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Review article

Saturated fatty acids trigger TLR4-mediated inflammatory response

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ABSTRACT

Toll-like receptors (TLR) mediate infection-induced inflammation and sterile inflammation by endogenous molecules. Among the TLR family, TLR4 is the best understood. However, while its downstream signaling pathways have been well defined, not all ligands of TLR4 are currently known. Current evidence suggests that saturated fatty acids (SFA) act as non-microbial TLR4 agonists, and trigger its inflammatory response. Thus, our present review provides a new perspective on the potential mechanism by which SFAs could modulate TLR4-induced inflammatory responses: (1) SFAs can be recognized by CD14-TLR4-MD2 complex and trigger inflammatory pathways, similar to lipopolysaccharide (LPS). (2) SFAs lead to modification of gut microbiota with an overproduction of LPS after a high-fat intake, enhancing this natural TLR4 ligand. (3) In addition, this metabolic endotoxemia leads to an oxidative stress thereby producing atherogenic lipids – oxLDL and oxidized phospholipids – which trigger CD36-TLR4-TLR6 inflammatory response. (4) Also, the high SFA consumption increases the lipemia and the mmLDL and oxLDL formation through oxidative modifications of LDL. The mmLDL, unlike oxLDL, is involved in activation of the CD14-TLR4-MD2 inflammatory pathway. Those molecules can induce TLR4 inflammatory response by MyD88-dependent and/or MyD88-independent pathways that, in turn, promotes the expression of proinflammatory transcript factors such as factor nuclear kappa B (NF-κB), which plays a crucial role in the induction of inflammatory mediators (cytokines, chemokines, or costimulatory molecules) implicated in the development and progression of many chronic diseases.

1. Introduction

The microbial recognition process is mediated by pattern recognition receptors (PRRs) which are linked to the innate immune system, and are mostly expressed in macrophages and dendritic cells, but they are also present in nonimmune cells [1,2]. The major PRRs include toll-like receptors (TLRs) and C-type lectin receptors. The TLRs are transmembrane proteins expressed on cell surfaces which recognize mainly microbial membrane components. They are the best characterized PRRs and are linked to

Abbreviations used: AKT, PKB – protein kinase B; ASC, apopto-sis-associated speck-like protein containing a CARD; CD14, cluster of differentiation 14; CD36, cluster of differentiation 36; COX2, ciclo-oxigenase-2; DAMP, danger-associated molecular pattern; Gro 1, Cxcl1 – chemokine (C-X-C Motif) ligand 1; IFN, type I interferon; IKK, IκB kinase; IL, interleukin; IRAK, IL-1R-associated kinase; IRF3, interferon regulating factor 3; IκB, inhibitor of NF-κB; LBP, LPS-binding protein; LDL, low-density lipoprotein; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; MCP1, monocyte chemoattractant protein 1; MD2, myeloid differential protein-2; MIP, macrophage inflammatory protein; mmLDL, minimally modified low-density lipoprotein; MyD88, myeloid differentiating primary response gene 88; NF-κB, factor nuclear kappa B; NLRP3, NOD-like receptor family, pyrin domain containing 3; oxLDL, oxidize low density lipoprotein; oxPL, oxidize phospholipids; PAMP, pathogen-associated molecular pattern; PI3K, phosphatidylinositol 3-kinase; PRR, pattern recognition receptors; PUFA, polyunsaturated fatty acid; RANTES, regulated on activation, normal t cell expressed and secreted; RIP1, receptor-interacting protein 1; ROS, reactive oxygen species; SFA, saturated fatty acid; TAB1, TGF-beta activated kinase 1/MAP3K7 binding protein 1; TAK1, transforming growth factor-β-activate kinase; TBK1, TRAF family member-associated NF- kB activator (TANK) binding kinase-1; TIR, toll-interleukin receptor; TIRAP, TIR domain containg adaptor protein; TLR, toll-like receptor; TNF, tumor necrosis factor; TRAF, TNF-receptor associated factor; TRAM, TRIF related adaptor molecule; TRIF, TIR domain–containing adaptor-inducing IFN-β; VCAM1, vascular cell adhesion molecule-1.

