonists could be considered prospective drugs for curing mastitis and increasing milk fat percentages in dairy cows.

LXR Distribution

LXRs are distributed in many mammalian tissues. LXRα and LXRβ are found in many regions of the brain, and LXRβ is expressed 2–5 times more than LXRα in the brain [26]. Researchers have confirmed that LXRs are present in cultured neuron, glia, astrocytes, sebaceous glands, and sweat gland epithelia [27, 28]. Evidence shows that LXRβ is ubiquitously expressed at lower concentrations than LXRα in the liver, spleen, intestines, kidneys, adipose tissue, lungs,

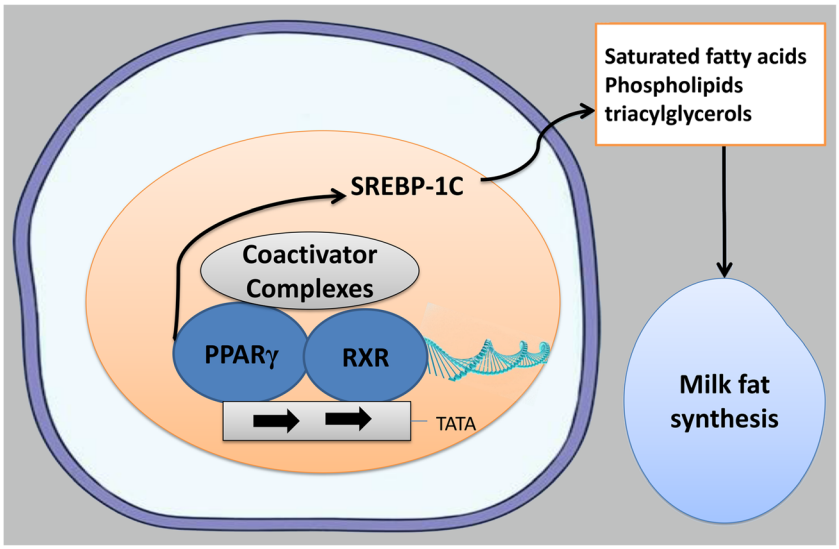

Fig. 1 The role of PPARγ in the regulation of milk fat synthesis. PPARγ bind to specific response elements in target genes as heterodimers with retinoid X receptors (RXRs), which are also members of the nuclear receptor superfamily. In the presence of ligands, PPARγ/RXR heterodimers activate transcription through the recruitment of coactivator complexes that contain NCoR, SMRT, and histone deacetylases (HDACs). Ligand-activated PPARγ/RXR heterodimers increase expression sterol response element-binding protein 1 (SREBP1).Up-regulation of SREBP-1 lead to increase the expression of saturated fatty acids, phospholipids, and triacylglycerols, which are important components of milk

macrophages, and adrenal glands [29–33]. Importantly, LXRs have been found in mammary gland tissue, where they are involved in regulating inflammatory responses, and milk fat synthesis [34–36]. Expression of ABCG2, SREBP1, SREBP2, LXRα, and PPARβ are increased in postpartum bovine mammary glands, and these genes all affect milk yield and fat concentrations in cattle [34, 37]. Evidence also proved that LXRα is predominantly present in goat mammary glands, small intestine, liver, and spleen than other tissues, and the mammary gland epithelial cells. Treatment of goat mammary epithelial cells with T0901317 causes increased SREBP-1 and FASN (fatty acid synthase) mRNA expression [36].

LXRs Ligands

LXRs are involved in many diseases and may serve as promising pharmacological targets. LXRs ligands activate LXRs by regulating target genes. Many LXRs agonists have been discovered over the past years. LXRs agonists can be divided into three types, endogenous, synthetic, and natural (Table 1), and these agonists may be potential candidates for developing new therapeutic approaches.

