


Saturated Fatty Acids in Obesity-Associated Inflammation

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Abstract: Obesity is a major risk factor for the development of various pathological conditions including insulin resistance, diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD). Central to these conditions is obesity-associated chronic low-grade inflammation in many tissues including adipose, liver, muscle, kidney, pancreas, and brain. There is increasing evidence that saturated fatty acids (SFAs) increase the phosphorylation of MAPKs, enhance the activation of transcription factors such as nuclear factor (NF)- κ B, and elevate the expression of inflammatory genes. This paper focuses on the mechanisms by which SFAs induce inflammation. SFAs may induce the expression inflammatory genes via different pathways including toll-like receptor (TLR), protein kinase C (PKC), reactive oxygen species (ROS), NOD-like receptors (NLRs), and endoplasmic reticulum (ER) stress. These findings suggest that SFAs act as an important link between obesity and inflammation.

Keywords: saturated fatty acids, obesity, inflammation, Toll-like receptor, reactive oxygen species, lipid rafts, protein kinase C

Introduction

Obesity is an increasingly prevalent global issue. According to the 2018 World Health Organization (WHO) fact sheet, the number of people with obesity worldwide has nearly tripled since 1975, and more than 650 million adults were obese in 2016 (<http://www.who.int/mediacentre/factsheets/fs311/en/>). There is significant evidence that obesity is associated with the development of a range of pathological conditions including cardiovascular diseases, insulin resistance, diabetes, and non-alcoholic fatty liver disease (NAFLD).¹ Chronic low-grade inflammation has been reported in the adipose tissue,² liver,³ muscle,⁴ kidney,⁵ and hypothalamus⁶ of obese human subjects. Circulating levels of TNF- α and C-reactive protein (CRP) are also increased in obese children and adolescents.⁷ Elevated circulating IL-6 and higher levels of IL-1 β , monocyte chemoattractant protein (MCP)-1, and IL-8 have been reported in the placenta of obese pregnant women.⁸

Inflammation is also detected in various tissues of both genetic and dietary animal models of obesity. For example, production of inflammatory mediators is increased in the liver, muscle, adipose tissue of ob/ob and db/db mice compared to control mice.^{9–11} Mice fed with palmitic acid-supplemented high-fat diet (HFD) also exhibit inflammation in the adipose tissue, liver, muscle, kidney, and hypothalamus compared to control animals.^{9,12–16}

There is increasing evidence that chronic inflammation is an important underlying cause of various obesity-associated conditions.¹⁷ For example, tumor necrosis

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factor (TNF)- α , a proinflammatory cytokine, has been shown to induce insulin resistance when increased and improve insulin resistance when neutralized¹⁸ while decreased expression of adiponectin, an anti-inflammatory adipokine, has been implicated in the development of obesity-associated cardiovascular diseases.¹⁹

A significant number of studies have been conducted to identify the cause of obesity-associated inflammation with many focused on free fatty acids (FFAs). Circulating fatty acids are generally transported either free (nonesterified) or bound to cholesterol and other protein molecules. The circulating levels of FFAs may be increased in obesity and its associated conditions as a result of increased amount of adipose tissue, reduced response to insulin's antilipolytic effect of obese adipose tissue, and decreased re-esterification of FFAs by obese adipocytes.^{20–22} Circulating levels of FFAs have been reported to be increased in obese subjects,²² morbidly obese subjects,²³ overweight/obese subjects with diabetes mellitus,²⁴ patients with severe non-insulin-dependent diabetes mellitus,²⁵ and obese NAFLD patients.^{24,26} Karpe et al conducted a literature search on non-esterified fatty acids (NEFA) or FFA as well as obesity on PubMed in July 2009 and found 43 original reports on 953 nonobese (control) subjects and 1410 overweight/obese subjects with most studies reporting greater FFA level in the obese/overweight group even though the average difference is modest, and concluded that FFA concentration is undeniably higher in certain groups of obese individuals.²⁷

Circulating FFAs may vary in the degree of saturation with saturated fatty acids (SFAs), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). They may also vary in the number of carbons with short-chain, medium-chain, and long-chain FFAs. Considering that the effects of different FFAs on innate immunity are quite complex depending on the number of carbons, degree of saturation, and location of the C=C double bond in the hydrocarbon chain, this paper is focused on examining how long-chain SFAs may contribute to inflammation.

Long-Chain SFAs Increase the Production of Inflammatory Mediators

Palmitic acid (C16:0) has been reported to increase the phosphorylation of mitogen-activated protein kinases (MAPKs) including p38, JNK, and extracellular-signal-

regulated kinases (ERKs), enhance the activation of transcription factors including activator protein (AP)-1 and nuclear factor (NF)- κ B, and induce the mRNA expression of cyclooxygenase (COX)-2, IL-1 β , IL-6, and TNF- α in macrophages, monocytes, and monocyte-derived dendritic cells.^{28–34} Stearic acid (C18:0) has been reported to trigger the release of TNF- α , IL-1 β , and IL-6 from astrocytes.³⁵ Both stearic acid and palmitic acid induce the activation of NF- κ B and stimulate the secretion of pro-inflammatory mediators in trophoblast cells isolated from human placentas,^{36,37} microglial cells,³⁸ and prostate epithelial cells.³⁹ Similarly, palmitic acid significantly activates JNK in HEPG2 cells;⁴⁰ increases the expression of MCP-1 in mesangial cells;¹⁵ induces the expression of IL-6, IL-8, and MCP-1 in smooth muscle cells;^{41,42} increases the activation of p38, JNK, and NF- κ B with enhanced expression of TNF- α in C2C12 skeletal muscle cells;^{43,44} enhances the activation of NF- κ B with increased production of IL-6 and TNF- α in adipocytes;^{23,45} and induces the activation of p38, ERK, and JNK with increased expression of COX-2, IL-6 and MCP-1 in fibroblast cells.^{46,47}

