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# CD14: Biology and role in the pathogenesis of disease

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ABSTRACT

Human monocyte differentiation antigen CD14 is a pattern recognition receptor (PRR) that enhances innate immune responses. CD14 was first identified as a marker of monocytes to signal intracellular responses upon bacterial encounters. Given the absence of an intracellular tail, CD14 was doubted to have the signaling capacities. Later CD14 was confirmed as the TLR co-receptor for the detection of pathogen-associated molecular patterns. However, CD14 has been revealed as a multi-talented receptor. In last decade, CD14 was identified to activate NFAT to regulate the life cycle of myeloid cells in a TLR4-independent manner and to transport inflammatory lipids to induce phagocyte hyperactivation. And its influences on multiple related diseases have been further considered. In this review, we summarize advancements in the basic biology of the CD14 including its structure, binding ligands, signaling pathways, and its roles in the pathogenesis of inflammation, atherosclerosis, tumor and metabolic diseases. We also discuss the therapeutic potential of targeting the CD14 in related diseases.

Human monocyte differentiation antigen CD14 was the first identified pattern recognition receptor (PRR) that binds directly to LPS. It has long been known as a co-receptor for several Toll-like Receptors (TLRs) which transfers bacterial cell wall products to TLRs to engage signaling cascade both at the cell surface and in the endosomal compartment to make innate immune system react readily to insults such as infection or injury resulting in cell damage [1,2]. In addition to its functions in innate immunity, CD14 is proposed to take a more general role in regulating cancer, atherosclerosis, metabolic disease and so on. In this review, we summarized the basic biology of CD14 and it influences on the pathogenesis of disease and focused on the recent progress on the multiple roles exerted by CD14.

## 1. Structure of CD14

The CD14 gene is located at bands 5q23-q31, encoding 1400 bp RNA. After the translation, the C-terminal guide sequence (28–32 amino acids) was replaced by glycosylposphatidylinositol (GPI) anchor. Therefore, membrane-bound forms of CD14 (mCD14) is anchored on the surface of cell membrane by GPI tail. Soluble forms of CD14 (sCD14) could be secreted by activated cells which release CD14 by proteinase dependent (48 kDa) or independent shedding (55 kDa) [1]. mCD14 is highly expressed on myeloid lineage cells, such as monocytes, macrophages, DCs and microglia, and is present at lesser extent in non-immune cells. sCD14 exists in serum, cerebrospinal and other body fluids, to confer LPS-responsiveness to cells not expressing CD14 [3–5].

As a co-receptor, both mCD14 and sCD14 sensitize cells to LPS by transfering LPS molecules to TLR4 [2]. Enough attention has been paid to the function sites in CD14 binding to LPS. Structural analyses show that CD14 has several amino acid sequences associated with LPS binding—26DEES29, 37PKPD40, 50AADVE54, 73ADLGQF78. These sequences cluster outside the entrance to a large hydrophobic pocket on CD14 at the N-terminal side of the horseshoe-like structure containing leucine-rich-repeat proteins [6] (Figs. 1 and 2).

Regions in CD14 responsible for LPS signaling are different from regions for LPS binding. The sequences of Glu7–Asp10, Asp9–Phe13, or Leu91–Glu101 in human CD14 or Pro151–Leu153 in mouse CD14 are responsible for LPS signaling. These regions are also clustered in a separate area near the NH2-terminal pocket on the same side of CD14 [7] and may play an important role in the interactions.

## 2. Ligands of CD14

The generous size of the pocket on CD14 allows structural variation in the hydrophobic portion of ligands. Hence, CD14 has wide range of ligands including PAMP (mainly from bacteria and virus) and

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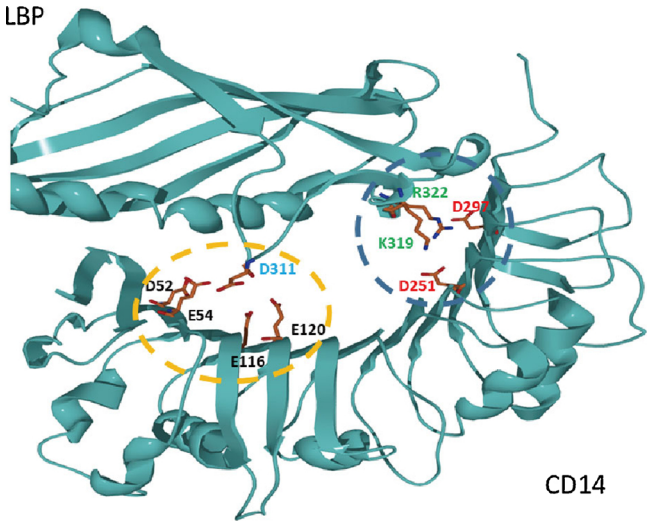


**Fig. 1.** Potential interactions between LBP (up) and CD14 (down) during LPS transfer to CD14. The identified functional motifs in the CD14 required for LBP binding are circled in yellow (acidic residues) and blue (basic residues).

endogenous molecule such as heat shock protein, phospholipid and amyloid. CD14 is required to cell effect induced by part of ligands, such as LPS, LTA and HSP70. To most of other ligands, CD14 only functions as an adaptor and a coreceptor of TLR to increase their affinity to TLR and augments their activity.