Role of LXRs in Mastitis

Regulatory Mechanism of Mastitis

Mastitis is an inflammatory disease of the mammary gland tissues in humans and other mammals. *Escherichia coli* is one of the main pathogens that causes mastitis. This pathological process reduces milk quality and causes enormous economic losses [1, 93–95]. Lipopolysaccharide (LPS), the major component of *E. coli's* outer membrane, is an important virulence factor in inflammatory diseases [96]. LPS stimulates the innate immune system and causes substantial pro-inflammatory cytokines production. This process leads to inflammatory responses in the mammary glands, which in severe cases can lead to sepsis or death if not properly treated in a timely fashion [97–100].

The innate immune response is the first line of defense against pathogen invasion. Pattern recognition receptors (PRRs) recognize and interact with pathogens, activating the innate immune system [101, 102]. The PRR-induced innate immune response causes pro-inflammatory cytokine and interferon production, and this inflammatory mediums production is linked to the PRR-mediated signaling transduction pathway [103]. Toll-like receptors (TLRs) are PRRs expressed by innate immune cells that are stimulated by pathogen-associated molecular patterns (PAMPs) [104–107]. More than ten TLRs have been discovered in animals and humans. TLR4 is recognized as LPS -specific. LPS first interacts with the LPS-binding protein (LBP) formatting LPS-LBP. This compound is then recognized by MD-2 and CD14, thus activating the TLR4 signaling pathway [108]. Many studies have reported that the TLR4 signaling pathway plays a crucial role in the bovine mastitis induced by some gram-negative bacteria such as *E.coli* [109, 110]. TLR4 recognizes LPS and activates the signaling cascade leading to pro-inflammatory cytokine production in response to the pathogen during mastitis [111]. The TLR4 signaling pathway includes the MyD88-dependent and MyD88-independent pathways. The MyD88-dependent signaling pathway mediates a signaling pathway that activates NF-κB and MAPK and controls production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. The MyD88-independent signaling pathway, activates the IRF3 transcription factor, inducing IFN-β and RANTES expression [112–114]. Recently, studies showed that lipid rafts played a critical role in the regulation of TLR4 signaling pathway [115, 116].

Lipid rafts were initially proposed by Simons in 1997 [117, 118]. Lipid rafts are specialized cholesterol and glycosphingolipid-rich membrane microdomains that act as lipid-ordered platforms on eukaryotic surfaces. Some reports have suggested that lipid rafts participate in activating of signaling transduction and play crucial roles in the LPS-induced signaling activation in macrophages [119, 120]. TLR4 is recruited to lipid rafts after LPS stimulation in cells, and LPS-induced NF-κB activation and cytokines production were reduced after treatment with lipid rafts disrupting drugs [115, 121]. Our laboratory also found that decreasing cholesterol expression in lipid rafts suppresses TLR4 from translocating lipid rafts, which reduces the pro-inflammatory cytokines production induced by LPS during mastitis [122, 123].

LXR Regulating Inflammatory Response in Other Tissues

LXRs play an important role in regulating of cholesterol levels [124–126]. ABCA1 and ABCG1 are two key genes in cholesterol regulation by LXRs [127–132]. LXRs activation upregulates of LXRs-dependent ABCA1 and ABCG1 genes expression and cholesterol transport. ABCA1 and ABCG1 transport cholesterol in the cells to apolipoprotein A1 (ApoA1) and high density lipoprotein (HDL), then induce cholesterol efflux, which reduces cholesterol expression in the cell membrane and disrupts lipid rafts formation [133–135]. LXRs act as cholesterol levels sensors, and are involved in regulating inflammatory signaling. LXRs activation inhibits pro-inflammatory cytokines production in macrophages derived from wild type mice rather than from LXRα and LXRβ-knockout mice. This suggests that both LXRα and LXRβ are involved in regulating inflammatory responses [131]. GW3965, a LXRs synthetic agonist, suppressed

