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Role of CD14 in human disease

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Abstract

The cell surface antigen CD14 is primarily understood to act as a co-receptor for toll-like receptors (TLRs) to activate innate immunity responses to pathogens and tissue injury in macrophages and monocytes. However, roles for CD14 are increasingly being uncovered in disease responses in epithelial and endothelial cells. Consistent with these broader functions, CD14 expression is altered in a variety of non-immune cell types in response to a several of disease states. Moreover, soluble CD14 activated by factors from both pathogens and tissue damage may initiate signaling in a variety of non-immune cells. This review examined the current understanding CD14 in innate immunity as well as its potential functions in nonimmune cells and associated human diseases.

Keywords

CD14; Immunity; Organ injury; Inflammation; LPS; Metabolism; Human disease

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Authors contributions:

D.S, K.L and T.H reviewed the literature and prepared the draft of the manuscript. T.H, K.L, C.W and T.Z reviewed, provided input throughout and edited the manuscript. T.H finalized the manuscript for submission.

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The authors declare that this review was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Introduction:

Canonically, the CD14 glycoprotein receptor has been shown to promote macrophage activation upon binding either LPS or oxidized lipids. CD14 was initially recognized as a membrane receptor for lipopolysaccharides (LPS) on macrophages and to mediate their host cytokine response to sepsis, most notably TNF [1]. In addition to macrophages, CD 14 has expression has been detected in a variety of other immune cell types including human and mouse neutrophils and dendritic cells [2] and at lower levels in human T-cells and B-cells and liver resident Kupffer cells [3–6]. In the non-immune compartment, CD14 expression was also detected in human enterocytes [7] human and mouse hepatocytes [8, 9] and pancreatic islet beta cells [10]. CD14 has also been found to bind other pathogen-associated molecular pattern (PAMP) type ligands such as Lipoteichoic acid (LTA) and Biglycan [11, 12]. In addition, CD14 participates in the inflammatory responses by binding oxidized lipids with damage-associated molecular patterns (DAMPs) that accumulate following organ injury, autoimmune disorders and atherosclerosis [13, 14]. After binding to either PAMPs or DAMPs in response to infection or organ injury, CD14 initiates signaling involved in the early activation phase of the innate immune system. During both acute and chronic innate immune activation, CD14 dependent signaling also regulates metabolic processes. Of note, the soluble form of CD14 enhances the LPS response in non-inflammatory cells, implicating it in functions beyond innate immunity [14, 15]. Indeed, soluble CD14 originating from the liver was identified as an acute phase response protein in chronic inflammatory disease [16]. This review relates the role of CD14 in human diseases to potential novel functions that may contribute to disease pathologies.

CD14 Structure:

CD14 is biologically active as either a monomeric protein [17] attached to the cell membrane via a glycosylphosphatidylinositol (GPI) anchor (mCD14) or as a secreted soluble protein (sCD14) that enables epithelial and endothelial cells to respond to LPS [18]. Known CD14 ligands, including PAMPs and DAMPs are listed in Table 1. In human glioblastoma cells, the crystal structure of CD14 protein revealed a bent solenoid structure containing thirteen β strands, eleven of which overlap with leucine-rich repeat regions (LRRs). Eleven parallel and two antiparallel β strands create a concave surface, where disulfide bonds and N-linked glycosylation near the n-terminal β strands are crucial for proper folding and signaling [19]. The ligand binding pocket at the N-terminus of CD14 consists of hydrophobic residues in $\alpha 1 - 5$, $\beta 1 - 6$ with charged residues around the pocket rim. The charged residues have been proposed to orient the binding of the phosphate groups attached to the core oligosaccharide of LPS. Ligand binding to soluble murine CD14 occurs at four regions: $_{26}$DEES$_{29}$, lying between the $\beta 1$ and $\beta 2$ strands, $_{37}$PKPD$_{40}$ in the loop between the $\beta 2$ strand at $_{50}$AADVE$_{54}$ in the $\alpha 1$ helix and the $\beta 3$ strand, and at $_{73}$ADLGQF$_{78}$ in the loop between the $\alpha 2$ and $\alpha 3$ helices [20]. While the human CD14 binding pocket cannot accommodate all the acyl chains of a ligand, these chains may bind to additional grooves at the C-terminal side of the pocket and to the flexible hydrophilic rim. These adjacent residues also participate in activating intracellular signaling by the target cell. The bent solenoid structures of mouse and human CD14 are highly superimposable (root mean square deviation: 1.089 Å). However, differences exist in charged residues on the rim and