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bacterial and viral infection response [2,3].

Among TLRs, TLR4 is unique due to its ability to activate both MyD88-dependent and MyD88-independent pathways expressing predominantly inflammatory molecules and type I interferons (IFNs), respectively. Also, TLR4 is the only known member of the TLR family that engages all four toll-interleukin receptor (TIR) domain-containing adaptor proteins to signaling the inflammatory response [3,4].

Different sources of pathogen-associated molecular patterns (PAMPs) derived from bacterial, viral and fungus pathogens activate the TLR signaling [5]. The LPS of Gram-negative bacterial cell walls are the major PAMP, and a natural TLR4 ligand [5]. Also, TLR4 are activated by endogenous danger-associated molecular patterns (DAMPs) released as a consequence of injury and inflammation, such as oxidized low density lipoprotein (oxLDL) and oxidized phospholipids (oxPL) [5,6]. This sterile inflammatory, likewise microbial induced inflammation, can recruit neutrophils and macrophages leading to production of pro-inflammatory cytokines and chemokines, mainly tumor necrosis factor (TNF) and interleukin (IL)-1 [7].

Other possible nonmicrobial agonists for TLR4 include saturated fatty acids (SFA), but little has been explored on this subject. In fact, evidence suggests that SFA and LPS share the same inflammatory signaling pathway as TLR4, thus promoting expression of pro-inflammatory transcript factors, such as factor nuclear kappa B (NF-κB) and cyclooxygenase 2 (COX2) [8].

In order to improve our understanding on the inflammatory process mediated by SFA, we present a new perspective on the potential mechanism by which SFAs could act as TLR4-activating promoters and trigger pro-inflammatory responses involved in the development and progression of many chronic diseases and metabolic disorders, including cancer, cardiovascular diseases, metabolic syndrome and obesity-induced insulin resistance.

2. SFA trigger TLR4 inflammatory pathways

SFA particularly lauric acid (C12:0), similarly to LPS, modulate the activation of TLR4 [8–10]. In fact, the LPS is recognized by an accessory protein cluster of differentiation 14 (CD14) which is a glycoprotein, either glycosylphosphatidylinositol present in two forms: membrane bounded – at the outer leaflet of the plasma membrane – or soluble in blood [1,11]. The CD14 is best characterized for its capability to interact with LPS-binding protein (LBP) and transfer LPS to the TLR4 accessory molecule myeloid differential protein-2 (MD2). The TLR4-MD2 forms a dimer in the plasma membrane lipid [1,6]. Upon LPS recognition, the CD14-TLR4-MD2 complex engages TIRAP-MyD88 adaptors and leads do MyD88-dependent response, subsequently the CD14-TLR4-MD2 complex is endocytosed and recruits TRAM-TRIF adaptors which elicits MyD88-independent response [1,3], as we will describe below. Lee et al. (2003) suggest that both CD14 and MD2 are required for TLR4 activation by a lauric acid like LPS, signaling the inflammatory pathway of CD14-TLR4-MD2 complex [8].

Gut microbiota is a huge reservoir of LPS, which under normal conditions causes no harm in the intestinal lumen. However, a high-fat diet has been shown to induce gut microbiota alterations, raising the proportion of Gram-negative bacteria with an over-expansion of LPS, and increasing the intestinal permeability. Thus, this process promotes a bacterial translocation of Gram-negative bacteria, and endotoxin-produced bacteria from intestinal mucosa to the blood stream. This metabolic endotoxemia caused by LPS can activate the TLR4 mediated by LBP, CD14 and MD2, which leads to a MyD88-dependent and MyD88-independent response [12].

Besides the LPS, which is a classical PAMP, DAMPs derived from gut microbiota can also activate the TLR4 inflammatory pathway. Those DMAPs, such as oxLDL and oxPL, can be formed from an overproduction of LPS by inflammatory response and oxidative stress [6].