Table 1 Agonists of LXRs

Types	Name	Effects on LXRs	Expression or source	Advantages or disadvantages	References
Endogenous agonists	24(S)-hydroxycholesterol (24(S)-HC)	Activation of LXRα/β	Plasma, adult brains, endoplasmic reticulum	Advantages: regulates cholesterol, Disadvantanges: cytotoxicity	[38–40]
	22(R)-hydroxycholesterol (22-HC)	Activation of LXRα/β	Steroidogenic tissues	Advantages: regulates cholesterol, decrease amyloid β production, inhibition the proliferation of cancer cells.	[41–44]
	24(S),25-Epoxcholesterol (24,25-EC)	Activation of LXRα/β	Midbrain, liver	Advantages: regulates cholesterol, reduces progenitor proliferation, promotes dopaminergic neurogenesis	[45–47]
	27-hydroxycholesterol	Activation of LXRα/β	Cholesterol loaded cells	Advantages: regulates cholesterol, protects against breast cancer	[46, 48, 49]
	25-hydroxycholesterol	Activation of LXRα/β	The hydroxylated derivatives of cholesterol	Advantages: regulates cholesterol, regulates immune system	[50–53]
	20(S)-hydroxycholesterol (20(S)-HC)	Activation of LXRα/β	Brains, human placenta	Advantages: regulate cholesterol, induces osteoblast differentiation, inhibits adipogenic differentiation	[54–56]
	6α-hydroxylated bile acids	Activation of LXRα	Derived from bile acid pathways	Advantages: regulates bile acids	[57]
	5α,6α-Epoxycholesterol	Activation of LXRα/β	Human plasma, chylomicrons, lipoproteins	Advantages: regulates cholesterol, antioxidant	[58, 59]
Synthetic agonist	T0901317	Activation of LXRα/β	Tularik (now Amgen)	Advantages: anti-inflammation, antioxidant, anti-diabetic, regulates milk fat Disadvantages: no-specific LXRs ligand	[10, 60–67]
	GW3956	Activation of LXRα/β	GlaxoSmithKline	Advantages: anti-inflammation, anti-cancer Disadvantages: expensive	[67–72]
	GW6340	Activation of LXRα/β	GlaxoSmithKline	Advantages: anti-inflammation, protects against cardiovascular diseases Disadvantages: Intestinal-specific LXR agonist	[67, 73, 74]
Natural agonist	Diterpenes	Activation of LXRα/β	Plants, insects	Advantages: antibacterial, antiviral, anti-inflammation, cytotoxic, anti-cancer Disadvantages: lack of specificity	[75, 76]
	Fucosterol	Activation of LXRα/β	Marine algae	Advantages: anticancer, antidepressant, anticonvulsant, anti-inflammation, antimicrobial Disadvantages: lack of specificity	[77, 78]
	Cyanidin	Activation of LXRα/β	Fruit, vegetables	Advantages: antioxidant, anti-inflammation, antihyperglycemic Disadvantages: lack of specificity	[79, 80]
	Honokiol	Activation of LXRβ	Magnolia officinalis	Advantages: anti-inflammation, anti-angiogenesis, anti-arrhythmic, antioxidant Disadvantages: lack of specificity	[81, 82]
	Paeoniflorin	Activation of LXRα/β	*Paeonia lactiflora* Pall	Advantages: anti-inflammation, immunomodulatory, anti-cancer, liver and nerve protective Disadvantages: lack of specificity	[83, 84]
	Iristectorigenin	Activation of LXRα/β	Belamcanda chinensis	Advantages: anti-inflammation, anti-angiogenic, anti-cancer, anti-mutagenic, hypoglycemic Disadvantages: lack of specificity	[85, 86]

Table 1 (continued)

Types	Name	Effects on LXRs	Expression or source	Advantages or disadvantages	References
	Taraxasterol	Activation of LXRα	*Taraxacum officinale*	Advantages: anti-inflammation, antioxidant, anti-cancer Disadvantages: lack of specificity	[87, 88]
	Platycodin D	Activation of LXRα	*Platycodon grandiflorum*	Advantages: anti-cancer, anti-diabetic, anti-inflammation, immunomodulatory Disadvantages: lack of specificity	[89, 90]
	Saikosaponin a	Activation of LXRα	Radix bupleuri	Advantages: amti-inflammation, neural protection, anti-septic, pain relieving Disadvantages: lack of specificity	[91, 92]