### 2.1. Gram-negative bacteria

Gram-negative bacteria have outer membrane containing LPS. LPS-rich membranes or LPS aggregates are bound by LPS-binding protein (LBP) to form LPS-LBP complex, which interacted with C-terminal acidic patch of CD14 (D251 and D297) [8]. Then the electrostatic repulsion between LBP and N-terminal acidic patch (D52, E54, E116, and E120) mediates the rapid dissociation of CD14-LPS complex from LBP-LPS [9] (Fig. 1). These complexes directly transfer monomeric LPS to myeloid differentiation factor 2 (MD2) [1]. Cells that normally express mCD14 at a very low level can also transfer LPS to MD2-TLR4 complex with the help of sCD14 in plasma [3]. In addition, TLR2 also plays a role in CD14-dependent LPS recognition [2].

The extent of CD14 requirement for LPS recognition is affected by concentration and chemotype of LPS. For instances, CD14 is required to activate TLR4 with low LPS concentration treatment [10]. And CD14 is not required by rough LPS (rLPS) to lead to MyD88-dependent responses while is strictly required by rLPS at low dose or smooth LPS (sLPS) to lead to TRIF-dependent signaling pathway [11]. This discriminatory requirement is in one hand based on ability of CD14 to recognize different degrees of glycosylation on sLPS and rLPS, which TLR4 lacks [2]. On the other hand, after the formation of CD14-LPS complex, CD14 is assumed to leave the LPS molecule in the cell membrane to be picked up by MD2 and then to catalyze the rapid insertion of LPS into phospholipid bilayers [12,13]. Hydrophobic rLPS in comparison with sLPS facilitates the membrane insertion and integration of LPS into the plasma membrane. So rLPS can be directly incorporated into the rafts and trigger TLR4 signaling without CD14 requirement [14]. In the same way, treatment of cells with high doses of LPS could also facilitate a direct insertion of LPS into the plasma membrane and activate TLR4 in a CD14-independent pathway [2].

However, not all CD14-LPS complexes can provoke signal pathway. First, high concentration of sCD14 and LBP can suppress LPS-responsiveness by competitively removing LPS from mCD14 [2]. Second, LPS can be transferred to lipoproteins such as reconstituted high density lipoprotein (R-HDL) by LPS-sCD14 complexes and then be neutralized [3,15]. Third, CD14- and SR-A-mediated uptake of LPS is thought to overlap with the macropinocytosis of LPS which is induced only in cells that naturally express CD14 (BMDM, DCs, and MEFs, but not A20 B cells) in a TLR4 dependent manner. This non-signaling mediated uptake of LPS competes with the TLR4/LPS endocytosis [16].

CD14 also directly binds to triacyl lipopeptides to drive TLR2/TLR1 complex formation and facilitates recognition and internalization of the lipopeptides by the receptor complex [17]. It also helps lipid Flavolipin, Porphyromonas gingivalis FimA, fimbriae protein CsgA to activate cells [18].

### 2.2. Gram-positive bacteria

CD14 binds to Peptidoglycan (PGN) with partially identical conformational binding sites on CD14 compared with LPS and then leads to TLR2-mediated transcription factors NF-κB, CREB/ATF and AP-1 activation in human and mouse monocytes to produce proinflammatory mediator [19]. Cell wall lipoproteins and lipoteichoic acid (LTA) that commonly co-purify with PGN may account for CD14-dependent inflammatory reaction [20]. CD14 markedly enhances LTA binding to the plasma membrane to promote NF-κB activation [21]. Then LTA is internalized along with the lipid raft containing CD14, CD36 and TLR2 via a clathrin-independent endocytic route, but this internalization is not required for signaling [22]. In addition, N-terminal 152 amino acids of sCD14 was reported to interact with lipoarabinomannan to stimulate CD14/TLR2-dependent signaling [19].

### 2.3. Virus

Viral nucleic acids are effective PAMPs. CD14 is believed to bind directly to a synthetic analog of dsRNA pIpC, aids cellular uptake of pIpC and brings it to TLR3 to yield cell activation [23] but plays no significant role in ssRNA-induced TLR7/8-dependent cell activation [24]. For ssDNA virus, CD14 binds to CpG-DNA directly to promote TLR9-dependent CpG-DNA recognition and proinflammatory cytokine secretion [24]. sCD14 differentially enhances human TLR9 activation with treatment of different class of CpG oligodeoxynucleotides [25]. CD14 may mediate the process of CpG-DNA internalization, which indicates CD14 appears as TLR9 coreceptor by enhancing ligand endocytosis [24].