The oxLDL is known as a specific ligand of cluster of differentiation 36 (CD36) [13]. The CD36 is a glycosylated protein member of the class B scavenger receptor family, which plays an important role in glucose and fatty acid metabolism [13]. This scavenger receptor is found on the surface of diverse cell types and is also involved in TLR-dependent inflammatory response induced by various ligands such as lipid-associated products of microbial or endogenous origin [1,13].

oxLDL is sequestered by CD36 and induces intracellular CD36-TLR4-TLR6 heteromerization [14]. The CD36-TLR4-TLR6 signaling propagates by both MyD88 and TRIF adaptors, inducing pro-inflammatory mediators through MyD88-dependent and MyD88-independent pathways in absence of MD2 and CD14 that are essential cofactors for recognition of LPS by the TLR4 complex [14]. Furthermore, the CD36-TLR4-TLR6 complex acting via NF-κB and reactive oxygen species (ROS) primes the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome in response to oxLDL. Also, oxLDL recognition and endocytosis by CD36 results in the formation of intracellular cholesterol crystals that activates NLRP3 via lysosomal destabilization and stimulates IL-1β and IL-18 formation [2,15]. Moreover, oxPL has been proposed as a -TLR4 agonist, which activates MyD88-independent pathways and induces IL-6 production [16], but to date, little has been explored about this subject.

Furthermore, SFA cause a more pronounced lipemia than mono and polyunsaturated fatty acids (PUFA) [17]. Also, after consumption of a high-fat meal, the lipid peroxidation by ROS results in a minimally modified low-density lipoprotein (mmLDL) formation and the generation of extensive amounts of oxLDL [18]. The mmLDL represents an early product of progressive LDL oxidation, formed before the oxLDL [19]. Both are known as pro-inflammatory and pro-atherogenic lipoproteins [11,20]. In addition, occurs a local production of oxPL [16].

Although the polyunsaturated fatty acids (PUFA) are more prone to oxidation and oxLDL synthesis due to their high degree of unsaturation [21], experimental studies have shown that n-3 PUFA inhibit the TLR4-induced signaling pathways and target gene expression [8,10]. This fact seems to be related to the anti-inflammatory effects of PUFA mediated by the G protein-coupled receptor 120 (GPR120). The stimulation of GPR120 with n-3 PUFA inhibit TLR4 signaling probably by its association with β-arrestin2. This complex is internalized, and β-arrestin2 binds to TAB1 (TGF-beta-activated kinase 1/MAP3K7 binding protein 1), resulting in inhibition of TAK1 (transforming growth factor-β-activate kinase) phosphorylation and activation and, consequently, the inactivation of the TLR4 signaling [22]. In addition, n3 PUFA disrupts the translocation of TLR4 into lipid raft, preventing its activation [9].

Like oxLDL, the mmLDL is an endogenous TLR4 ligand which is not recognized by scavenger receptors but binds to a CD14 receptor, and like LPS, stimulates the classic TLR4 response through a CD14-TLR4-MD2 complex and induces the activating protein-1 (AP1) and phosphatidylinositol 3-kinase (PI3K) activation [1,19]. Notable, unlike oxLDL, the mmLDL is not internalized [18]. Moreover, the increased exposure of mmLDL can enhance sterile inflammation by increased uptake of oxLDL, probably mediated by a higher expression of CD36 [11].

3. TLR4 activation

Specifically, TLR4 engages all four toll-interleukin receptor (TIR) adaptors proteins to signing the chain reaction needed to activate intracellular signaling inflammatory response, unlike other TLRs

family members [4]. The four TIR domain-containing adaptors are MyD88, TIRAP, TRAM and TRIF. These adaptors initiate a chain of phosphorylation and ubiquination reaction, and the adaptor "choice" determines the transcriptional response [3]. The MyD88 is an adaptor protein recruited by TIRAP and is involved in the expression of pro-inflammatory molecules, which is a MyD88-dependent response. Whereas, in the MyD88-independent pathway, TRIF recruited by TRAM elicts a type I interferon response, and also mediates the production of pro-inflammatory molecules in a delayed signaling through endocytosis mechanisms (late signaling) [1,23].

