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REVIEW

The biological function and significance of CD74 in immune diseases

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Abstract CD74 (MHC class II invariant chain, Ii) is a non-polymorphic type II transmembrane glycoprotein. It is clear that, in addition to be an MHC class II chaperone, CD74 has a diversity of biological functions in physiological and pathological situations. CD74 also participates in other non-MHC II protein trafficking, such as angiotensin II type I receptor. In addition, CD74 is a cell membrane high-affinity receptor for macrophage migration inhibitory factor (MIF), D-dopachrome tautomerase (D-DT/MIF-2) and bacterial proteins. CD74 also regulates T-cell and B-cell developments, dendritic cell (DC) motility, macrophage inflammation, and thymic selection. The activation of receptor complex CD74/CD44 may lead to multiple intracellular signal pathways, such as the activation of the extracellular signal regulated kinase (ERK) 1 and 2, the PI3K-Akt signal transduction cascade, NFκB, and the AMP-activated protein kinase (AMPK) pathway. CD74 plays important roles in many inflammatory diseases, such as liver fibrosis, type I diabetes, systemic lupus erythematosus, and Alzheimer disease. In this study, we will focus on the immunological functions of CD74 molecules and its roles in immune-relevant disorders.

Keywords CD74 · MIF · Inflammation · Innate immunity

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Introduction

CD74 (MHC class II invariant chain, Ii) is a non-polymorphic type II transmembrane glycoprotein. It was initially identified to act mainly as an MHC class II chaperone. However, it is clear that CD74 has a much wide range of biological functions in physiological and pathological situations in addition to its regulatory roles on cell surface MHC II expression [1, 2]. CD74 also participates in other non-MHC II protein trafficking. Importantly, CD74 molecule is a cell membrane high-affinity receptor for macrophage migration inhibitory factor (MIF), D-dopachrome tautomerase (D-DT/MIF-2), and bacterial proteins that also behave as an accessory signaling molecule, which undergoes regulated intramembrane proteolysis (RIP) upon its ligand binding [1, 3–6]. In this study, we will focus on the immunological functions of CD74 molecule and its roles in immune disorders.

The expression of CD74 in immune cells

Mouse CD74 molecule has a short N-terminal cytoplasmic tail of 28 amino acid (aa), a 24-aa transmembrane region and an approximately150-aa luminal domain [7]. The intracellular domain of CD74 molecule lacks homology

with tyrosine or serine/threonine kinases, so CD74 likely lacks intracellular signaling motifs, but it may signal through binding to signaling proteins [6]. Furthermore, it may undergo phosphorylation and regulate intramembrane proteolysis (RIP) [6]. Splicing of the transcription products of CD74 gene in mice generates two different isoforms, p31 and p41. Human CD74 molecule has 29–46 NH2-terminal intracytoplasmic residues, a 26-aa hydrophobic transmembrane region, and a 160-aa extracytoplasmic domain containing two N-linked carbohydrate chains [8–10]. The most common isoform is 33 kDa (p33), but there are also p35, p41, and p43 isoforms in humans [11]. CD74 molecules are predominantly localized intracellularly and about 2–5 % resides on the monocyte cell surface independently of MHC class II expression [3]. The surface half-life of CD74 molecule is less than 10 min in a human B-cell line due to the rapid internalization, indicating that CD74 remains on the cell surface for a very short period [12].

MHC class II-positive cells, including dendritic cells (DCs), monocytes/macrophages, langerhans cells, B cells, thymic epithelial cells, and gastric epithelial cells express CD74 molecules on cell surface. In addition, CD74 is expressed in a number of cell types independently of MHC class II [13]. CD74 expression is increased in diverse tissue injury disorders, such as heart ischemia–reperfusion injury, Alzheimer disease, atherosclerotic plaques, toxin-induced liver fibrosis, and a broad range of malignant cells [14–22]. Thus, CD74 may modulate tissue injury and homeostasis of immune system and beyond. The expression of CD74 molecule may be used as an independent prognostic factor for survival and therapeutic target in patients with malignancy [18].