Dietary supplementation with high-fat diet (HFD) or infusion of Liposyn II (a 20% triglyceride nonpyrogenic emulsion), lipid/heparin, soybean oil, lard oil, or fatty acids has been used to increase circulating FFA level in human and animal model studies.^{48–51} Infusion of ethyl palmitic acid increases the expression of chemokines including MCP-1 and keratinocyte chemoattractant (KC) in β cells and the recruitment of monocytes/macrophages into the mouse islets.⁵² Intracerebroventricular administration of arachidic acid (C20:0) induces mRNA expression of TNF- α , IL-1 β , IL-6, and IL-10 in the hypothalamus of rats.⁵³ In addition, Dumas et al reported that subjects on high palmitic acid diet exhibit elevated circulating levels of IL-6 and IL-1 β than subjects on low palmitic acid/high oleic acid diet.⁵⁴ These studies suggest that increased level of SFAs may represent a key link between obesity and inflammation.

Involvement of TLR2 and/or TLR4 in SFA-Induced Inflammation

Toll-like receptors (TLRs) are pattern recognition receptors (PRRs) that recognize different pathogen-associated molecular pattern (PAMP) molecules. TLR4 is a TLR family member well known to recognize lipopolysaccharide (LPS), a main component of Gram-negative bacterial cell wall. Upon being brought to TLR4 and MD-2, LPS

promotes the formation of TLR4-MD2-LPS complex, which, in turn, recruits myeloid differentiation primary response 88 (MyD88) and Toll-IL-1 receptor domain-containing adaptor inducing IFN- β (TRIF), initiating a MyD88-dependent and MyD88-independent signaling pathways respectively.^{55,56} Activation of MyD88-dependent pathway leads to the activation of MAPKs and transcription factors such as NF- κ B and AP-1, ultimately increasing the expression of inflammatory markers such as cytokines and chemokines.^{57,58} Activation of MyD88-independent pathway leads to the activation of IFN-regulatory factor (IRF)-3, ultimately increasing the expression of inflammatory genes such as IP-10.⁵⁹

TLR2, another member of the TLR family, has been shown to recognize a broad range of ligands by forming a heterodimer with other TLRs. Triacyl lipopeptide (LP) from Gram-positive bacterial cell wall promotes the formation of TLR2/1 heterodimer and diacyl LP promotes the formation of TLR2/6 heterodimer,^{60–62} which, in turn, initiates the MyD88-dependent signaling pathway, ultimately increasing the expression of inflammatory markers.^{63,64}

A number of studies have examined the role of TLR in SFA-induced inflammation. Knockdown of TLR4 has been found to markedly attenuate palmitic acid-induced NF- κ B activation and IL-8 expression in human aortic vascular smooth muscle cells,⁴² and significantly reduce palmitic acid-induced increase of NF- κ B activation and release of IL-1 β and MCP-1 in THP-1 cells.⁶⁵ Inhibition of TLR4 reduces palmitic acid-induced production of TNF- α and IL-6 in astrocytes³⁵ and trophoblast cells.³⁶ Dominant-negative TLR4 inhibits lauric acid-induced activation of NF- κ B and expression of COX-2 in RAW 264.7 cells.³² Pretreatment with TLR4 antibody also inhibits palmitic acid-induced mRNA expression of TNF- α , IL-6, and IL-1 β in microglial cells³⁸ (Table 1). These *in vitro* studies suggest the necessary involvement of TLR4 in SFA-induced expression of inflammatory genes.

Moreover, the absence of a functional TLR4 protects mice from the obesogenic effects of HFD with lard and palmitic acid,¹² attenuates HFD-induced expression of TNF- α , IL-6, and MCP-1 in the adipose tissue,^{12,28} abolishes palmitic acid-induced expression of MCP-1 and KC in β cells,⁵² and diminishes palmitic acid-induced degradation of I- κ B α , activation of NF- κ B, and phosphorylation of JNK in isolated muscles compared to control mice.⁵³ Furthermore, intracerebroventricular co-administration of TLR4 antibody attenuates arachidic acid (C20:0)-induced increase of TNF- α , IL-1 β , IL-6, and IL-10 in the hypothalamus⁵³ (Table 1).

Taken together, both *in vitro* and *in vivo* studies suggest that TLR4 is clearly implicated in SFA-induced inflammation (Figure 1).