In addition to nucleic acid, several virus proteins, like the fusion protein of respiratory syncytial virus, cytomegalovirus (CMV) virions, HBV HBsAg, also can be recognized by CD14 to induce innate immune response [26–28].

### 2.4. Heat shock protein

In the human monocytes, CD14 is required by exogenous HSP70 to elicit a rapid intracellular calcium flux and to induce proinflammatory cytokine production [29]. Stress-inducible endogenous HSP70 from human myocardial cells are released into the circulation and provoke similar effects with CD14 involved [30]. In addition, CD14 is required by extracellular HSP72 to stimulate human neutrophil chemotaxis, by Chaperonin 60.1 from *Mycobacterium tuberculosis* and Chaperonin 60.3 from *Rhizobium leguminosarum* to induce cytokine synthesis [31–33]. However, it had been reported that contamination of LPS and associated molecules in recombinant HSP60 and HSP70 preparation were responsible for the induction of TNF-α release by murine macrophages [34,35]. In addition, Grp78, the member of HSP70 family, was reported to colocalize with CD14 at plasma membrane to downregulate the production of inflammatory cytokines and promote TLR4 endocytosis to favor the resolution of inflammation [36,37]. According to multiple sequence alignment, all CD14-related heat shock protein has a common conservative domain (G-x(2,9)-S-x-[LY]-F-x(10)-L-x-D-A-x-[ILV]) which may bind to CD14.

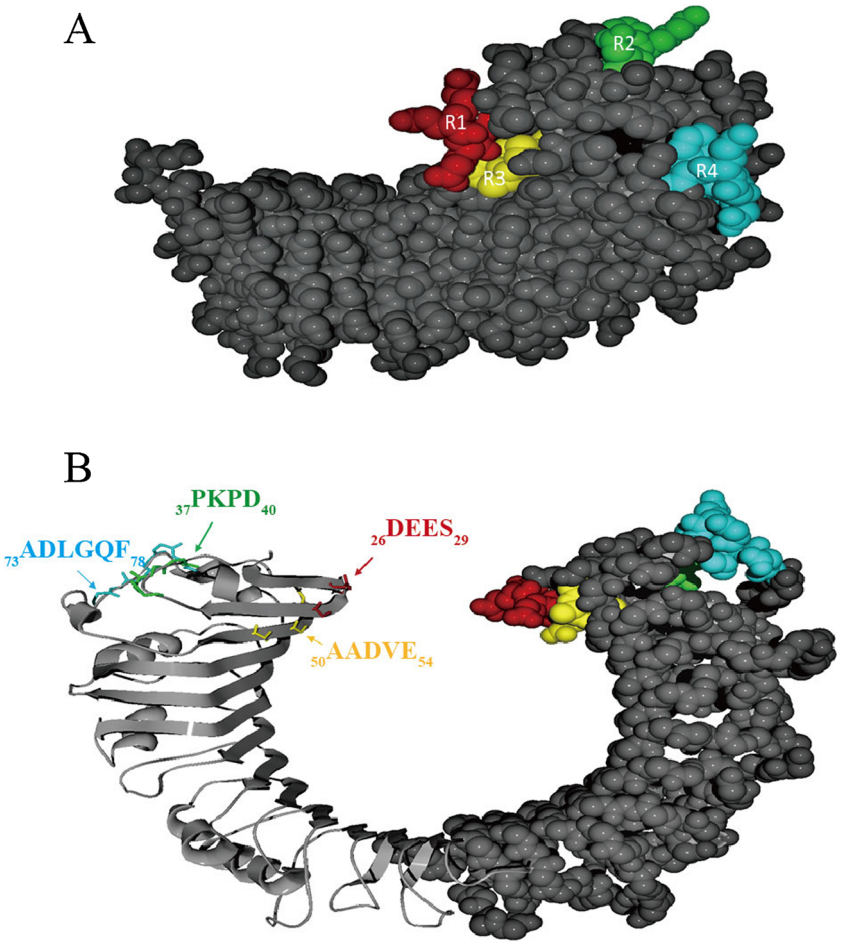


**Fig. 2.** A. The four LPS-binding regions of CD14 monomer is depicted. R1–R4 are colored in red, green, yellow and blue. B. Overall structure of the CD14 dimer. The left half is shown in ribbon and the right in space filling structure.

### *2.5. Other endogenous molecules*

Serum phosphatidylinositides (PI) can be bound to CD14 at the LPS binding site with high affinity to inhibit LPS-induced cellular responses [38], as well as Palmitoyl-oleoyl-phosphatidylglycerol (POPG) and dimyristoylphosphatidylglycerol (DMPG). Afterwards, mCD14-bound extracellular PI is rapidly internalized and used as a source of arachidonate for leukotriene synthesis [31]. Because of high affinity binding, sCD14 acts as a shuttle for LPS and phospholipids to mediate their influx and efflux from membranes to HDL particles [39].