The expression of CD74 molecule is regulated by multiple pathways. In immature DCs, the cytoplasmic domain of CD74 molecule is exposed to the proteolytic activity of caspases, such as caspase-1 and caspase-4. The degradation of CD74 molecule by caspases in immature DCs was inhibited upon treatment with nitric oxide (NO) donor. Inducible nitric-oxide synthase (iNOS, NOS2) can directly interact with the cytoplasmic domain of CD74 and catalyzes the production of NO, which inhibits caspases and protects CD74 from proteolytic degradation, promoting the cell surface expression of MHC class II molecules in maturing DCs [23]. Thus, the increasing cell surface localization of MHC class II molecules in maturing DCs is partially due to the increased CD74 protein expression caused by iNOS and NO. It was recently demonstrated that intramembrane proteolysis of the final membrane-bound N-terminal fragment (NTF) of CD74 molecules is catalyzed by signal peptide peptidase-like 2a (SPPL2a) and that this process is indispensable for the development and function of B cells in mice [24, 25].

The bio-functions of CD74

A wide range of biological functions of CD74 have been described over the years [1, 2]. CD74 was initially identified to function mainly as an MHC class II chaperone. However, it later became clear that CD74 also participates in other non-MHC II protein trafficking. In addition, CD74 is a cell membrane receptor for MIF, D-dopachrome tautomerase (D-DT/MIF-2), and bacterial proteins, so that CD74 also acts as an accessory signaling molecule which undergoes regulated intramembrane proteolysis (RIP) upon its ligand binding [3–6].

CD74 molecule, as an MHC class II chaperone, directly associates with the MHC class II α and β chains in the endoplasmic reticulum (ER) forming a complex, prevents peptide binding in ER, promotes the exit of the complex from ER, directs transport of the complex to the endosomal compartments, and contributes to peptide editing in the MHC class II compartment [26, 27]. The class II-associated invariant chain peptide region of CD74 molecule lies in the binding groove of the MHC class II α and β heterodimer and prevents binding of peptides prior to the arrival of the non-americ complex at the endosomal compartments where the digested exogenous antigenic proteins are located [1]. While CD74 molecule is degraded by proteases and released from MHC class II molecules in endosomes, MHC class II molecules form dimers that bind antigenic peptides and subsequently traffic to the cell surface for antigen presentation. Inhibition of CD74 phosphorylation greatly impairs the trafficking of newly synthesized MHC class II molecules to antigen processing compartments. CD74 molecule is also required for an MHC class I endolysosomal cross-presentation pathway [28].

In addition to the essential role of CD74 molecules in antigen presentation pathway, CD74 also regulates trafficking of additional molecules, such as angiotensin II type I receptor (AT1) (Table 1). CD74 directly associates with AT1 early in the biosynthetic pathway, and impedes its intracellular trafficking. Consequently, coexpression of CD74 molecules causes AT1 accumulation in the ER and AT1 proteasomal degradation [29]. The longer molecules (p41 and p43 in humans) have a thyroglobulin type I domain that binds to and stabilizes cathepsin L, allowing accumulation of the resulting CD74-cathepsin L complex in the extracellular space [28].

CD74 significantly regulates B-cell development, DC motility, and thymic selection [30]. CD74 controls the maturation of B cells through NF-κB p65/RelA homodimer and its coactivator TAFII105 [6, 7]. Peripheral B-cell homeostasis is disturbed by the accumulation of the unprocessed CD74 NTF in SPPL2a-deficient mice. The absence of SPPL2a at the protein level in human B cells

Table 1 A brief summary of the CD74 biological functions

	Ligand or partner molecule	Function
1	MHC class I and II, AT1, cathepsins, NOS2	Regulation of protein trafficking, chaperone
2	MIF, D-DT/MIF-2, H. pylori urease B subunit	Receptor (interactions with CD44 and CXCR2), accessory signaling molecule

also promotes an accumulation of the CD74 NTF [24, 25]. Thus, SPPL2a may regulate B-cell development through CD74-dependent manner in mice and humans.