There is also evidence that SFA-induced expression of inflammatory markers may involve TLR2. Lauric acid is able to induce NF- κ B activation in 293T cells co-transfected with TLR2 and TLR1 or TLR6, but not in 293T cells transfected with TLR1, 2, 3, 5, 6, or 9 individually,⁶⁶ suggesting that lauric acid-induced NF- κ B activation involves TLR2 with TLR1 or TLR6. Palmitic acid has also been found to induce the association of MyD88 with TLR2 in C2C12 skeletal muscle cells.⁴⁴ Furthermore, knockdown of TLR2 attenuates palmitic acid-induced expression of proinflammatory cytokines in primary endothelial cells⁶⁷ (Table 1). Taken together, TLR2 may also be involved in SFA-induced activation of NF- κ B and expression of inflammatory markers (Figure 1).

Do SFAs Act as Ligands for TLR4 and TLR2?

While there is much evidence for the involvement of TLR2 and TLR4 in SFA-induced inflammation, questions remain as to how SFAs activate the TLR signaling. The lipid portion of LPS and LP critical for their binding to TLRs^{56,68–72} is structurally similar to SFAs,^{73,74} therefore SFAs have been postulated as ligands for TLRs. Nicholas et al also demonstrated the possibility of fitting 5 molecules of palmitic acid into the hydrophobic binding pocket in MD-2 using a theoretical approach.³³ However, stearic acid is unable to compete with LPS in its binding to LPS-Trap fusion protein consisting of FLAG-tagged extracellular part of TLR4 fused to full-length MD-2.⁷⁵ Lancaster et al also reported that multiple palmitic acid molecules would make the TLR4/MD2 active complex unstable using molecular simulations,⁷⁶ suggesting the unlikelihood of palmitic acid to act as a TLR4 ligand.

Despite insufficient evidence for the physical binding of SFAs to TLRs, SFAs have been shown to induce dimerization of TLRs. For example, lauric acid induces the formation of TLR4 dimer/MD-2 complex in RAW264.7 cells.^{77,78} Panter et al showed that the chimeric protein consisting of the transmembrane and cytoplasmic domains of TLR4 and the MD2 or CD14 forms a constitutively active dimer that is able to activate the expression of luciferase reporter under the control of NF- κ B promoter,⁷⁹ suggesting that TLR4 dimerization is sufficient to activate TLR4 signaling. Furthermore, expression of LPS-induced

Table 1 Studies on the Mechanisms of SFA-Induced Inflammation

TLR4	In vitro	TLR4 knockdown markedly attenuates PA-induced NF- κ B activation and IL-8 expression in human aortic vascular smooth muscle cells.	42
		TLR4 knockdown significantly reduces PA-induced increase of NF- κ B activation and release of IL-1 β and MCP-1 in THP-1 cells.	65
		Inhibition of TLR4 reduces PA-induced production of TNF- α and IL-6 in astrocytes and trophoblast cells.	35,36
		Dominant-negative TLR4 inhibits LA-induced activation of NF- κ B and expression of COX-2 in RAW 264.7 cells.	32
		Pretreatment with TLR4 antibody inhibits PA-induced mRNA expression of TNF- α , IL-6, and IL-1 β in microglial cells.	38
TLR2	In vivo	LA induces the formation of TLR4 dimer/MD-2 complex in RAW264.7 cells.	77,78
		Absence of a functional TLR4 attenuates HFD-induced expression of TNF- α , IL-6, and MCP-1 in animal adipose tissue.	12,28
		Absence of a functional TLR4 abolishes PA-induced expression of MCP-1 and KC in β cells.	52
		Absence of a functional TLR4 diminishes PA-induced degradation of I- κ B α , activation of NF- κ B, and phosphorylation of JNK in muscles. Intracerebroventricular co-administration of TLR4 antibody attenuates AA-induced increase of TNF- α , IL-1 β , IL-6, and IL-10 in the hypothalamus.	53
		LA induces NF- κ B activation in 293T cells co-transfected with TLR2 and TLR1 or TLR6, but not in 293T cells transfected with TLR1, 2, 3, 5, 6, or 9 individually.	66
Lipid rafts	In vitro	PA induces the association of MyD88 with TLR2 in C2C12 skeletal muscle cells.	44
		TLR2 knockdown attenuates PA-induced expression of proinflammatory cytokines in primary endothelial cells.	67
		Both LA and PA induce heterodimerization of TLR2 with TLR1 or TLR6.	34,66
		SFAs induce the dimerization and recruitment of TLRs into lipid rafts.	34,65,77,78
		Disruption of lipid rafts inhibits LA-induced TLR4 dimerization, activation of NF- κ B, and expression of TLR target genes in RAW264.7 cells.	77
PKC	In vitro	PA induces the activation of PKC θ , IKK β , and JNK in 3T3-L1 adipocytes.	97
		Disruption of PKC activity suppresses PA-induced activation of JNK and IKK and diminishes PA-induced IL-6 expression in 3T3-L1 adipocytes.	45,97-99
		PA activates PKC θ , PKC α , PKC β and PKC δ in muscle cells.	94,95,100
PKC	In vivo	PKC ϵ is also activated in red muscles from rats fed with HFD compared to those fed with high-starch diet.	96