CD14 is also required for β-amyloid (Aβ)-promoted microglial activation [40] and for curli-amyloid mediated activation of TLR2/TLR1 complex [18], which suggests that CD14 is a common receptor for other amyloid-forming proteins [41]. In addition, biglycan directly binds to CD14, induces TNF-α and chemokine release in macrophages and promotes acute inflammation [42].

## 3. Signaling pathway Signaling pathway

### *3.1. Signaling from the plasma membrane*

#### *3.1.1. MyD88-dependent signaling*

As we have discussed before, CD14 helps ligands to promote TLR4-MD2 activation, which in turn recruits TIRAP-MyD88 adaptors to TIR domains [43]. LPS-induced clustering of CD14 triggers accumulation of PIP5KIα and PIP5KIγ and therefore generation of PI(4,5)P2 in rafts [44]. PI(4,5)P2-containing membranes facilitate TIRAP to engage MyD88 for the initiation of TLR signaling. MyD88 recruits IL-1R-associated kinase-4 (IRAK4) that, in turn, phosphorylates, actives and degrades IRAK1/2 to assemble a higher-order filamentous structure called the myddosome [45]. The myddosome then associates with TNF-receptor associated factor-6 (TRAF6) to elicit Lys63-linked poly-ubiquitination, subsequently activating NF-κB and MAPK pathways, thereby stimulating the transcription of proinflammatory factors such as TNF-α, IL-1β, IL-6 etc [2] (Fig. 3A).

#### *3.1.2. CD14-NFAT signaling*

Following LPS stimulation, in a TLR-independent manner, CD14 recruits src family kinase (SFK) and phospholipase Cγ2 (PLCγ2) at the lipid rafts, in turn, hydrolyzes membrane phosphatidylinositol bisphosphate (PIP2), leads to an extracellular $Ca^{2+}$ influx and, consequently, the activation of the phosphatase calcineurin [46] (Fig. 3B). Then cytoplasmic NFAT is dephosphorylated and migrates to the nucleus to trigger the expression of many genes such as IL-2, Nur77 and mPGES-1, all of which regulate many biological processes of DCs [46]. For instance, they inhibit myeloid lineage development [47], maintain monocyte-derived DCs in the immature stage [48] and induce a proapoptotic pathway in terminally differentiated DCs [46]. However, the CD14/NFAT pathway found in DCs does not work in macrophages because macrophages do not show a $Ca^{2+}$ response or activation of NFAT upon LPS stimulation and, consequently, not undergo LPS-induced apoptosis [16,46].

There are several speculations about how CD14 transduces this signaling pathway. First, CD14 directly induces Ca2+ mobilization by recruiting SFK and PLCγ2 at the lipid rafts because similar process has been observed in other GPI-anchored receptors. For instance, CD59

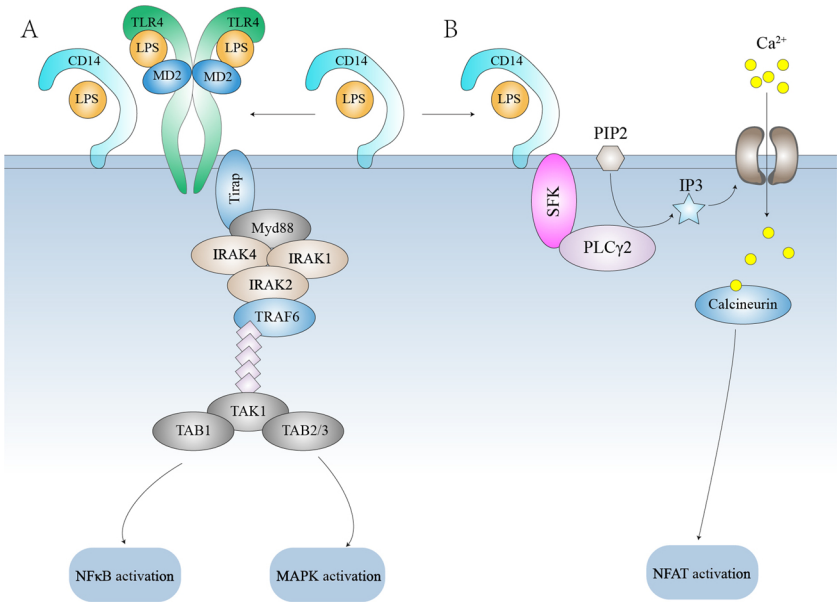


**Fig. 3.** CD14-dependent signaling from the plasma membrane A. CD14 activates TLR4-MD2 complex and promotes TLR4 dimerization after binding with LPS. TLR4 engagement induces formation of the Myddosome, which is based on MyD88 and also contains IRAKs. IRAK1 activation induces TRAF6 activation following K63-linked polyubiquitination on TRAF6 itself and TAK1. TAK1 activation subsequently leads to the activation of NFκB and MAPKs. B. CD14 induces Src-family kinase and phospholipase Cγ2 activation, which convert PIP2 to IP3. IP3 binds to IP3R and promotes influx of extracellular $Ca^{2+}$ and calcineurin-dependent nuclear NFAT translocation.

