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REVIEW

Recent advances of cluster of differentiation 74 in cancer

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Abstract

Cluster of differentiation 74 (CD74) performs multiple roles in B cells, T cells, and antigen-presenting cells within the immune system; it also participates in major histocompatibility complex class Ⅱ-restricted antigen presentation and inflammation. Recently, a role for CD74 in carcinogenesis has been described. CD74 promotes cell proliferation and motility and prevents cell death in a macrophage migration inhibitory factor-dependent manner. Its roles as an accessory signal receptor on the cell surface and the ability to interact with other signaling molecules make CD74 an attractive therapeutic target for the treatment of cancer. This review focuses on the original role of CD74 in the immune system and its emerging tumor-related functions. First, the structure of CD74 will be summarized. Second, the current understandings about the expression, cellular localization, molecular mechanisms and signaling pathways of CD74 in immunity and cancer will be reviewed. Third, the examples that suggest CD74 is a promising molecular therapeutic target are reviewed and discussed. Although the safety and efficacy of CD74-targeted strategies are under development, deeply understanding of the regulation of CD74 will hold promise for the use of CD74 as a therapeutic target and may develop the CD74-targeted therapeutic agents such as neutralized antibody and compounds.

Key words: Cluster of differentiation 74; Invariant chain; Immune; Inflammation; Tumorigenesis; Cancer metastasis

Core tip: There are several structural and functional variants of cluster of differentiation 74 (CD74), each with their own expression pattern. Although this diversity may be required for normal homeostasis, it can lead to aberrant proliferation when dysregulated. This review focuses on the primary role of CD74 in the immune system and how the activity of this evolutionarily conserved molecule is subverted during tumorigenesis.

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STRUCTURE AND GENOMIC ORGANIZATION OF CLUSTER OF DIFFERENTIATION 74 AND ASSOCIATED VARIANTS

The cluster of differentiation 74 (*CD74*) gene, which is located on chromosome 5q32, encodes the type Ⅱ integral membrane glycoprotein CD74; there are four major isoforms of this protein in humans[1]. This evolutionarily