TNF-α and prostaglandin E2 (PEG2) levels in Kupffer cells induced by LPS [136]. In addition, T090131 inhibited IFN-γ, TNF-α, and IL-12 production in Th-1 cells [137]. LXRs have wide anti-inflammatory effects, however, their exact regulatory mechanism is unclear. Recent, evidence suggests that LXRα activation suppresses inflammatory cytokines production by inhibiting TLR2, TLR4, TLR9 and their downstream NF-κB and MAPK signaling pathway gene expressions [138]. Others reported that activating LXRα induced ABCA1 signaling expression to inhibit MyD88 and TRAF6 transcription to the membrane lipid organization [138]. Saikosaponina-A (SSa) inhibited TLR4 translocation to lipid raft and suppressed lipid raft formation by reducing cholesterol levels after LPS stimulation in HUVECs. In addition, SSa induced LXRα-ABCA1 signaling pathway activation, and the anti-inflammatory effects of SSα were abolished after LXRα knockdown. This suggests that SSa activated the LXRα-ABCA1 signaling pathway, which disrupted lipid raft formation by depleting cholesterol, suppressed TLR4 from interacting with lipid rafts, and inhibited the LPS-induced inflammatory response [139].

LXR Regulating Inflammatory Response in the Mammary Gland

Recently, a large amount of studies has been focused on the role of LXRs on mammary gland inflammatory response. Evidence proved that Ingenuity Pathway analysis® network depicted that LXR/RXR activation was the most activated during heat stress. This suggested that LXR/RXR signaling pathway is affected by heat stress and might play an important role in the regulation of fat metabolism and inflammatory signaling [140]. Our laboratory research also found that activation of LXRα significantly inhibited the production of LPS-induced TNF-α, IL-1β and IL-6 through inhibiting NF-κB signaling pathway. Furthermore, treatment with T0901317 activated ABCA1, disrupted lipid rafts and inhibited translocation of TLR4 to lipid rafts, which may lead to the inhibition of inflammatory response in LPS-stimulated primary bovine mammary epithelial cells [141]. In vivo, the results also suggested that T0901317 significantly attenuated LPS-induced mammary gland inflammatory response via activating LXRα [66]. Furthermore, the results showed that platycodin D (PLD) inhibited LPS-induced TNF-α, IL-1β and IL-6 production through regulating NF-κB and LXRα expression. The inhibition of PLD on NF-κB activation and pro-inflammatory cytokines production were reversed by GGPP, the inhibitor of LXRα. These data suggested that PLD inhibited LPS-induced inflammatory response in bovine mammary epithelial cells by activating LXRα [142]. C3G (cyanidin-3-o-β-glucoside), derived from anthocyanin pigment, suppressed TLR4-mediated NF-κB signaling pathway activation by activating the LXR-α-ABCG1 pathway during LPS-mastitis in mice [123]. The above evidence suggests that LXRα plays a crucial role mastitis development, and it may be a potential novel target receptor for curing mastitis.

Role of LXRs in Milk Fat Synthesis

Milk fat is the major nutritional component in milk, and is crucial in dairy products. Fat is also the main contributor to milk's energy density, and it affects many of its physical properties and organoleptic characteristics [143]. Bovine milk fat are 98% triglycerides, and the remaining 2% is comprised of free fatty acids, mono-and diglycerides, phospholipids, sterols and hydrocarbons [144–146]. Milk fat is synthesized in the mammary gland epithelial cells and is secreted along with lipids to form fat globules [147]. High-quality milk, with sufficient milk fat, is necessary for healthy food production. Reports suggested that modifying milk fat composition of dairy cows have benefic effective on human health by enhancing fatty acids [148]. Others suggested that bovine milk fat globule membrane (MFGM) that have the potential to elicit

beneficial effects on health-related variables. The heath-beneficial components of MFGM have protects against colon cancer, gastrointestinal pathogens, Alzheimer's disease, depression, and stress properties [149]. Therefore, measures must be adoted to improve milk yield and milk fat content, as this is an important issue that should be solved immediately.