recruits Gαi2, Lyn, PLCγ2 and then transduces the extracellular signal to the intracellular IP3–$Ca^{2+}$ signal [49,50]. Furthermore, disruption of lipid raft integrity with a cholesterol-depleting agent abolishes the ability of wild-type DCs to induce a $Ca^{2+}$ response to LPS [12]. Second, a crosstalk between CD14 and other transmembrane proteins occurs in this process. For instance, the ligation of ITAM-coupled receptors such as FcR and DAP12 in myeloid cells leads to the phosphorylation of SFK followed by recruitment of PLC and activation of NFAT in the same way of CD14-dependent pathway [51]. These ITAM-coupled receptors mediate CD14-dependent TLR4 endocytosis, which implies that LPS-activated CD14 might, in turn, also promote signaling of these receptors [16].

### 3.2. Membrane transport and signal transduction

Binding with ligands promotes endocytosis of CD14 and its complex and triggers signal transduction. Both CD14 and TLR4 endocytosis is dependent on the spleen tyrosine kinase (Syk) which binds to proteins containing ITAM domain and activates downstream effector PLCγ2. PLCγ2 then promotes generation of inositol trisphosphate (IP3) and subsequent release of $Ca^{2+}$ from intracellular stores which leads to CD14 and TLR4 internalization [16,52] (Fig. 4A). In these process, although CD14 works mainly as a transporter rather than directly participates in the downstream signaling, it controls these trafficking and signaling functions [16,53]. In addition, CD14 undergoes similar signaling pathway as it contributes to receptor endocytosis and NFAT activation, which implies these two pathways may crosstalk.

#### 3.2.1. TLR4-dependent TRIF signaling

CD14 is the key regulator of LPS-induced TLR4 endocytosis in several TLR4-bearing cells [16,54]. It binds to LPS directly, accumulates with TLR4 with lower mobility and stablizes tight heterodimerization of TLR4/MD2, which promotes the selection of TLR4 complex as cargo for endocytosis. Although most of LPS-induced internalized TLR4 complex is degraded in late endosomes/lysosome [55], it also triggers signaling pathway in the early/sorting endosomes through the adaptors TRAM and TRIF which mediate the activation of the interferon regulatory factor-3 (IRF3), resulting in production of IFN-β, IP-10 and other genes, as well as delayed and weak NF-κB activation [16] (Fig. 4A). By the means of phagocytosis of E. coli or LPS-coated latex beads, TLR4/LPS uptake leading to TRIF activation does not strictly require CD14. This phenomenon indicates that the primary function of CD14 in TRIF signaling is to deliver TLR4 to endosomes, rather than physically change the conformation of TLR4 to permit TRIF signaling [16]. After TLR4 endocytosis, CD14 will never reassociate with LPS in any intracellular compartment to transfer it to TLR4 [8].

Even without TLR4 ligands, CD14 ligation by its specific Ab also directly induces the internalization of surface TLR4 [56]. Similarly, CD11b directly interacts with CD14 to facilitate TLR4 endocytosis in BMDCs [57]. CD14 also acts as a key receptor for secreted GRP78 to promote internalization of TLR4 to lysosomes, and therefore induces a TLR4 deficiency that renders cells poorly responsive to subsequent encounters with LPS [36]. When it comes to TLR3, which only resides in endosome, CD14 is not absolutely required for TLR3-mediated, TRIF-dependent cytokines and chemokines secretion [58].

#### 3.2.2. TLR-independent inflammasome signaling

oxPAPC, a lipids mixture derived from dying cells, directly binds to CD14 and promotes CD14 endocytosis in the similar mechanism with LPS. CD14 helps oxPAPC to be transported into cytoplasm to bind with caspase-11 and lead to NLRP3 inflammasome assembly and secretion of IL-1 and IL-18. This CD14-mediated oxPAPC endocytosis induces an inflammasome-dependent state of higher T-cell activation potential. Cytosol LPS, in turn, activates caspase-11, which cleaves gasdermin D (GSDMD) to trigger pyroptosis [59]. oxPAPC-induced CD14 endocytosis diminishes the abundance of CD14 at the plasma membrane, creating an inducible CD14 deficiency that significantly suppresses the subsequent response to LPS. Therefore, OxPAPC-induced CD14 internalization inhibits both MyD88 and TRIF-signaling pathway induced by LPS [53,60] (Fig. 4B).