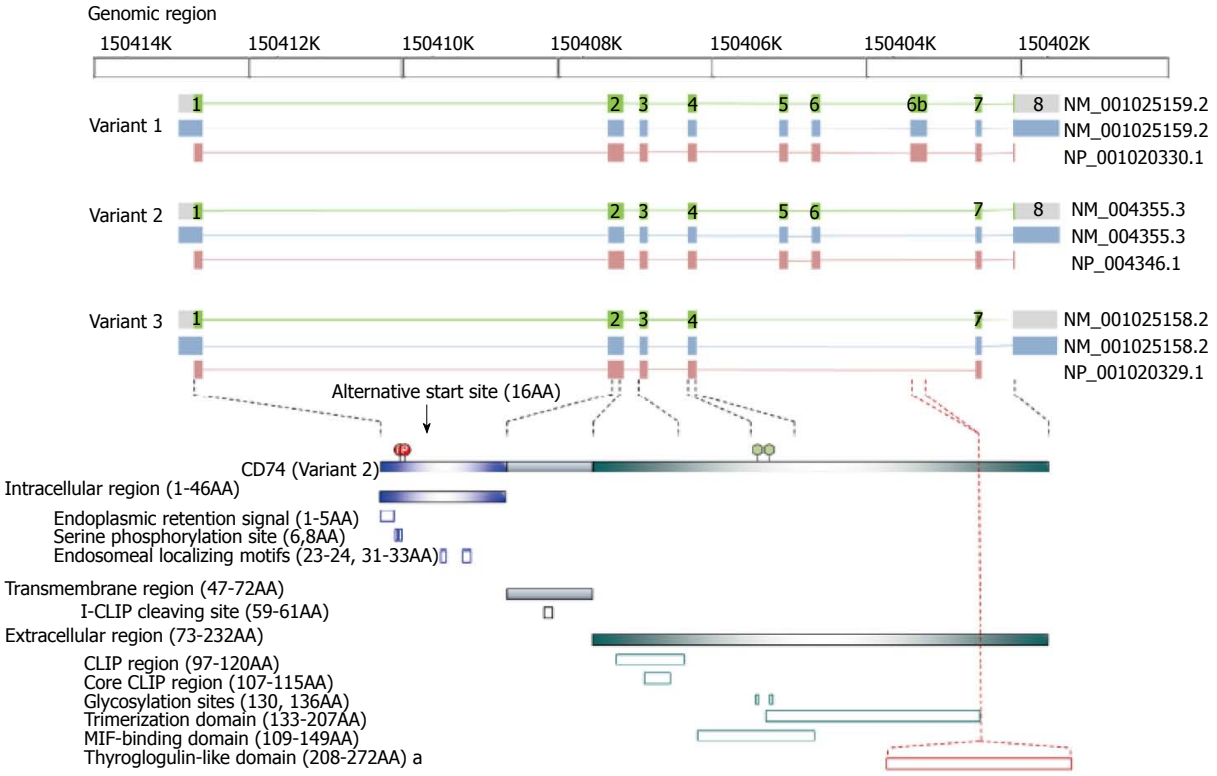

Figure 1 The variants and the corresponding protein structures of cluster of differentiation 74. The upper panel illustrates the corresponding position among genomic region, NCBI reference sequence number and reference protein accession, exon (green box) and intron (green line) localization of DNA, transcripts (light blue box), and protein (pink box) of the three cluster of differentiation 74 (CD74) variants. The lower panel, CD74 variants contains three regions including intracellular, transmembrane and extracellular regions with the indicated functional domains and identified residues for post-translational modification. Variant 2 transcripts two isoforms, p33 and p35 caused by the alternative start site. Variant 1 transcripts two isoforms, p41 and p43, with an exon 6b-encoded thyroglobulin type I domain to interact with cathepsin. Variant 3 lacks exon 5, 6, and 6b, which translates truncated trimerization domain and truncated macrophage migration inhibitory factor (MIF)-binding domain and remains only the CLIP region to function as major histocompatibility complex class II mask. The amino acid residues refer to human variant 2 (p35).

conserved molecule is the membrane form of the major histocompatibility complex class Ⅱ (MHC class Ⅱ) invariant chain (Ii) because none of the original isolates harbored polymorphisms[2]. The most common isoform of CD74 is the p33 isoform (with a molecular weight of 33 kDa), which has a 29-residue N-terminal intracellular region, a 26-residue hydrophobic transmembrane region, and a 160-residue C-terminal extracellular region containing two N-linked glycosylation sites[3,4]. The p35 isoform is also produced because of differential initiation of translation[5], whereas p41 and p43 isoforms arise because of alternative splicing of the exon 6b transcription products that encode a thyroglobulin type I cathepsin-binding domain[6-8]. Both the p33 and p35 isoforms regulate MHC class II antigen presentation through rapid internalization from the cell surface to endosomes (half-life under 10 min) when MHC class Ⅱ-CD74 complexes are formed. However, approximately 2%-5% of these cell surface isoforms are not found in MHC class Ⅱ complexes. Although the role(s) for the membrane-localized CD74 on some parenchymal epithelial cells remain largely unclear, the finding that it is involved in proliferative responses associated with intramembrane proteolysis (RIP)-processed led researchers to investigate its role in cancer[9]. Domains, motifs, and active residues as well as the corresponding functions within the intracellular[10-13], transmembrane[14], and extracellular region[7,9,15-21] of CD74 have been identified. Figure 1 illustrates the CD74 variants and their corresponding protein structures.

THE PHYSIOLOGICAL ROLE OF CD74 IN THE IMMUNE SYSTEM

CD74 has several functions related to MHC class Ⅱ-restricted antigen presentation, including the prevention of MHC class Ⅱ to bind non-processed peptide and self-antigen[22]. CD74 was originally reported to be a molecular chaperone for regulating MHC class Ⅱ folding in the rough endoplasmic reticulum (ER), where it was thought to play a major role in processing and transporting of MHC class Ⅱ molecules in the immune system, and in particular in antigen-presenting cells. Once synthesized, CD74 self-assembles into a trimer and serves as a scaffold onto which nascent MHC class Ⅱ molecules assemble. After trafficking to the late endosome, CD74 is cleaved by cathepsin S (cathepsin L in thymic epithelial cells), leaving a small peptide, CLIP, to block the peptide binding cleft of MHC class Ⅱ and in turn to prevent premature binding of antigenic peptides to MHC class Ⅱ. The CLIP-MHC class Ⅱ complex will then transport through the endosomal pathway[5]. Upon binding of