Furthermore, in response to oxLDL, CD36 induces intracellular CD36-TLR4-TLR6 heteromerization [15], and both MyD88 and TRIF adaptors induce pro-inflammatory mediators through MyD88-dependent and MyD88-independent pathways [14].

3.1. MyD88-dependent pathway

TLR4 ligands, such as LPS endotoxin and SFA, with the help of CD14 and MD2, promote CD14-TLR4-MD2 activation and induce TLR4 dimerization, which in turns recruit TIRAP-MyD88 adaptors to TIR domains [1,6]. The TIRAP-MyD88 signaling pathway is induced from the plasma membrane [3], initiating the MyD88-dependent downstream signaling. MyD88 recruits IL-1R-associated kinase-4 (IRAK4) that, in turn, recruits, actives and degrades IRAK1. The IRAK1 then associates with TNF-receptor associated factor-6 (TRAF6), thereby activating TAK1 that activates the IκB kinase (IKK) and mitogen-activated protein kinase (MAPK) pathways [4]. The activation of the IKK complex (IKKα, IKKβ, IKKγ) leads to phosphorylation of the N-terminal of IκB proteins and, consequently, activation of NF-κB, thereby stimulating the transcription of COX2, TNF-α, IL1-β, IL6, IL8, IL12, IFN-γ, MIP1-α, MIP1-β, MIP-2, MCP1, VCAM1, RANTES [1,18,24,25]. Moreover, the MAPK leads to increased transcription factor AP1 which plays a crucial role in the induction of inflammatory-response genes including COX2 [8,26,27].

3.2. MyD88-independent pathway

A second set of TIR domain adaptors, TRIF and TRAM, is involved in a MyD88-independent pathway. These adaptors activate the expression of interferon regulating factor 3 (IRF3) by TRAF3 which associates with TBK1 (TRAF family member-associated NF-κB activator (TANK) binding kinase-1) and IKKi (also known as IKKε) mediate the dimerization and translocation of IRF3, and thereby stimulates the production of IFN [4]. The TRAM-TRIF pathway is induced from an intracellular compartment (endosome), a requisite step in TLR4 signaling and production of IFN [3].

Kagan et al. (2008) propose that the CD14-TLR4-MD2 complex is activated in plasma membrane and initiates TLR4 signals trough TIRAP-MyD88 and TRAM-TRIF, sequentially. During endocytosis, TIRAP-MyD88 complex is released from the invaginating membrane and allows the TRAM-TRIF adaptors to engage the TIR domain of TLR4 on early endosomes, leading to induction of the IFN expression from endosomal compartment [3].

Also, TRIF-TRAM adaptors participate in a late-phase activation of NF-κB and MAPK signaling. This delayed MyD88-independent activation of NF-κB and MAPK involves the TRIF adaptor that, in turn, recruits TRAF6 and receptor-interacting protein 1 (RIP1), thus facilitating TAK1 activation, and results in a robust NF-κB activation [4,23].

TLR4 agonists can also modulate TLR4 downstream signaling involving PI3K and AKT (also known as protein kinase B (PKB)) which, in turn, can activate NF- κB [8]. The AKT activation mechanism remains controversial, but it seems to be dependent on the presence of MyD88 and/or TRIF adaptor proteins [28].

3.3. CD36

OxLDL recognition by CD36 induces intracellular CD36-TLR4-TLR6 heteromerization, independent of MD2 and CD14 that are well known components of the TLR4 complex [3]. The CD36-TLR4-TLR6 signaling leads to the expression of MyD88-dependent response upregulating the expression of Gro 1, MIP-1 and MIP-2; and also MyD88-independent genes, inducing the RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) transcription in response to oxLDL. Thus, engaging both adaptor pathways [3] which mediate the PI3K/AKT pathway activation, will result in activation of IKK and NF-κB [18].