between the shape of the N-terminal pocket. For instance, a positively charged K38 residue in murine CD14 is represented by a negatively charged D44 residue at this position in human CD14. Further, hydrophobic interactions between residues F45, F78, L49, and I81 in mouse CD14 close off one side of the pocket, while corresponding T85 and L89 residues in human CD14 allow the extension of the pocket diameter [20, 21]. However, both human and mouse CD14 likely bind similar ligands to activate concordant cellular pathways [6].

CD14 binding to LPS:

The first discovered and most studied ligand of CD14 is the endotoxin lipopolysaccharide (LPS). The outer membrane of gram-negative bacteria consists of LPS, lipid A, a core oligosaccharide, and an O-antigen chain of variable length [22]. In serum, soluble CD14 recognizes various LPS chemotypes in complex with LPS-binding protein (LBP). This includes “rough” colonies that have truncated versions of the O-antigen chain or “smooth” colonies that preserve the O-antigen chain [23]. Macrophages from wild-type $CD14^{+/+}$ mice recognize smooth LPS at lower picomolar concentrations than rough LPS. Whereas, $CD14^{-/-}$ macrophages demonstrate no significant preference for either smooth or rough LPS but have a 150,000 fold reduction in overall sensitivity to LPS induced TNF-α production [24]. These data strongly demonstrate a critical role for CD14 in the response of macrophages to the smooth LPS ligand.

CD14 binding to toll-like receptors:

Toll-like receptors (TLRs) function in the innate immune system as pattern-recognition receptors (PRRs) to identify pathogen-associated molecular patterns (PAMPs) on bacteria and viruses [25]. Upon such engagement, TLRs initiate pro-inflammatory signaling that activates transcription factors such as NF-κB and IRFs in dendritic cells to initiate adaptive immunity. In addition, primarily TLR4 responds to accessory molecules on the plasma membrane, such as MD-2 and RP105, and the endoplasmic reticulum, such as PRAT4A and Gp96. CD14 acts a co-receptor in this process by directly binding to TLRs and by transferring LPS to the TLR-MD-2 complex. CD14 further promotes TLRs to engage with adapter proteins, such as MyD88, Mal (TIRAP), TRIF, and TRAM, to initiate intracellular signaling [25].

Signaling Pathways involving CD14:

Nuclear Receptor in Activated T Cell (NFAT) Signaling—Engagement of the CD14-LPS complex initiates TLR4-independent NFAT activation in a variety of inflammatory cell types. In human and murine dendritic cells, upon binding LPS, CD14 localizes to lipid rafts and directly recruits src family kinase (SFK) and phospholipase Cγ2 (PLCγ2) [26, 27]. Subsequent Ca^{2+} influx activates the calcineurin phosphatase which dephosphorylates NFAT to promote its translocation into the nucleus where it drives pro-apoptotic gene expression that enables self-tolerance (Figure1a) [28]. Due to its GPI anchor, the direct role of CD14 in Ca^{2+} mobilization has been questioned. An alternate model posits that Ca^{2+} influx is primarily initiated by agonization of the Fc receptor gamma chain receptor (FcR γ) and DAP12 signaling adaptor which results in phosphorylation of its immunoreceptor

tyrosine-based activation motif (ITAM) motif and recruitment of SYK that in turn activates Phospholipase C gamma (PLCγ) [29].

MyD88-TIRAP Signaling—In murine macrophages, association of the CD14-LPS complex with TLR4-MD-2 in lipid rafts promotes TIRAP-MyD88 to bind to the TIR domains of TLR4 (Figure 1b). For non-immune cells that express inadequate levels of mCD14, LPS is transferred to MD2 by circulating sCD14 resulting in TLR pathway activation [30, 31]. Such activation involves MyD88 recruitment of IL-1R-associated kinase-4 (IRAK4) and IRAK2/1 [32] resulting in assembly of the myddosome; a large oligomeric signaling complex that elicits an inflammatory immune response in the innate host response to infection. The myddosome triggers activation of NF-κB and MAPK by activating the TNF-receptor associated factor (TRAF) [33]. Consequently, the proinflammatory cytokines TNF-α, IL-1β, and IL-6 are secreted. Such signaling was also described in endothelial cells [34] and neutrophils [35], whereas in LPS-stimulated murine mast cells, The TRAM signaling branch leading both to NF-kB activation and enhanced proinflammatory cytokine production is absent [36].