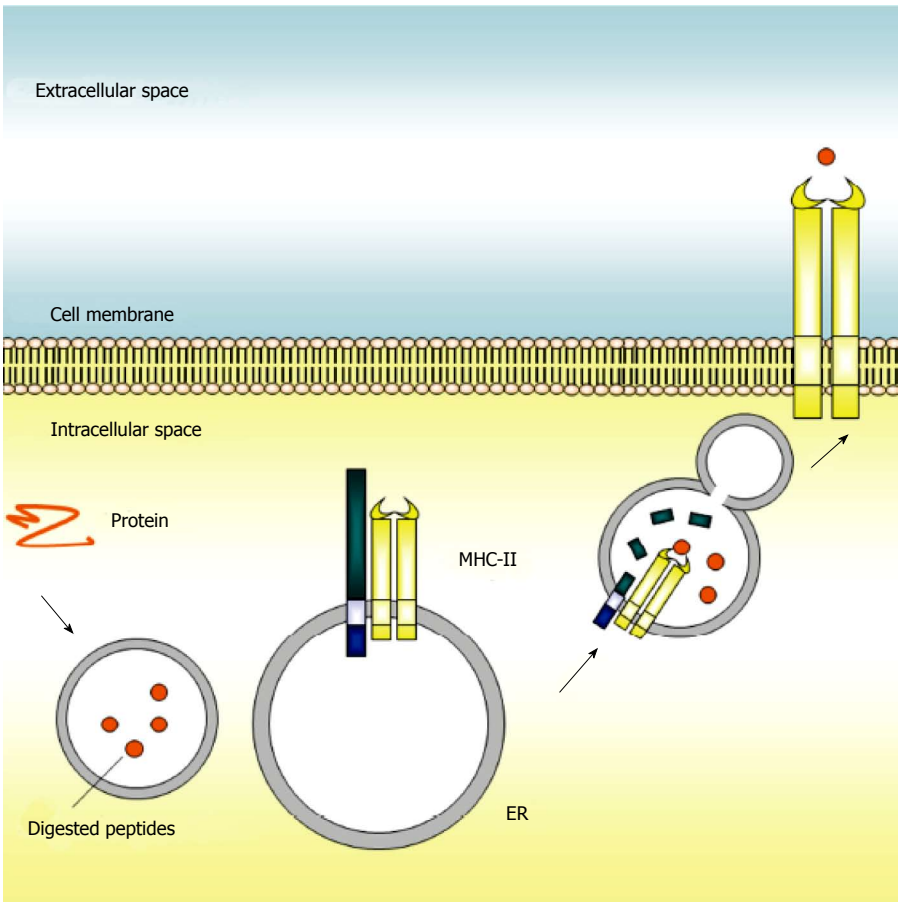

Figure 2 The canonical function of cluster of differentiation 74 in the immune system. Cluster of differentiation 74 (CD74) is present on endoplasmic reticulum (ER) where it can interact with major histocompatibility complex class Ⅱ (MHC class Ⅱ) and contribute to antigen presentation. Once synthesized, CD74 self-assembles as a trimer and serves as a scaffold onto which nascent MHC class Ⅱ assemble. After trafficking to the late endosome, CD74 is cleaved into a small peptide, CLIP, to block the peptide binding cleft of MHC class Ⅱ, prevent premature binding of antigenic peptides, and direct the MHC class Ⅱ complex to the endosomal pathway. The MHC class Ⅱ molecules with bound antigenic peptides are then exported to the surface of the antigen presenting cell for presentation of foreign peptides to $CD4^+$ T cells.

HLA-DM to MHC class Ⅱ, CLIP is released, which allows the peptide-binding cleft of MHC class Ⅱ to open and bind further antigenic peptides. The MHC class Ⅱ molecules with bound antigenic peptides are then exported to the surface of the antigen-presenting cell for presentation of foreign peptides to $CD4^+$ T cells[23,24]. Meanwhile, CLIP peptide is degraded by proteasomes, and newly synthesized CD74 is then generated.