## 4. Role of CD14 in pathogenesis

### 4.1. In inflammation

The role of CD14 during microbial infections remains largely to be defined, considering the functional versatility of CD14 was uncovered in innate immunity. Conventionally, as it orchestrates functions of TLR4 and related immune receptors, CD14 is indispensable for inflammatory disorders [2]. For instance, CD14 significantly promoted the LPS-induced inflammation in lung [61], intestine [62], liver [63], in early abdominal aortic aneurysm formation [64] and in the scenario of skin edema [65]. CD14 deficiency resisted the LPS or E. coli-induced lethal inflammation in systemic septic shock [10]. Accordingly, many drugs

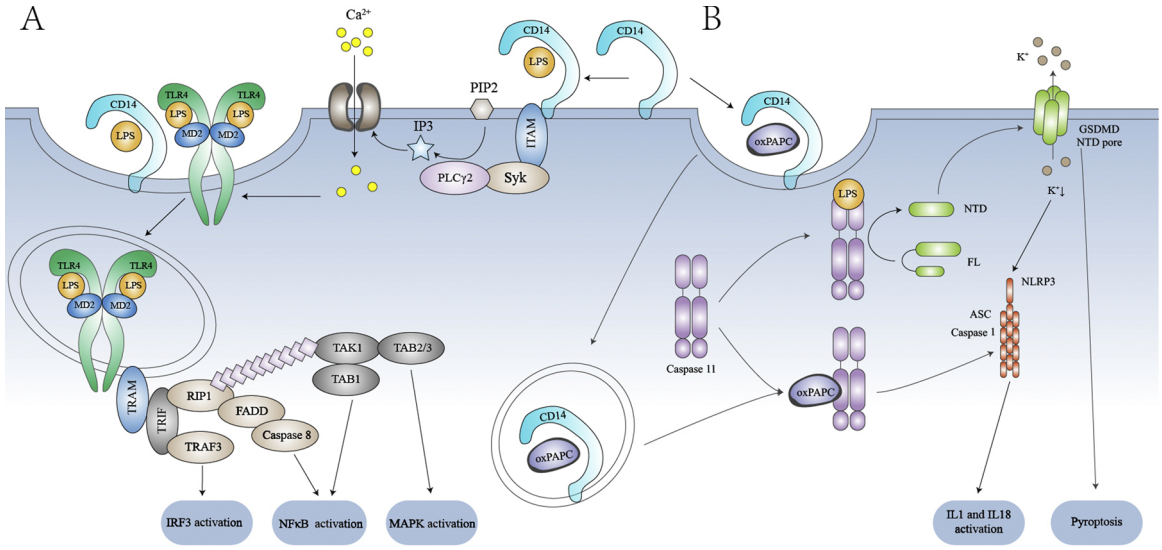


**Fig. 4.** CD14-induced membrane transport and signal transduction in the cytoplasm. A. CD14 activates tyrosine kinase Syk and its downstream effector PLCγ2 through an ITAM-containing receptor. Then PLCγ2 promotes influx of extracellular $Ca^{2+}$ and transports TLR4 dimer to endosome. In the endosome TLR4 induces TRIF activation following RIP-1 and TRAF3 recruitment. RIP-1 activates the TAK1 complex and Caspase 8 and the following MAPK and NFκB. TRAF3 recruits downstream adaptors for IRF3 phosphorylation. B. Both oxPAPC and LPS could directly bind to CD14 and promote the complex endocytosis. Active caspase-11 bound by cytosol LPS cleaves GSDMD to liberate its NTD, which migrates to the plasma membrane to form pores. Accumulation of GSDMD pores on the plasma membrane eventually leads to pyroptotic cell death. The NLRP3 inflammasome is activated following formation of the GSDMD pores, due to the dissipation of intracellular $K^+$ through the pores. The oxPAPC-caspase-11 complex directly activates NLRP3 inflammasome and promotes IL1 and IL18 release without participation of GSDMD. FL, full-length; NTD, amino-terminal domain.

have been developed to blunt CD14-mediated inflammation. For instance, synthetic lipid A analogs like Eritoran (E5564) bind to CD14 directly to inhibit LPS-induced TLR2 and TLR4 signaling and therefore have been discovered to resist the toxic effects of endotoxin [66]. Other factors also aggravate inflammation via activating CD14 or increasing the expression of it. For instance, microglial CD14 activated by iNOS contributes to neuroinflammation in cerebral ischemia, GM-CSF promotes neuroinflammation through increasing the expression of CD14 and TLR2-derived peptides are developed to target CD14 to rescue proinflammatory responses of immunosuppressed sepsis patients [67–69].