TRAM-TRIF Signaling—CD14 also regulates the microbial induced endocytosis of Toll-like Receptors (TLRs) to enable intracellular signaling that promotes innate immunity. Upon dendritic cell exposure to inflammatory mediators, CD14 activates ITAM-containing adaptor proteins that stimulate the tyrosine kinase Syk and PLCγ2 to initiate the delivery of the TLR4/MD2 complex from the plasma membrane to endosomal compartments [37]. In vesicles, CD14 further enables LPS to stimulate the TRAM-TRIF pathway to illicit interferon-3 regulatory factor (IRF3) production and subsequent type-1 IRF production (Figure1c,d) [38]. However, the activation of TRAM-TRIF can be CD14-independent if LPS is delivered to endosomal compartments via microbeads or liposome combinations [39].

Inflammasome Signaling through a non-TLR pathway—In the airway epithelium, $CD14^+$ macrophages and dendritic cells recognize signatures associated with cell death to promote inflammasome assembly, independent of TLRs. When CD14 is bound to LPS or oxidized lipids (Oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine, aka oxPAPC) during tissue damage, its endocytosis allows it to directly promote inflammasome assembly [40]. OxPAPCs function as damage-associated molecular patterns (DAMP) that induce CD14 to activate NLRP3 mediated inflammasome assembly that results in the release of IL-1β and Il-18 without cell death (Figure 1e) [41]. Whereas LPS associated CD14 activates non-canonical caspase3 containing inflammasomes that induce a specialized form of cell death termed pyroptosis [42]. In addition to its effects on inflammasomes, endocytosis of CD14 allows it to also recognize sLPS and consequently to inhibit both the MyD88-TIRAP and TRIF-TRAM pathways [42].

CD14 in human diseases:

CD14 In Infectious diseases—Many studies found a critical role for CD14 in the host response to sepsis. The levels of CD14 in serum both associates with severity and prognosis of sepsis in neonates [43]. CD14 levels also predict sepsis in burn patients [44]. In sepsis-related acute lung injury, CD14 levels are upregulated and its inhibition in animal

models decreases injury [45]. In both porcine and primate models, CD14 inhibition with neutralizing antibodies associates with improved prognosis from E. Coli induced sepsis [46]. CD14 is also elevated in patient populations with a number of acute infectious processes including active tuberculosis infections [47], periodontitis [48], influenza [49], HIV, HCV [50], and covid-19 [51]. For covid-19, CD14 levels significantly predict disease severity. CD14 blockade was proposed as a potential strategy to control inflammation and organ injury due to SARS-CoV-2 infection [52]. Furthermore, methotrexate, a widely used immunosuppressive agent against psoriasis, decreases both CD14 expression and the responsiveness of macrophage to LPS [53].

CD14 Involvement in Metabolic Disease—Several studies find a role for CD14 in metabolism and insulin sensitivity. CD14 has been shown to influence adrenal function to increase glucose responsiveness [54] consistent with its observed decrease in patient serum after weight loss. Injection of recombinant human CD14 in lean and obese mice has also been found to result in sepsis independent changes in adipose cell expression of metabolic genes. Interestingly, *CD14*-deficient mice subjected to high-fat diet are more resistant to obesity, insulin resistance and cardiovascular disease [55]. Subsequently, CD14 has been shown to regulate SIRT1 activity, a master regulator of metabolism [56]. In addition, CD14 may modulate leptin responsiveness during the pathogenesis of steatohepatitis associated with obesity [57]. Interestingly, NFAT signaling, one of the downstream signals of CD14, was found necessary for fat accumulation in high-fat diet models [58]. More recently, the description of TLR-dependent inflammasome activation in adipose tissue of patients with cancer cachexia [59] indicates a potential role of CD14 in cancer associated cachexia. In skeletal muscle, NFAT pathway plays an important role in oxidative metabolism and fiber type switching after exposure to thymol [60]. Taken together, CD14 has a significant role in the metabolic response to both infection and other inflammatory states.