MIF is a key cytokine closely involved in autoimmune and inflammatory diseases. MIF attracts and subsequently retains activated immune cells from the periphery to the inflamed tissues [31]. The biological effects of MIF are predominately mediated through its primary receptor, CD74 (Fig. 1) [32]. The comprehensive analysis recently shows that MIF controls the activation of CD74 [33]. MIF inhibits the directed migration of monocytes to chemokines, such as monocyte chemoattractant protein 1. MIF promotes the arrest of monocytes and T cells in vitro [34]. MIF increases the secretion of proinflammatory cytokines like IL-1, IL-2, IL-6, IL-8, INF-γ, and TNF-α, and the expression of adhesion and inflammatory molecules such as iNOS [35–38]. All these actions of MIF are mediated through CXCR2 and CXCR4 which are closely magnified by CD74 [32, 34]. MIF counteracts glucocorticoid inhibition of proinflammatory cytokine secretion in response to lipopolysaccharide in macrophages [39, 40]. T cells and macrophages release MIF in response to glucocorticoid and autocrine MIF then overrides glucocorticoid inhibition of T-cell proliferation and cytokine secretion [41, 42]. The antagonistic ability of MIF on the anti-inflammatory effects of glucocorticoids is observed in mouse models of experimental arthritis and acute respiratory distress syndrome [43–45]. The underlying mechanisms for such antagonism are not fully understood. MIF fails to change the glucocorticoid receptor expression and affinity [46], but it prolongs the activation of ERK and p38 MAP kinases, which may result in molecular antagonism on glucocorticoid receptor signals [46].

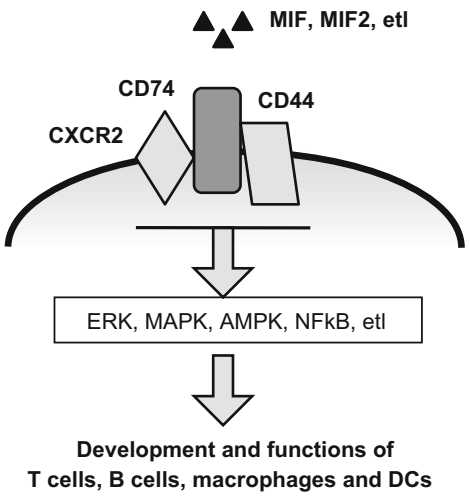

Fig. 1 The signal pathways activated by CD74 molecule and its partners on cell membrane. CD74 molecules expressed on cellular surface can interact with CD44 or CXCR2/CXCR4 to form a molecular complex. Ligands such as MIF, MIF2 et al. directly bind to this complex, so as to activate intracellular pathways, such as ERK, MAPK, AMPK and NFkB, which subsequently regulate the development and functions of T cells, B cells, macrophages, and DCs

In addition, CD74 is also involved in many inflammatory diseases by various mechanisms. HIV-1 Vpu can downregulate MHC class II through Vpu binding to the cytoplasmic domain of CD74 [47]. CD74 molecule binds to the amyloid-β (Aβ) precursor protein and can suppress Aβ processing. CD74-induced alteration of Aβ processing could improve Alzheimer's disease-associated memory deficits in mice [48]. Cathepsins S regulates CCL2 expression in tumor cells through CD74 [49]. CD74-deficient NOD mice fail to spontaneously develop type 1 diabetes. The numbers of $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells in the thymus and periphery of CD74-deficient NOD mice are similar to those found in control NOD mice, suggesting that Treg cells are unaffected in their selection and survival by the absence of CD74. However, the number of conventional effector $CD4^+$ T cells is reduced in CD74-deficient NOD mice [50]. The alteration in the balance of effector T cells to Treg cells may contribute to diabetes prevention.

The intracellular signal pathways of CD74

The binding of MIF to its receptor complex CD74/CD44 leads to the activation of the extracellular signal regulated kinase (ERK) 1 and 2 in the mitogen-activated protein kinase (MAPK) pathway, and the PI3K/Akt/SRC signal transduction cascade [3, 51, 52], which, in turn, increase cell proliferation, decrease cell apoptosis, and enhance cell migration [53, 54]. Inhibition of MIF activity or MIF expression reduces microbial products-induced phosphorylation of p38 and ERK1/2 MAPKs and secretion of cytokines. High doses of MIF counter-regulate adenosine and prostaglandin E2-mediated inhibition of ERK1/2 activation and TNF-α production in newborn monocytes

exposed to *Escherichia coli* [55]. In contrast, other studies show that MIF could activate the AMP-activated protein kinase (AMPK) pathway to decrease cell proliferation, cell viability, and metastatic ability in some cancers [56, 57]. Overexpression of CD74 leads to upregulation of NFκB-dependent genes encoding cytokines in macrophages [58].