Absence of CD74 results aberrant MHC class Ⅱ-dependent antigen processing and perturbs host defenses. Deficiency of CD74 in mice is associated with aberrant MHC class Ⅱ synthesis[25], delayed MHC class Ⅱ presentation by antigen-presenting cells[26], and impaired maturation of $CD4^+$ T cells[27]. However, knockout of CD74 in mice was able to mount an efficient response against viral infection[28]. Although how this efficient response for viral infection could work required further elucidated, an event that the function of $CD4^+$ T_H2 cells in CD74-null mice is compromised by $CD4^+$ T_H1 cells could in part explain the current observation[29]. In addition, this compromise emphasizes the crucial role of CD74 in immune regulation. An alternative strategy would be to specifically inhibit the antigen presentation mechanism and allow the pathogen to co-exist with the host during the initial phase of pathogen entry without promoting an immune reaction. This approach would be based on the observation that blockade of CD74 reduces migration inhibitory factor (MIF)-dependent monocyte arrest, chemokine expression, and neutrophil recruitment[30]. In other words, although initial inflammatory mediators are required for recruitment of neutrophils and to resolve infection-induced innate immunity, an over-robust response would generate excessive inflammatory mediators and trigger a hypersensitivity response, which could ultimately cause tissue damage and pathology. As further support of the hypothesis that attenuating CD74 function may be of benefit in some cases, mice that lack CD74 are known to be protected against bacterial infection[31]. However, a fine balance must be struck between modulating the host immune response and preventing the deleterious effects of pathogen exposure. All of these observations have generated considerable interest in CD74, as they suggest that the protein-binding ability of MHC class Ⅱ molecules could be enhanced by modifying the expression and function of endoplasmic reticulum CD74. Figure 2 illustrates the canonical antigen presentation function of

CD74 in the immune system.

ASSOCIATION OF CD74 WITH CANCER

New functions and novel interactions associated with the evolutionarily conserved CD74 protein are continually being revealed. Rare single-nucleotide polymorphisms (SNPs) in the *CD74* gene have been reported, but SNPs in molecules that interact with CD74, such as MIF[9], CD44[32] and MHC class Ⅱ[15] are more frequent and are associated with the development of cancer[33-37]. The imbalance in the regulation of inflammation that occurs in many cancers can induce cellular damage. This stimulates interaction between immune cells and the damaged cells, which then proliferate, invade, and subsequently develop into tumors[38]. Together with its role in several immunological processes, these findings indicate that CD74 is a potential therapeutic target.

CD74 as a cell surface receptor

A decade ago, CD74 was reported as an accessory signaling molecule in cancers because of its localization on the plasma membrane in certain cell types, and its role as a surface-binding receptor for MIF, a pro-inflammatory cytokine[9]. Indeed, it is now generally accepted that the oncogenic role of CD74 is MIF-dependent. In B cells, MIF induces NF-κB activation, cell proliferation, and survival[39]. MIF also induces upregulation of anti-apoptotic proteins Bcl-2 and Bcl-X_L[14]. These findings suggest that CD74 stimulation initiates a pro-survival signal. Genomic and immunohistochemical studies have revealed upregulation of CD74 in various cancers, suggesting that it may have some relationship with tumorigenesis. Table 1 summarizes the current information regarding expression and clinical significance of CD74 in human cancers. One interpretation of these observations is that persistent overexpression of CD74 in the intracellular space and on the cell surface could impair MHC class Ⅱ antigen presentation by tumor cells, thereby contributing to immune escape and facilitating tumor metastasis[40]. The underlying reasons for CD74 overexpression in cancer have remained largely unclear. However, the *CD74* locus is a common insertion site for viruses in murine B lymphomas[1]; by inference, similar virus-mediated upregulation may occur in human tumors.

Oncogenic signaling through cell surface CD74

MIF is a multifunctional cytokine that is produced by several cell types, including epithelial cells and cells that participate in the innate and adaptive immune responses[41-43]. CD74 is a receptor for extracellular MIF that is expressed in human B cells[14], gastric epithelial cells[44] and type Ⅱ alveolar epithelial cells[45]. Following MIF binding, CD74 is rapidly internalized, leading to downstream signaling cascades that trigger NF-κB activation[39], prostaglandin E2 production[9,46], TAp63 upregulation[47], and secretion of survival factors such as IL-8[48] and VEGF-D[49] *via* phosphorylation of ERK[9,50] and AKT[51]. The signaling cascades trigger cell proliferation and migration, and prevent apoptosis[14,49]. Overexpression of CD74 in HEK293 cells initials MIF-dependent MEK/ERK and PI3K/AKT activation. This is followed by NF-κB activation, which in turn triggers VEGF-D upregulation and VEGF-D-dependent cell proliferation and motility. The ultimate consequence is an increase in tumor mass, tumor-induced angiogenesis, and metastasis in xenograft-bearing mice[49].