CD14 involvement in cardiovascular diseases—Elevated levels of CD14 in patients associates with higher levels of cholesterol coupled with greater risks of myocardial infarction and cardiovascular-associated death [61]. CD14 also appears to enhance the severity of cardiomyopathic conditions that result from third degree burn injury [62] and Chagas disease [63]. Finally, CD14 levels have been suggested to predict patient outcomes following acute myocardial infarction [64]. The role of CD14 in cardiovascular function has been linked to its ability to activate cytokine secretion and inflammation in macrophages by the atherosclerosis-inducing low-density lipoprotein (LDL) metabolites that are highly linked to cardiovascular disease progression. This is supported by findings that CD14 neutralization in macrophages results in the inhibition of secretion of cytokines stimulated by LDL as well as the suppression of proinflammatory cytokine activation to a greater extent than any TLR examined [65]. High levels of CD14 therefore appear to be highly causal in the genesis of atherosclerosis and associated heart disease as well as myocardial dysfunction.

CD14 and autoimmune conditions—Significant evidence indicates that CD14 promotes the pathogenesis of autoimmune diseases. CD14 levels in serum may serve as a biomarker for rheumatoid arthritis prognosis and response to methotrexate [53].

CD14 polymorphisms associated with greater CD14 expression levels are also increased in patients with systemic lupus erythematosus [66]. Whereas elevated levels of CD14 in celiac disease decline with resolution of inflammation [67]. CD14 has also been identified as a potential mediator of amyotrophic lateral sclerosis (AMLS) [68] and strategies for CD14 neutralization for AMLS treatment are being pursued. A more general role of CD14 in autoimmune conditions is supported by its elevated levels in patients with systemic sclerosis [69], psoriasis [70], Kawasaki's disease [71], acute pancreatitis [72], osteoarthritis [49], vasculitis [73], and primary biliary cholangitis [74].

CD14 involvement in cancer—CD14 polymorphisms that result in increased CD14 expression levels are associated with increased risks of developing several malignancies [75]. High levels of CD14 in tumor associated macrophages associate with reduced anti-cancer CD8+ inflammatory T cell activity; partly through the increased secretion of the chemokine CXC12 and acetylation of p53 [56]. In patients, CD14 expression associates with more aggressive colorectal and kidney cancers and poor patient outcomes [76]. In gastric cancer, CD14 is implicated in increasing tumor invasiveness through activation of E-cadherin [77]. Whereas, CD14 levels are elevated in ovarian cancer, pulmonary non-small cell cancers [78], hepatocellular carcinoma [79], bladder cancer [80], and laryngeal cancer [81]. Conversely, analysis of 10 cancer stem cell markers revealed that CD14 marks a subpopulation of non-tumorigenic breast cancer cell line [82]. In pancreatic cancer, CD14/TLR pathways prime the tumor associated macrophages to exert anti-tumor action [83]. Despite the accumulating evidence for a role of CD14 in numerous cancers, the lack of functional and mechanistic studies may explain the lack of therapeutic approaches to target CD14 in human cancer.

CD14 gene expression changes in pathogenesis—Gene expression studies showed concordant dysregulation of CD14 expression in several human diseases (Table 2, Supplementary table 1). This suggests that signaling downstream of CD14 might play a role in many pathologies. Unfortunately, most of these gene expression studies did not provide mechanistic insights on how CD14 is leading to pathogenesis. Although, changes in CD14 expression clearly correlate with diseases, for instance, the role of CD14 in carcinogenesis and other pathological metabolic processes is still unclear.

Integrating our understanding of the *in vivo* role of CD14:

Eicke Latz has described CD14 as a factor that "shapes the immune response" [84]. Consistently, a large body of research finds that CD14 acts as a critical early mediator of the innate immune response to sepsis, organ injury and a variety of chronic inflammatory diseases such as atherosclerosis and cancer. Beyond its described expression and function in immune cells, the detection of CD14 mRNA and protein in non-immune cells such as hepatocytes, hepatic stellate cells, breast granular cells, proximal enterocytes and Langerhans cells in the skin (https://www.proteinatlas.org/ENSG00000170458-CD14/single+cell+type) suggests CD14 involvement in other physiological processes, including liver metabolism and regeneration [85, 86]. Consistently, soluble CD14 acts on many cell types including endothelial and epithelial cells. Evidence is mounting that this may represent a significant part of the action of CD14. This in part could be due to the predicted ability of