In addition, the oxLDL uptake by CD36 and its subsequent nucleation into cholesterol crystals inside the cell cause lysosomal destabilization and NLRP3 activation. The NLRP3 assembles with the adaptor protein apopto-sis-associated speck-like protein containing a CARD (ASC) and caspase-1 into a multiprotein complex – inflammasome – which cleaves the inactive precursors to the active forms of IL1-β and IL18 [2,15]. OxLDL also primes the NLRP3 inflammasome through a mechanism that involves the up regulation of NF-κB expression [15].

4. Concluding remarks

While the downstream signaling pathways have been well defined, not all ligands of TLR4 are currently known. Thus, we propose a link of SFA to innate inflammatory response through TLR4 (Fig. 1). As we have shown SFA could be recognized by the CD14-TLR4-MD2 complex, and trigger TLR4 inflammatory pathways. In addition, the SFA can lead to a gut microbiota modification and an overexpansion of LPS in the blood stream. This metabolic endotoxemia could activate the TLR4 complex mediated by LBP, CD14 and MD2. Besides, DAMPs – including oxLDL and oxPL – derived from gut microbiota, formed from an overproduction of LPS, and also produced after the consumption of a high-fat meal, can activate the TLR4 inflammatory pathways. OxLDL, recognized by CD36, induces the CD36-TLR4-TLR6 complex that leads to an inflammatory response-independent MD2 and CD14, known components of the TLR4 homodimeric complex. Another atherogenic lipid, such as mmLDL, results of LDL oxidative modifications by ROS produced after a high-fat intake, is also able to induce the CD14-TLR4-MD2 complex. Those microbial – LPS – and non-microbial patterns – mmLDL, oxLDL, oxPL and SFA – that can trigger inflammation and regulate inflammatory pathways through TLR4 activation involving a MyD88-dependent and/or a MyD88-independent response that, in turn, leads to the expression of several inflammatory mediators (cytokines, chemokines or co-stimulatory molecules), as described.

Overall, the present review indicates a relationship between SFA and TLR4 associated with a subclinical inflammation. Increasing evidence has established a link between chronic inflammation and many chronic diseases and metabolic disorders, including cancer, cardiovascular diseases, metabolic syndrome and obesity-induced insulin resistance [29–32]. Therefore, the present review indicates that a reduction of potential TLR4 ligands may have positive impact on the prevention and treatment of such disorders. In addition, reduction in the SFA intake would be interesting when exploiting the TLR4 as an important control point in the inflammatory response, which may be useful in the future development of new therapeutic approaches to prevent and treat subclinical inflammation. However, more clinical studies are required in order to validate the proposed mechanisms, and a deeper knowledge of lipid metabolism is needed for a better understanding of its