ROS	In vitro	PKC inhibition diminishes PA-induced ROS production in vascular smooth muscle cells, endothelial cells, and cardiomyocytes.	110,111
		PA increases the production of ROS in RAW264.7 cells, monocytes, vascular endothelial cells, adipocytes, smooth muscle cells, cardiomyocytes, and skeletal muscle cells.	34,77,110-113
		SFAs upregulate the expression of several components of the NADPH oxidase including NOX3, NOX4 and p22phox in HepG2 cells.	114
		SFAs stimulate the enzymatic activity of NOX2 in NIT-1 β -cells.	115
		LA induces NADPH oxidase-dependent production of ROS in RAW264.7 cells. NAC inhibits LA-induced recruitment of TLR4 to lipid rafts and TLR4 dimerization in RAW264.7 cells.	77
		Inhibition of NADPH oxidase-dependent production of ROS suppresses PA- and LA-induced phosphorylation of JNK and ERK and expression of COX-2 and TNF- α in RAW264.7 cells in low-serum medium.	31
		Silencing of p47phox significantly reduces PA-induced activation of NF- κ B and release of IL-1 β and MCP-1 in THP-1 cells.	65
		Silencing of NOX4 also inhibits PA-induced expression of MCP-1 in adipocytes.	113
		Inhibition of NADPH oxidase-dependent production of ROS attenuates PA-induced IL-1 β secretion.	34
		Inhibition of NOX2 diminishes PA-induced ROS production in smooth muscle cells, endothelial cells, and cardiomyocytes.	110,111
NLRs	In vivo	NOX4 mRNA level is markedly increased in the adipose tissue of both ob/ob and db/db mice relative to non-obese controls. Silencing of NOX4 decreases PA-induced ROS generation in adipocytes.	113
		PA-induced production of ROS is abolished in cardiomyocytes from NOX2 ^{-/-} mice.	111
	In vitro	LA-induced activation of NF- κ B and IL-8 expression is inhibited by dominant negative forms of NOD1 and NOD2 in HCT116 cells.	124
		The mRNA expression level of IL-1 β and NLRP3 in the visceral adipose tissue is correlated with body weight and adiposity, and IL-1 β processing is increased in the adipose tissue of diet-induced obese mice. 40% caloric restriction leads to significant reduction of NLRP3 and IL-1 β mRNA in mouse visceral adipose tissue. Caloric restriction and exercise intervention reduce the expression of NLRP3 and IL-1 β mRNA in subcutaneous adipose tissue of obese-T2DM subjects.	122
		PA activates NLRP3 inflammasome and increases the secretion of IL-1 β in human Sw.71 placental cells, macrophages, and hepatocytes.	30,37,125,126

(Continued)

Table 1 (Continued).

ER stress	In vitro	PA increases the levels of ER stress markers in different cells including skeletal muscle cells, monocytes, and hypothalamic neurons.	34,128,129
		Inhibition of PA-induced ER stress attenuates IL-1 β production in monocytes.	34
	In vivo	Inhibition of PA-induced ER stress suppresses the expression of TNF- α and IL-6 in the adipose tissue of animals fed with high fat diet.	51
		Oral administration of chemical chaperones to alleviate ER stress improves chronic inflammation in adipose tissue of obese mice.	132
		Rats infused with lard express markers of ER stress and expression of inflammatory markers in liver and adipose tissue compared to control.	50,131
		Animals fed with high fat diet exhibit increased phosphorylation of eIF2 α and PERK and/or elevated expression of GRP78 in the liver and adipose tissue compared to control animals.	51,130
		Mice deficient in XBP-1 decreases the activation of JNK in the liver.	130

Abbreviations: AA, arachidic acid; COX, cyclooxygenase; eIF2 α , α -subunit of eukaryotic translation initiation factor-2; ER, endoplasmic reticulum; GRP78, 78-kDa glucose-regulated protein; HFD, high-fat diet; IL, interleukin; I- κ B, inhibitor of kappa B; IKK, I- κ B kinase; JNKs, c-Jun N-terminal kinases; KC, keratinocyte chemoattractant; LA, lauric acid; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; NAC, N-acetyl cysteine; NF- κ B, nuclear factor- κ B; NLRs, NOD-like receptors; NLRP3, NOD-like receptor protein-3; NOD, nucleotide-binding oligomerization domain; PA, palmitic acid; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PKC, protein kinase C; ROS, reactive oxygen species; SFAs, saturated fatty acids; TLR, toll-like receptor; TNF- α , tumor necrosis factor- α ; XBP1, X-box protein-1.

inflammatory genes is significantly reduced when LPS-induced TLR4 dimerization is inhibited,⁸⁰ suggesting that dimerization is necessary for the activation of TLR4. In terms of TLR2, both lauric acid and palmitic acid have been shown to induce heterodimerization of TLR2 with TLR1 or TLR6.^{34,66} Several studies further demonstrated that TLR2 exists as inactive, loosely bound heterodimer with TLR1 or TLR6 without the ligand and that the binding of LP to the preformed heterodimer brings the TLRs closer in proximity and stabilizes the heterodimer.^{62,81–83} These studies suggest that SFAs induce the dimerization of TLRs and thereby activate TLR signaling. Questions still remain as to how SFAs induce the dimerization of TLR4 or stabilize TLR2 dimers with TLR1 or TLR6.