the large hydrophobic pocket of CD14 to accommodate interactions with a wide variety of ligands in addition to the CD14/LPS interactions widely studied in the immune context [21]. For instance, the interaction of CD14 with oxidated phospholipids has been shown recently to promote the clearing of dead cells [13]. Furthermore, high-affinity binding of CD14 to biglycan initiates macrophage activation in response to biglycan accumulation [12]. Future studies aiming to modulate CD14 expression in chronic diseases will therefore benefit from considering potential non-canonical actions of CD14 in a variety of conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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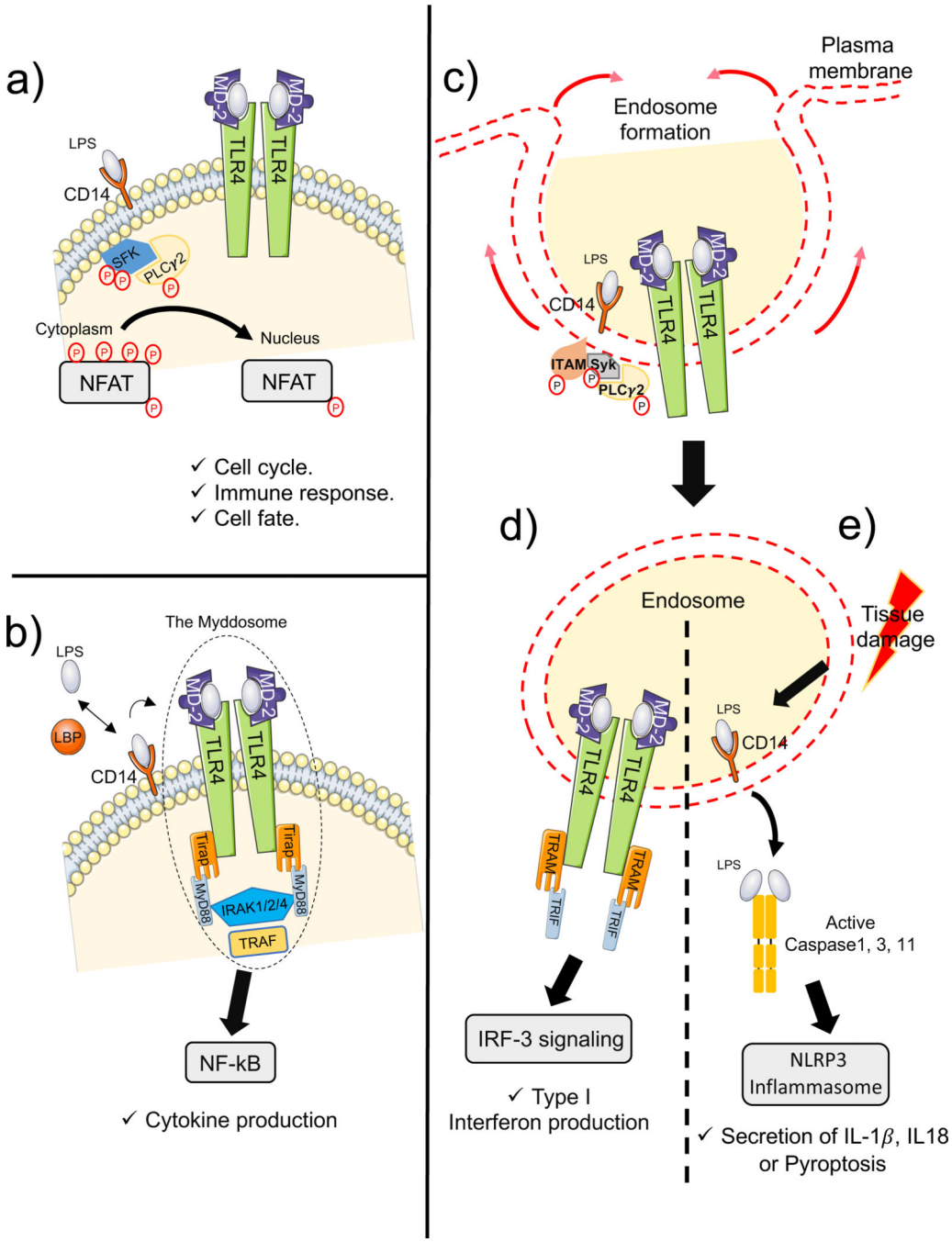