CD74 controls B-cell differentiation and maturation in the spleen of mice [4, 59, 60]. Activation of CD74 by MIF or activating antibodies results in a signaling cascade in B cells that involved Syk tyrosine kinase, PI3K, and Akt and leads to CD74 intramembrane cleavage and CD74 intracellular domain (CD74-ICD) release, NFκB activation, BclxL upregulation, and cell survival [4]. CD74 ectodomain undergoes a first proteolytic cleavage in the endocytic compartment and a secondary intramembrane domain cleavage by the γ-secretase-presenilin complex to liberate CD74-ICD from the lipid bilayer into the cytosol. Transport to the endocytic compartment is essential for CD74 processing and intramembrane cleavage. CD74-ICD then translocates to the nucleus and activates NF-κB p65/RelA homodimer and the B-cell-enriched coactivator, TAFII105 [59, 60]. The signal is terminated by degradation of the active CD74-ICD fragment [61]. Clearance of the final membrane-bound N-terminal fragment (NTF) of CD74 is mediated by the intramembrane protease signal peptide peptidase-like (SPPL)2a, which is a process critical for B-cell development. SPPL2a deficiency provokes the accumulation of CD74 NTF in endocytic vesicles, which leads to a B-cell maturation arrest at the transitional 1 stage in mice [62, 63]. Mechanism studies showed that SPPL2a-deficient B cells had a compromised BCR-induced PI3K/Akt activation and a dysregulation of the transcription factor forkhead box class O (FOXO) 1, causing enhanced transcription of proapoptotic genes. This pathway is the major cause of the B-cell maturation defect in SPPL2a-deficient mice [64]. Therefore, SPPL2a-mediated processing of CD74 NTF is indispensable to maintain appropriate levels of BCR signaling to promote B-cell maturation. Since CD74 signaling is significantly inhibited in SPPL2a-deficient mice, SPPL2a inhibitors may offer new approaches to block CD74 signaling [65].

MIF can blocks JAB1-mediated rescue of fibroblasts from cell growth arrest. MIF remarkably inhibits JAB1-induced JNK and AP-1 activity by enhancing p27Kip1 expression through stabilization of p27Kip1 protein. Further studies showed that optimal composition and function of the Skp, Cullin, F-box containing complex, a multiprotein E3 ubiquitin ligase complex catalyzing the ubiquitination of proteins destined for proteasomal degradation, is essential for MIF-mediated downregulation of JAB1 [66]. When an MIF [50–65] peptide was endocytosed, it will override the effects of glucocorticoids and enhance cell proliferation by its direct bound to JAB1 to stimulate ERK1/2 phosphorylation and increase p27Kip1 levels [67, 68]. Pretreatment of aged mesenchymal stem cells (MSCs) with MIF enhances cell growth, cell survival, and secretion of VEGF, bFGF, and HGF. MIF increases CD74-dependent phosphorylation of AMPK and FOXO3a in MSCs [69]. Further studies indicate that MIF can rejuvenate MSCs from a state of age-induced senescence by interacting with CD74 molecules and subsequently activating AMPK-FOXO3a signaling pathways [69].

Ribosomal protein S19 (RPS19), a component of the 40S small ribosomal subunit, can bind MIF and behaves as an endogenous blocker of MIF binding to CD74 [70]. The small molecule MIF antagonist 3-(3-hydroxybenzyl)-5-methylbenzooxazol-2-one (MIF098) decreases MIF-CD74 binding and attenuates MIF-dependent ERK1/2 phosphorylation in human synovial fibroblasts [71]. MIF098 promotes hyperoxia-induced lung injury in vivo [72], supporting the tissue-protective properties of MIF/CD74 pathway. The HLA-DRα1 domain binds to and downregulates CD74 expression on monocytes, so it directly inhibits MIF binding to CD74 molecules and blocks downstream inflammation in mouse autoimmune encephalomyelitis.

Human B-lymphoma cells with decreased CD74 expression are more sensitive to FasL-induced apoptosis and Fas signaling-dependent chemotherapies than control cells [73]. On the other hand, overexpression of full-length CD74 molecule in liver protected the mice from a lethal challenge with agonistic anti-Fas antibody Jo2 [73]. A detailed analysis of Fas signaling reveals that the absence of CD74 increases Fas receptor expression on cell surface and cleavage/activation of pro-caspase-8 and corresponding enhancement of caspase-3 activation [73]. Thus, targeting on CD74 molecules on the cell surface may improve effectiveness of chemotherapy regimens for hematological malignancies.