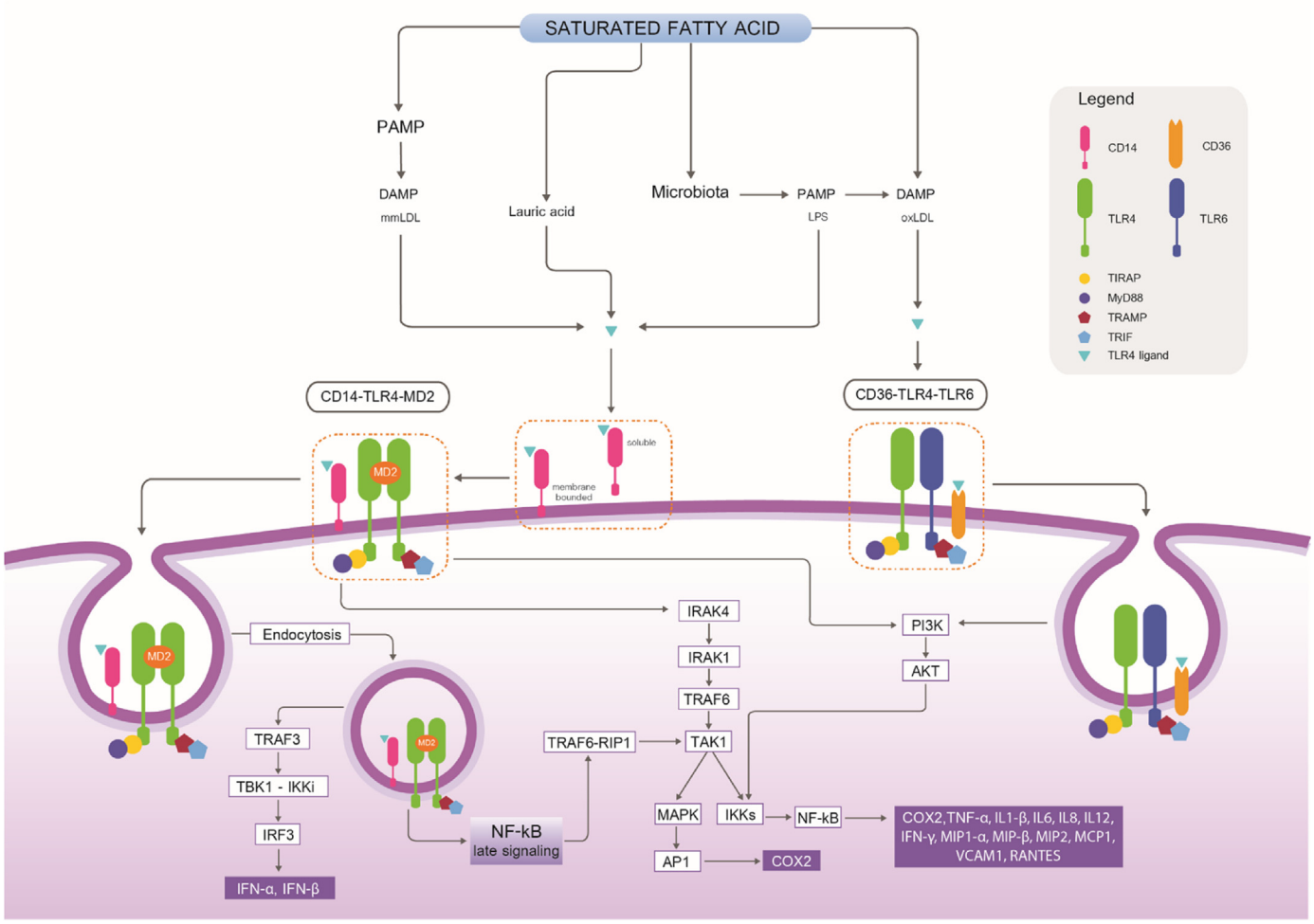

Fig. 1. Activation of pro-inflammatory mediators by saturated fatty acids though TLR4. The saturated fatty acids (SFA) act as non-microbial TLR4 agonists or indirectly promotes the TLR4 activation, triggering its inflammatory response: 1) Similarly to LPS, the SFA can be recognized by CD14-TLR4-MD2 complex and trigger inflammatory pathways; 2) Also SFA leads to gut microbiota modification with an LPS overproduction after a high-fat intake, enhancing this natural TLR4 ligand; 3) In addition, this metabolic endotoxaemia leads to an oxidative stress thereby producing atherogenic lipids – oxLDL and oxidized phospholipid – which trigger CD36-TLR4-TLR6 inflammatory response; 4) And the high-SFA consumption increases the lipemia and the mmLDL and oxLDL formation through oxidative modifications of LDL. The mmLDL, unlike oxLDL, is involved in activation of the CD14-TLR4-MD2 inflammatory pathway. All those molecules can induce TLR4 inflammatory pathways by MyD88-dependent and/or MyD88-independent that in turn promotes the expression of pro-inflammatory transcript factors such as NF-κB (factor nuclear kappa B), which plays a crucial role in the induction of inflammatory mediators (cytokines, chemokines or co-stimulatory molecules) implicated in the development and progression of many chronic diseases.

relationship with inflammation and the development and progression of chronic diseases.

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