Involvement of Lipid Rafts in SFA-Induced TLR Activation

Lipid rafts are specialized microdomains of plasma membrane that are insoluble in non-ionic detergents and highly enriched with cholesterol, sphingolipids, and glycolipids.⁸⁴ Lipid rafts serve as a platform for bringing receptor molecules close together, formation of receptor complexes, receptor activation, assembly of various signaling proteins, and downstream signaling.^{85–89} TLR4 without ligands is generally believed to reside outside of lipid rafts.⁸⁷ Ligand binding induces TLR4 recruitment to lipid rafts coupled to TLR4 dimerization and subsequent downstream signaling.^{77,83,90,91} TLR2 without ligands is believed to exist in pre-formed weakly bound dimers with TLR1 or TLR6,⁹² which are brought to closer proximity upon ligand binding, initiating the recruitment of downstream signaling molecules.^{81,86,92}

SFAs have been reported to induce the dimerization and recruitment of TLRs into lipid rafts^{34,65,77,78} (Figure 1). Disruption of lipid rafts inhibits lauric acid-induced TLR4 dimerization, activation of NF- κ B, and expression of TLR target genes in RAW264.7 cells⁷⁷ (Table 1). Therefore, even though SFAs may not act as ligands that physically bind to TLRs, SFAs may alternatively modulate TLR activity by affecting their recruitment into the lipid rafts, which may in turn impact the formation of TLR receptor complexes and recruitment of downstream signaling mediators. It is currently unclear how SFAs induce the recruitment of TLRs to lipid rafts and the dimerization of TLRs. It has been suggested that SFAs may facilitate the recruitment of TLRs to the lipid rafts and TLR dimerization by affecting the physical composition of lipid rafts and the reorganization and remodeling of these microdomains.⁷⁸ Another possible scenario

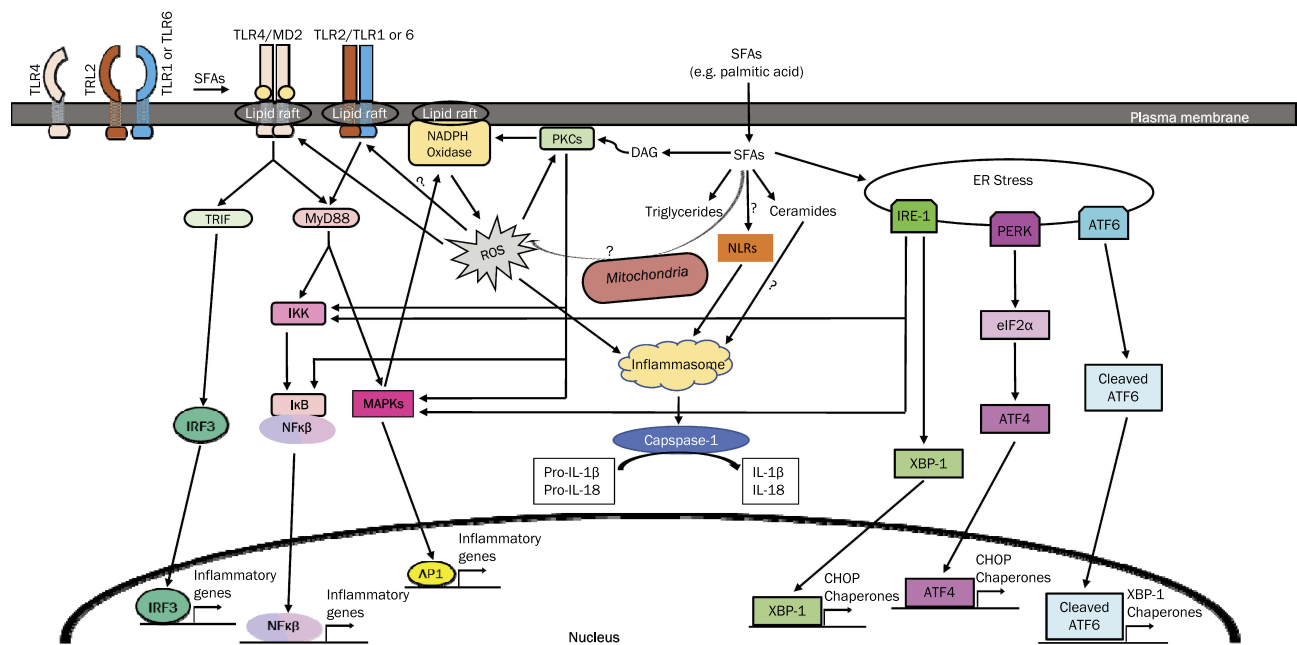


Figure 1 SFAs induce inflammation via several potential mechanisms.

may involve the association of TLR2/6 with CD36, a resident membrane protein in caveolae-lipid rafts, which may facilitate SFA-induced recruitment of TLR2/6 into lipid rafts.⁸³ It remains to be determined how CD36 may help to recruit specific TLRs to lipid rafts in response to elevated levels of SFAs.