The involvement of CD74 in immune disorders

MIF is a proinflammatory cytokine involved in cell-mediated immunity and delayed-type hypersensitivity. Deficiency of MIF, one of the ligands of CD74, significantly promoted interstitial fibrosis and inflammation following ureteral obstruction, whereas treatment with recombinant MIF reduced fibrosis [74]. CD74 deficiency was also associated with increased interstitial fibrosis and inflammation following ureteral obstruction and ischemia–reperfusion [74]. By contrast, CD74 deficiency may be beneficial for some inflammatory diseases. CD74-deficient mice are protected from glomerular injury induced by anti-GBM antiserum and liver fibrosis [15, 74]. However, there is no protection from ureteral obstruction-induced kidney

inflammation or fibrosis [75]. An oral small molecule MIF antagonist, CPSI-1306, significantly decreased blood glucose levels and reduced circulating proinflammatory cytokines in diabetic animals [76]. MIF-deficient MRL/lpr mice exhibited significantly prolonged survival and reduced renal and skin manifestations of systemic lupus erythematosus without detectable changes in T- and B-cell activations and alterations in autoantibodies. However, the monocyte chemokine MCP-1 and renal macrophage recruitment were significantly reduced in MIF-deficient MRL/lpr mice [77]. Thus, MIF is a critical effector of nephritis, which is associated with reduction in systemic lupus erythematosus in MIF-deficient MRL/lpr mice.

In acute and chronic mouse models of 12-O-tetra decanoylphorbol-13-acetate (TPA)-induced earskin inflammation, TPA directly causes cytotoxicity accompanied by MIF release in mouse ear epidermal keratinocytes [78]. Treatment with MIF antagonist (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester considerably attenuates TPA-induced ear swelling, and the dermal infiltration of IFN-γ^+ NKT cells. The treatment with TPA and MIF in vitro promotes IFN-γ production and migration of NKT cells, respectively [78]. MIF specifically triggers the chemotaxis of NKT cells via CD74 and CXCR2, and depletion of NKT cells abolished TPA-induced skin inflammation [78]. Therefore, activation of CD74 on NKT cells by proinflammatory MIF secreted by TPA-damaged cells is closely involved in the skin pathogenesis in this model. MIF or CD74-deficient mice had a decreased median survival time following hyperoxia compared with wild-type mice. Treatment with MIF receptor antagonist results in a significant increase in bronchoalveolar lavage protein and lactate dehydrogenase, respectively [72]. Treatment with MIF decreases hyperoxia-induced H2AX phosphorylation in a CD74-dependent manner. Inhibition of CD74 in primary mouse lung endothelial cells decreases hyperoxia-mediated AKT phosphorylation and a reduction in the anti-apoptotic effect of MIF [72]. The MIF-CD74 axis in lung endothelial cells may be a novel protective approach against acute oxidative stress. Wild-type and MIF-deficient kidney or skin grafts transplanted into wild-type recipients or wild-type donor kidneys or skin grafted to wild-type and MIF-deficient mice show a similar degree of histological rejection, graft dysfunction, and immune cell infiltration [79]. These data suggest that either local or systemic MIF is not critically required for the rejection of fully mismatched skin but not renal allografts at least in mice.

Clinical trials using the anti-CD74 antibody hLL1, milatuzumab, to treat malignancy are undergoing [80–82]. Milatuzumab binds to CD74 molecules and promotes internalization of the antibody-CD74 complex, thus delivering conjugated anti-tumoral agents inside tumor cells with high CD74 expression [81]. Milatuzumab alters B-cell proliferation, migration, and adhesion molecule expressions [83]. Milatuzumab immunoliposomes markedly induce cell death in chronic lymphocytic leukemia by promoting accumulation of CD74 molecules on the surface of B cells [84].

Conclusions

In addition to be an MHC class II chaperone, type II transmembrane glycoprotein CD74 molecules also participate in other non-MHC II protein trafficking and are cell membrane high-affinity receptors for MIF, D-DT/MIF-2, CXCR4, and bacterial proteins. With our understanding on a wide range of biological functions of CD74 in physiological and pathological situations, we believe that CD74 may be a therapeutic target to treat the relevant immune disorders in the future.

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