LXRs play key roles in regulating milk fat synthesis when activated by agonists [46, 150, 151]. The two isoforms, LXRα and LXRβ, regulate lipogenic enzymes transcription by binding the retinoid X receptor (RXR), in a heterodimeric complex [152]. LXRα expression is augmented during the transition from pregnancy to lactation [59]. McFadden reported that de novo FA synthesis was increased after stimulation by T0901317 in bovine mammary gland epithelial cells [153]. Peet found that Acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and sterol regulatory element-binding protein-1(SREBP1) expression were all reduced in LXR gene-mutated mice [154]. Li provided that LXR regulated fatty acid synthase promoter activity by directly interacting with LXRE by increasing SREBP1 abundance [155]. Mcadden showed that SREBP 1 is regulated by LXR activation in bovine mammary epithelial cells (BME-UV), and LXR activation increased ATP-binding cassette transporter-G1 transcription and increased de novo fatty acid synthesis [153] . Mani discovered that administering LXR agonist induced lipid synthesis, SREBP1 expression was increased in bovine mammary gland epithelial cell lines [156], and ACC and FASN levels increased in MAC-T cells [157].

Peroxisome proliferator-activated receptor is also involved in the milk fat synthesis [158, 159]. PPARs were first identified in the liver and recently found to be expressed in bovine mammary epithelial cells [66]. Reports suggest that PPARs are required to express genes that participated in fatty acids metabolism and adipocyte differentiation [160]. PPARγ expression in early pregnancy is approximately 10 times that of the early lactation period in mouse mammary glands [161]. Reports also suggested that PPARγ mRNA expression was markedly increased in bovine mammary gland during lactation [162]. Gene silencing of PPARγ was recently reported to significantly down-regulated the expression levels of milk fat synthesis-related genes in cow mammary epithelial cells. Conversely, overexpressing PPARγ improved cell viability, proliferation, and triacylglycerol secretion [167]. Inhibiting of PPARγ signaling, including down-regulating of PPARγ, SREBF1 and several lipogenic targets, reduced milk fat synthesis in mouse mammary tissues [168].Thus, PPAR-LXR-SREBP-1 is a potential regulator signaling pathway in milk fat synthesis.

Perspectives for LXRs

Increasing evidence produced by basic research indicated that the activation of LXRs involved in the development of mastitis and regulation of milk fat synthesis. Numerous regulators and signaling targets LXRs have provided researchers with many opportunities to explore their underlying mechanisms. Though with the in-depth understanding of LXRs biology and the development of innovative drug discovery strategies, several LXRs agonist have emerged. Though new findings concerning about LXRs biology have been constantly updated, there has been no effective agent derived from LXRs used to treat mastitis or regulate milk fat synthesis clinically. However, it is undeniable that LXRs are important therapeutic for mastitis and regulation of milk fat synthesis fat. Hence, pinpointing effective LXRs agonists is significant for further clinical applications.

Conclusion

LXRs participate in cholesterol activities, lipid synthesis and glucose metabolism. Evidence also suggests that LXRs play crucial roles in regulating inflammatory signaling. LXRs may be novel and promising therapeutic targets for mastitis for their ability to protect against mammary gland injuries by inhibiting inflammatory media production. Activating LXRs also induces SREBP-1 expression, thereby increasing milk fat synthesis and improving milk quality. Thus, LXRs agonists, which are designed to combat the adverse effects of drugs, show promise as potential new and effective therapeutic for modulating the inflammatory response associated with mastitis and improving milk fat in the dairy-farming industry.

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