However, a variety of studies have challenged the traditional notion that CD14 simply served as a pro-inflammatory mediator. Lei et al reported that CD14 facilitated the resolution of inflammation by engaging Grp78 because this engagement induced the TLR4 internalization to create an inducible TLR4 deficiency [36,37]. CD14 deficiency make mice to show more severe and prolonged inflammation with less production of IL-10 upon Borrelia burgdorferi infection [70], and to exhibit significantly increased bacterial clearance upon P. aeruginosa corneal infection by production of CXC chemokines and neutrophil infiltration [54]. In IBD development, CD14 played a protective role by increasing intestinal barrier integrity to decrease the severity of intestinal lesions and ulcerations [71]. All these argued the important modulatory role of CD14 in inflammatory disorders.

CD14 deficiency causes either hypo- or hyper-inflammation, insufficient or exaggerated immune cell recruitment or worsened stroke outcomes, thus to disrupt the ability of CD14 to balance central nervous system responses to bacterial infection, traumatic and ischemic injuries [72]. This data indicates CD14 might act as an important modulator in CNS disorders.

In summary, CD14-mediated signaling cascades exert complex impact on the development and the consequence of inflammation. The terminal effects of CD14 in inflammation may depend on many factors including the site of inflammation, the essence of diseases, the level of CD14 expression, the characteristics of CD14 ligands and the competition among different CD14-dependent pathways. More studies are necessary for a full understanding of the CD14-mediated signaling to enlighten us about new strategies for regulating inflammation.

### 4.2. *In atherosclerosis*

Atherosclerosis is characterized by a chronic arterial wall inflammation. Disturbed immune responses and aberrant lipid metabolism are involved in its pathogenesis [73]. Quite a few of studies have indicated a vital role of the interactions between CD14 and many atherosclerosis-related factors in the development of atherosclerosis.

For instance, proatherogenic factors LPA/LPS [74] and 27-hydroxycholesterol [75] upregulate CD14 expression in mononuclear cells. In atherosclerotic lesion, CD14 in macrophages was found to be significantly higher than that in normal vascular intima [76]. Consequently, the amplified CD14-dependent signaling pathways accelerate the formation of foam cells via increasing the expression of oxidized LDL receptor SR-AI effectively [74] and facilitate the adhesion and migration of inflammatory cells into atherosclerotic lesion [75]. And electronegative LDLs can directly interact with CD14 in monocytes to dramatically augment the release of cytokines and affect the balance of the electronegative LDL-induced secretion of MMP9 and its inhibitor significantly, thus to increase the vulnerability of atherosclerotic plaque and to promote atherosclerosis [77]. CD14 can even bind to minimally modified LDL and heighten the F-actin response of macrophages to minimally modified LDL, which impairs their ability of cytoskeleton rearrangement for clearing apoptotic cells within atherosclerotic lesion [78]. Anti-CD14 antibody reduces electronegative LDL-induced release of MCP1, IL6 and IL10 by 75–80% [79]. And also through countering CD14-dependent inflammation could the oxidized phospholipid VB201 impair downstream cytokine production and constrain atherosclerosis progression [80].

Regulating the functions of vascular endothelial cells and smooth muscle cells is another way in which CD14 promotes atherosclerosis. In human microvascular endothelial cells, glutathione peroxidase-1 can modulate the expression of CD14 to decrease the LPS-induced adhesion molecules expression and thus attenuate human susceptibility to atherosclerosis [81]. Human coronary artery smooth muscle cells can express high level of CD14 and this confers themselves a remarkably

high sensitivity to pro-atherosclerotic risk factors [82].

These findings together suggest that CD14 can not only contribute to form inflammation milieu within vascular intima via enhancing the response of cells to atherosclerosis-related factors but also promote the formation of atherosclerotic lesion directly via modulating the fate of inflammatory cells and smooth muscle cells. Further investigations to explore how atherosclerosis-related factors affect the expression of CD14 and to elucidate the details of the interaction between CD14 and atherosclerosis-related factors are warranted.

### 4.3. In tumor

As a key component in TLR signaling pathway, CD14 plays a dual role for oncogenesis, which associates with activation of different signaling pathways in tumor cells or in tumor infiltrating immune cells.

Activation of CD14 in cancer cells induces MyD88 and TRIF signaling to orchestrate tumor-promoting inflammation and drive tumor cell proliferation to promote tumor growth. For instance, CD14hi bladder cancer cells form large, highly vascularized tumors by expressing high levels of IL6, IL8, M-CSF, VEGF-A and FGF-2 [83]. CD14-dependent TLR-Myd88-NFκB axis in colon and breast epithelial tumor cells directly increases tumor survival and growth in chronic lymphocytic leukemiacolon and breast cancers [84]. This MyD88–CD14–IRAK1 signaling pathway is even suggested as therapeutic targets to treat breast cancer patients who generally have a poorer prognosis. However, CD14 activation decreases cell viability and induce apoptosis in adrenocortical carcinoma [85] and in colorectal epithelial cells and contributes to normal epithelial transition to carcinogenesis through an unique PLC-PKCζ pathway [86].