Involvement of PKC in SFA-Induced Inflammation

Once taken up intracellularly, fatty acids may be catabolized via β -oxidation, incorporated into phospholipids, turned into triglycerides and diacylglycerol (DAG), or used in the synthesis of many other molecules. Intracellular level of DAG is increased with elevated levels of circulating FFAs.^{49,93} Palmitic acid increases DAG level in C2C12 skeletal muscle cells⁹⁴ and human muscle primary cultures.⁹⁵ DAG level is also increased in the red muscles of rats fed with high-fat diet compared with those fed with isocaloric high-starch diet.⁹⁶

DAG is a known activator for classical PKCs, such as PKC α , β I, β II, and γ , and novel PKCs, such as PKC δ , ϵ , η , and θ . When activated, PKCs are translocated from the cytosol to membranes, increasing the ratio of particulate to cytosolic PKCs. Palmitic acid treatment has been reported to induce the activation of PKC θ , IKK β , and JNK in 3T3-L1 adipocytes⁹⁷ (Table 1). Disrupting PKC activity suppresses palmitic acid-induced activation of JNK and IKK and diminishes palmitic acid-induced IL-6 expression in 3T3-L1 adipocytes,^{45,97–99}

suggesting that activation of PKC may contribute to palmitic acid-induced activation of IKK and JNK and expression of inflammatory genes in adipocytes (Figure 1). PKC ϵ is also activated in red muscles from rats fed with high-fat diet compared to those fed with high-starch diet.⁹⁶ Palmitic acid exposure activates PKC θ ,^{94,95} PKC α , PKC β and PKC δ ¹⁰⁰ in association with enhanced activation of NF- κ B,⁹⁴ increased activation of JNK, p38MAPK and ERK1/2,¹⁰⁰ and elevated expression of IL-6 and TNF- α in C2C12 skeletal muscle cells⁹⁴ (Figure 1). Kadotani et al reported that palmitic acid and stearic acid-induced COX-2 expression in myotubes requires activation of p38 MAPK and NF- κ B but may not involve PKC θ even though PKC θ phosphorylation is strongly augmented following treatment with saturated fatty acids.¹⁰¹ It should be noted that Kadotani et al used rottlerin as an inhibitor for PKC θ in their study. Rottlerin is a protein kinase inhibitor with some reported specificity for PKC δ and PKC θ and its efficacy has been questioned.¹⁰² More studies are needed to investigate whether and how various PKCs contribute to SFA-induced expression of inflammatory genes.

Involvement of ROS in SFA-Induced Inflammation

Reactive oxygen species (ROS) may affect various cellular processes including immunity, cell signaling pathways, and gene expression regulation.¹⁰³ ROS may be produced from different pathways including reduced nicotinamide adenine

dinucleotide phosphate (NADPH) oxidase, nitric oxide synthase, and mitochondria. NADPH oxidase is a multi-subunit protein with NOX as the catalytic subunit. NOX1-4 exists in stable complexes with membrane-bound p22phox. While NOX4-p22phox complex is constitutively active, activation of NOX1-3 requires further assembly with cytosolic components (p47phox, p67phox, p40phox and a GTPase Rac1 or Rac2).¹⁰⁴⁻¹⁰⁶ The assembly may take place at the lipid rafts¹⁰⁷ and is tightly regulated by protein-protein interactions and phosphorylation of p47phox.^{108,109} In response to stimulation, p47phox may become phosphorylated by a number of kinases including PKC- α , PKC- β II, PKC δ , PKC- σ , PKC- ζ , p38 MAPK, and ERK1/2, which leads to changes in its conformation, enabling p47phox to interact with other cytosolic and membrane components, and subsequent activation of the oxidase.^{108,109} In support, inhibition of PKC diminishes palmitic acid-induced ROS production in vascular smooth muscle cells, endothelial cells, and cardiomyocytes.^{110,111}

Palmitic acid has been shown to increase the production of ROS in a variety of cells including RAW264.7 cells, monocytes, vascular endothelial cells, adipocytes, smooth muscle cells, cardiomyocytes, and skeletal muscle cells.^{34,77,110-113} SFA-induced production of ROS may be mediated by the activation of NADPH oxidase. Firstly, SFAs have been reported to upregulate the expression of several components of the NADPH oxidase including NOX3, NOX4 and p22phox in HepG2 hepatocytes.¹¹⁴ Secondly, SFAs have been shown to stimulate the enzymatic activity of NOX2 in NIT-1 β -cells.¹¹⁵ Thirdly, NOX4 mRNA level is markedly increased in the adipose tissue of both ob/ob and db/db mice relative to non-obese controls.¹¹³ Fourthly, decreased activity of NADPH oxidase reduces SFA-induced production of ROS. For example, silencing of NOX4 decreases palmitic acid-induced ROS generation in adipocytes.¹¹³ Inhibition of NOX2 diminishes palmitic acid-induced ROS production in smooth muscle cells, endothelial cells, and cardiomyocytes.^{110,111} Palmitic acid-induced production of ROS is also abolished in cardiomyocytes from NOX2^{-/-} mice¹¹¹ (Table 1). These studies suggest that NADPH oxidase may be critical for and represent a key source of SFA-induced ROS (Figure 1). Consistently, lauric acid has also been shown to induce NADPH oxidase-dependent production of ROS in RAW264.7 cells.⁷⁷

It is not clear whether fatty acid oxidation in mitochondria may also contribute to the production of ROS in cells exposed to increased levels of fatty acids. While Frayn et al reported that after entering adipocytes, FFAs are predominantly rapidly converted to fatty acyl-coA and stored as

triglycerides without significant mitochondrial oxidation,¹¹⁶ Joseph et al showed that palmitic acid-induced increase of NOX2 activity is prevented by the inhibition of mitochondrial uptake of fatty acids,¹¹¹ and proposed that the mitochondrial uptake of palmitic acid may cause a small initial increase in mitochondrial ROS, which then activates PKC and NADPH oxidase to feed forward the production of ROS in the cytosol^{111,117} (Figure 1).