Figure1: CD14 activates multiple signaling pathways.

a) In both human and mouse dendritic cells, CD14-LPS complex initiates TLR4-independent NFAT activation in a variety of inflammatory cell types. CD14 localizes to lipid rafts and directly recruits Src family kinase (SFK) and phospholipase Cγ2 (PLCγ2). Subsequent dephosphorylation of NFAT promotes its translocation into the nucleus where it drives pro-apoptotic gene expression, thus enabling self-tolerance. **b)** LBP-dependent combination of the CD14-LPS complex with TLR4-MD-2 in lipid rafts promotes TIRAP-MyD88 to bind to the TIR domains of TLR4. The newly formed “myddosome” triggers

the activation of NF-κB and MAPK through the TNF-receptor associated factor (TRAF). Consequently, numerous proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 are secreted. **c)** LPS bound CD14 activates ITAM-containing adaptor proteins that stimulate the tyrosine kinase Syk and PLCγ2 to initiate the delivery of the TLR4/MD2 complex from the plasma membrane to endosomal compartments. **d)** In endosomal vesicles, CD14 further enables LPS to stimulate the TRAM-TRIF pathway to illicit interferon-3 regulatory factor (IRF3) production and subsequent type-1 IFN production. **e) In human monocytes, epithelial cells and keratinocytes,** when CD14 binds to LPS during tissue damage, its endocytosis allows it to bind and activate the inflammasome assembly independently of TLRs. CD14 activates the NLRP3-mediated inflammasome assembly that results in the release of IL-1β and Il-18 with or without cell death.

Table1:

List of some PAMPs and DAMPs recognized by CD14.

CD14 recognized PAMPs	Reference	CD14 recognized DAMPs	Reference
LPS	[87]	oxPAPC	[13]
CpG-DNA	[88]	S100A9	[89]
Peptidoglycan	[90]	mtDNA	[91]
Byglican	[12]	HSPs	[92]
Lipoteichoic Acid	[93]	Fibronectin	[94]
pLpC-dsRNA	[95]	Beta-Amyloid	[96]

Table 2:
CD14 mRNA expression in selected human diseases organized by organ/system.

Different diseases and conditions from human and experimental animal models are shown. Species studied are shown, H: Human, M: Mouse, R: Rat. UP: Upregulated. DN: Downregulated. Data and disease scores were generated using the Base space correlation engine / disease atlas / Illumina. The Full data on the query “CD14 in disease atlas” can be found in (Supplementary Table1).

Organ/System	Disease	CD14 mRNA	Score	References	Species
Hematopoietic	Bleeding	UP	76	[97]	M
	T-cell lymphoma	UP	72	[98]	H, M
	Transplant rejection	UP	61	[99]	H, M
	Hemoglobinopathy	DN	47	[100]	H
Genitourinary	Nephritis	UP	76	[101]	M
	Renal fibrosis	UP	63	[102]	H
	Urogenital injury	UP	55	[103]	M, R
	Kidney cancer	UP	50	[104]	H
Brain & nervous system	Brain hypoxia	UP	74	[105]	H, M
	Nerve injury	UP	73	[106]	M, R
	Huntington disease	UP	56	[107]	H
	Brain cancer	UP	48	[108]	H
Lung	Infectious disease of lung	UP	74	[109]	M
	Pneumonia	UP	64	[110]	H, R
Digestive system	Intestinal ulceration	DN	70	[111]	H
	Intestinal infectious disease	UP	51	[112]	H, M
	Inflammatory bowel disease	UP	47	[112]	H
	Gastric cancer	UP	41	[113]	H
Musculoskeletal system	Duchenne muscular dystrophy	UP	75	[114]	H
	Myopathy	UP	52	[115]	H
	Muscle atrophy	UP	46	[116]	H, M
Liver	Injury of liver	UP	85	[117]	M, R
	Liver cancer	UP	57	[118]	H
	Inflammatory disease of liver	UP	54	[119]	H, M
	Hepatic fibrosis	UP	39	[120]	H, M
Vascular system	Shock	UP	77	[121]	H, M
	Cardiomyopathy	DN	71	[122]	H
	Ischemia	UP	67	[123]	M, R