Activation of CD14 in tumor infiltrating immune cells not only promotes cancer-related inflammation, induces cancer immunosurveillance, but also promotes an immunosuppressive environment to facilitate tumor progression. For instance, CD14 activation can mitigate pancreas cancer derived M1 programming and confers anti-tumor potential in TAMs [87]. On the other hand, CD14 could cause the apoptotic death of terminally differentiated DCs through NFAT activation to prevent anti-tumor immunity to facilitate tumorigenesis [46]. CD14 expressed on tumor infiltrating DCs would be engaged by stress inducible Grp78 and subsequently induce DCs death to promote the immunosuppressive status [36,37]. Tumor cells even actively shape their microenvironment by inducing CD14 secretion in accessory monocytes to enhance their survival [88]. Serum sCD14 could be used as a tumor biomarker for the prognosis of hepatocellular carcinoma in HBV chronically infected patients [89].

These results suggest that context-dependent effects of CD14 merit consideration when targeting CD14 as the therapeutic and chemoprevention strategy.

### 4.4. In metabolic diseases

In obese people and patients with diabetes mellitus, CD14 is observed to be upregulated significantly in monocytes, adipocytes and whole adipose tissue [90,91]. A number of animal assays also reported a deleterious role of CD14 in the onset and the development of obesity, diabetes and steatohepatitis [92,93]. Emerging data has deepened our understanding of the role of CD14 in metabolic diseases.

CD14 plays a pivotal role in regulating the expression of tight junction proteins in intestinal epithelium of mice [71,94]. More importantly, CD14 was demonstrated to contribute to the transportation of a large number of bacteria from gut into blood and mesenteric adipose tissue, and therefore to promote the onset of diabetes in high-fat diet-fed mice [95]. These indicate that CD14 facilitates a crosstalk between gut microbiota, the innate immune system and tissues and is involved in metabolic diseases via affecting the integrity of intestinal barrier. As a result, bacteria and its fragments such as LPS were translocated from intestinal lumen into metabolic tissues where they triggered a chronic low-level metabolic inflammation to promote the onset and the development of metabolic diseases via activating immune system [96,97]. Thus, targeting intestinal CD14-dependent signaling to reduce the entrance of gut microorganisms and its fragments into circulation might be a fundamental strategy for decreasing individual susceptibility to metabolic diseases.

In addition, CD14 is involved in regulating insulin action and adipogenesis. Compared to CD14-inactivated mice, wild type mice showed a significantly lower LPS or HFD-induced expression of gene involved in lipid metabolism, glucose metabolism and insulin action in adipose tissues [91,93,98]. Given that LPS is a prerequisite to high-fat diet-induced obesity and glucose intolerance, as its receptor, CD14 expressed in adipose tissue resident cells could directly mediate adipose tissue inflammation and stimulate adipocyte progenitor cell and macrophages proliferation [98], therefore to deteriorate the infiltration and proliferation of macrophages in adipose tissues and upregulate the production of pro-inflammatory cytokines at the same time. Thus, CD14-mediated inflammation might be a vital part of the pathogenesis of body weight gain and insulin resistance. Inhibiting CD14-dependent signaling in macrophages and adipocyte precursors represents a potential strategy for preventing metabolic disorders [99]. Consistent with this, administration of sCD14 increased the insulin action through inhibiting the interaction between mCD14 and LPS in mice [91]. However, sCD14 released from epicardial adipose tissue impaired the insulin-triggered signaling cascades in rat cardiomyocytes and human umbilical vein endothelial cells in a LPS-independent manner [100]. Thus, sCD14 seems to be far more than just a receptor of LPS in the pathogenesis of metabolic diseases. This is in line with the speculation that unknown endogenous ligands may activate CD14-dependent signaling in metabolic disorders [2]. Apart from modulating metabolic inflammation to affect insulin action and adipogenesis, CD14 can regulate insulin sensitivity through influencing the activation of sympathoadrenal systems [93,101]. This argues a protective role for the crosstalk between CD14-dependent signaling and sympathoadrenal systems in metabolic diseases, but more researches are warranted to elucidate this crosstalk mechanistically.

CD14 also affects metabolic diseases in other ways. In the islet of Langerhans, CD14 monitors the endocrine environment and thus partly promotes the development of diabetogenic insulitis [102]. It recognizes both LPS and endogenous ligands(e.g. glycolipids released by β cells) to modulate glucose-dependent insulin release and may affect the cell viability [103]. These effects partly explain the observation that CD14-deifcient type 1 diabetes model mice had a significantly reduced prevalence of diabetes and they developed symptoms considerably later than the controls [104]. Besides, it is worth noting that CD14 also serves as a protective factor in T2D patients through physiologically taking part in modulating the insulinotropic effect of glucagon-like peptide-1 [105].

In summary, CD14 exerts significant impacts in the pathogenesis of metabolic diseases. Promoting metabolic diseases via modulating intestinal permeability and metabolic inflammation appears to be the dominant effect of CD14.

## Competing interests

The authors declare no competing interests.

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