Once generated, ROS may be involved in the production of inflammatory genes in different ways. For example, ROS has been shown to induce TLR4 recruitment into hepatic lipid rafts, and p47phox-deficient mice exhibit significantly less recruitment of TLR4 into lipid rafts in the liver.¹¹⁸ N-acetyl cysteine, an antioxidant, also inhibits lauric acid-induced recruitment of TLR4 to lipid rafts and TLR4 dimerization in RAW264.7 cells⁷⁷ (Table 1). These studies suggest that SFA treatment induces NADPH oxidase-dependent generation of ROS, which, in turn, helps to recruit TLR4 to the lipid rafts and contribute to subsequent TLR4 dimerization and activation (Figure 1).

Inhibition of NADPH oxidase-dependent production of ROS suppresses palmitic acid- and lauric acid-induced phosphorylation of JNK and ERK and expression of COX-2 and TNF- α in RAW264.7 cells in low-serum medium,³¹ and attenuates palmitic acid-induced IL-1 β secretion.³⁴ Silencing of p47phox significantly reduces palmitic acid-induced activation of NF- κ B and release of IL-1 β and MCP-1 in THP-1 cells.⁶⁵ Silencing of NOX4 also inhibits palmitic acid-induced expression of MCP-1 in adipocytes¹¹³ (Table 1). These studies suggest that NADPH oxidase-dependent generation of ROS may contribute to the recruitment of TLR to the lipid rafts and increase the production of inflammatory markers.

Involvement of NLRs in SFA-Induced Inflammation

A family of intracellular PRRs called nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) may also be implicated in SFA-induced inflammation. NLRs have been found to recognize both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs).¹¹⁹ Among the NLR family members, activation of NOD1 and NOD2 has been shown to orchestrate NF- κ B and MAPK signaling,^{120,121} and activation of NLRP3, NLRP1B, and NLRC4 recruits the apoptotic speck protein (ASC) and pro-caspase 1. The activated caspase 1, in turn, regulates the cleavage of

pro-IL-1 β and pro-IL-18 to form active IL-1 β and IL-18, respectively.^{119,122,123}

Lauric acid-induced activation of NF- κ B and IL-8 expression is inhibited by dominant negative forms of NOD1 and NOD2 in HCT116 cells.¹²⁴ The mRNA expression level of IL-1 β and NLRP3 in the visceral adipose tissue is correlated with body weight and adiposity, and IL-1 β processing is increased in the adipose tissue of diet-induced obese mice.¹²² Furthermore, 40% caloric restriction leads to significant reduction of NLRP3 and IL-1 β mRNA in mouse visceral adipose tissue.¹²² Vandanmagsar et al also reported that the caloric restriction and exercise intervention leads to reduced expression of NLRP3 and IL-1 β mRNA in subcutaneous adipose tissue of obese-T2DM subjects¹²² (Table 1).

Palmitic acid has been shown to activate NLRP3 inflammasome and increase the secretion of IL-1 β in human Sw.71 placental cells, macrophages, and hepatocytes.^{30,37,125,126} ROS and NF- κ B have been suggested to mediate palmitic acid-induced activation of NLRP3-ASC inflammasome may be mediated by^{30,126} (Figure 1). Further studies are needed to determine whether SFAs directly interact with any of the intracellular NLRs.

Involvement of ER Stress in SFA-Induced Inflammation

SFAs have been shown to induce significant endoplasmic reticulum (ER) stress in different cells due to accumulation of unfolded or misfolded proteins. As shown in Figure 1, there are three major ER stress pathways: protein kinase RNA-like endoplasmic reticulum kinase (PERK) undergoes autophosphorylation, which, in turn, phosphorylates α -subunit of eukaryotic translation initiation factor-2 (eIF2 α), slowing the rate of translation initiation of many mRNAs while increasing the translation of ATF4 and the expression of C/EBP-homologous protein (CHOP);¹²⁷ inositol-requiring kinase 1 (IRE1) undergoes autophosphorylation, which, in turn, leads to the activation of inflammatory pathways including JNK and NF- κ B, and the splicing of Xbp protein-1 (XBP1); transcription factor 6 (ATF6) is cleaved and activated, inducing the expression of XBP1 mRNA. ATF6 and XBP1 also regulate the expression of the 78-kDa glucose-regulated protein (GRP78), a major ER chaperone.⁹⁸

Palmitic acid increases the levels of ER stress markers in different cells including skeletal muscle cells, monocytes, and hypothalamic neurons.^{34,128,129} Animals fed with high-fat diet exhibit increased phosphorylation of eIF2 α and

PERK and/or elevated expression of GRP78 in the liver and adipose tissue compared to control animals.^{51,130} Rats infused with lard express markers of ER stress and expression of inflammatory markers in liver and adipose tissue compared to control^{50,131} (Table 1).

Moreover, ER stress may be implicated in obesity-induced inflammatory response. Inhibition of palmitic acid-induced ER stress attenuates IL-1 β production in monocytes,³⁴ and suppresses the expression of TNF- α and IL-6 in the adipose tissue of animals fed with high-fat diet.⁵¹ Oral administration of chemical chaperones to alleviate ER stress has also been reported to improve chronic inflammation in adipose tissue of obese mice.¹³² These studies suggest that ER stress may be implicated in SFA-induced inflammation. Consistently, mice deficient in XBP-1 decrease the activation of JNK in the liver.¹³⁰

Conclusions and Future Directions

Chronic low-grade inflammation is central to the development of various obesity-associated pathologies including insulin resistance, diabetes, cardiovascular diseases, and NAFLD. This paper examined the mechanisms by which SFAs induce the expression of inflammatory mediators and showed that SFAs may increase the activity of NF- κ B and AP-1, enhance the activation of MAPKs, and elevate the expression of inflammatory markers via the activation of several interacting pathways.

There is significant evidence that TLR4 and TLR2 pathways are involved in SFA-induced expression of inflammatory genes. While there is no sufficient evidence for the physical binding of SFAs to TLR2 or TLR4 receptor complexes as ligands, SFAs do induce the recruitment of TLRs to the lipid rafts and their dimerization (Figure 1). Further studies need to address how SFAs specifically recruit TLR4 or TLR2 to the lipid rafts and induce their activation.

There is also evidence suggesting the involvement of TLR-independent pathways in SFA-induced inflammation. Snodgrass et al reported that silencing of TLR2 suppresses palmitic acid-induced IL-1 β by 15% while suppressing Pam3CSK4-TLR2-induced IL1 β by 63%, and that TLR4 inhibition reduces palmitic acid-induced IL1 β by 19% while inhibiting LPS-TLR4-induced IL-1 β by 80%.³⁴ Furthermore, palmitic acid-induced gene expression pattern is different from that of LPS-TLR4 activation. For example, LPS abolishes palmitic acid-induced mRNA expression of arginase 1 while palmitic acid abolishes LPS-induced mRNA expression of C/EBP δ .¹³³ Palmitic

acid potentiates LPS-induced IL-1 β but reduces LPS-induced IL6 mRNA expression.¹³³ These studies suggest that SFAs may not act only through activation of TLR2 or TLR4 pathways.

Indeed, SFAs have been shown to increase the activation of PKCs which may, in turn, activate IKK, MAPK, and NADPH oxidase. Activation of IKK-NF- κ B and MAPKs leads to increased expression of inflammatory genes while activation of NADPH oxidase increases the production of ROS. ROS enhances the recruitment of TLRs to the lipid rafts, increases the activity of PKCs, and activates the NLRP3 inflammasome (Figure 1). Further studies are needed to address whether SFAs induce a rise in mitochondrial ROS and whether the initial increase in mitochondrial ROS stimulates NADPH-mediated production of ROS in the cytosol.

The intracellular NLRs may also be involved in SFA-induced activation of inflammatory genes (Figure 1). NOD1 and NOD2 have been shown to be critical for lauric acid-induced activation of NF- κ B and IL-8,¹²⁴ and NLRP3 inflammasome has been reported to be activated following treatment with palmitic acid and increase the secretion of IL-1 β in human Sw.71 placental cells, macrophages, and hepatocytes.^{30,37,125,126} Further studies are needed to determine how SFAs activate NLR pathways. There is also evidence suggesting that SFAs may increase the ER stress which, in turn, induces the expression of inflammatory genes and ER chaperones including GRP78 (Figure 1).

Besides the mechanistic pathways described above, SFAs may also induce inflammation via binding to G-protein-coupled receptors (GPRs)²³ or production of ceramides.^{29,134,135} The increased production of ceramides may contribute to the activation of NLRP3 inflammasome.¹²² Further studies are needed to delineate how ceramides activate NLRP3, what GPRs are activated by SFAs, and how different GPR pathways may interact to affect inflammation. There are also studies suggesting that high-fat diet may affect the gut microbiota¹³⁶ and increase the diffusion of LPS from the gut to the circulatory system and/or the absorption by enterocytes during chylomicron secretion^{137,138} while Dalby et al (2018) showed that changes in the composition of caecal microbiota is not consistent within genotypes following high-fat diet consumption.¹³⁹ The focus of this paper is on the mechanisms of long-chain saturated fatty-acids-induced inflammation. Many studies examining how unsaturated fatty acids affect inflammation^{140–142} are out of the scope of this paper. Considering the complexity of our diet, the effects our diet may have on gut microbiota, and the

intricate effects different fatty acids have on multiple pathways involved in inflammation, a wholistic approach needs to be taken when evaluating preventative and therapeutic strategies to target inflammation.

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Disclosure

The authors report no conflicts of interest in this work.

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