However, unlike other ligand-receptor axes, such as EGF/EGFR[52] and VEGF-A/VEGFR2[53], CD74 lacks intracellular signaling motifs for transducing downstream signals. Therefore, it must recruit other molecules in order to transduce signals in response to MIF stimulation. Indeed, the intracytoplasmic signaling domain of CD44, a transmembrane protein with kinase-activating properties, can relay signaling downstream of the MIF-CD74 interaction[32]. CD74 forms a complex with CD44, which leads to PKA-dependent serine phosphorylation and Src activation; this eventually leads to p53 dephosphorylation, thereby stimulating cell proliferation and preventing apoptosis[32]. Another transduction mechanism involves the functional interaction between CD74 and CXCR chemokine receptors during CD74-dependent cancer cell proliferation and invasion[30,49,54]. There are also reports of fusions between *CD74* and the oncogenic receptor tyrosine kinase, *ROS1*; the resultant fusion protein activates a novel invasiveness pathway through the phosphorylation of the extended synaptotagmin-like protein, E-Syt1, in non-small cell lung cancer[55-61]. Oncogenic CD74-ROS1 represents a tumor-specific target for drug therapy, against which next-generation kinase inhibitors can be developed. Whether CD74-ROS1 (or indeed, as yet unidentified CD74 fusion proteins) has additional substrates, and whether other coreceptors participate in CD74-dependent transformation, are important unresolved questions.

RIP-processed transcription factors

Most of the RIP-processed transcription factors are synthesized and maintained as inactive membrane-associated precursors that are activated after internal or environmental cues. Such stimuli include protease cleavage, which leads to release of intracellular fragments that translocate into the nucleus and drive transcription. This is exemplified by the functional interaction of CD74 with epithelial growth factor receptor (EGFR)[62]. The Leu-Leu-Leu intramembrane proteases (I-CLIPs) cleavage site within the transmembrane domain is essential for the cleavage of CD74, as mutation of these residues abolishes the release of intracellular domain (ICD) of CD74[14]. This cleavage occurs upon treatment with an activating anti-CD74 antibody, thereby liberating the CD74-ICD from the cell membrane into the cytoplasm. Following nuclear translocation, the CD74-ICD leads to the activation of the NF-κB p65/RelA homodimer and its coactivator, TAFII105, in CD74-overexpressed HEK293 cells and in mouse B lymphocytes[14,39,63-67]. Subsequently, the signaling cascade is attenuated by ubiquitin-dependent proteasomal degra-

Table 1 Expression levels and clinical significance of cluster of differentiation 74 in human cancers

Cancer type	Event	Method	Ref
Renal cell cancer	CD74 was detected in 53 of 60 (88.3%) renal cell cancer tissues	IHC	[90, 91]
	CD74 is a useful diagnostic marker for distinguishing clear cell RCC from chromophobe and oncocytoma RCC	IHC	[92]
	CD74 was upregulated in 34 of 40 (85.0%) of clear cell RCC tissues compared with the corresponding normal kidney tissues, and the expression level was positively correlated with VEGF-D (Pearson's correlation, $r = 0.65$, $P < 0.001$)	Quantitative real-time RT-PCR, IHC	[49]
Malignant fibrous histiocytoma	Differential expression of CD74 was found in atypical malignant fibrous histiocytoma (90% positive) and fibroxanthoma (10% positive), suggesting that CD74 may be a marker of tumor progression	IHC	[93]
Thymic epithelial neoplasm	CD74 was detected in 88% (15/17) of thymic carcinomas, 70% (14/20) of invasive thymomas, but only 33% (9/27) of benign thymomas (9/27), suggesting that CD74 is a useful marker for the classification of thymic epithelial neoplasms	IHC	[94]
Colorectal cancer	A linear increase of CD74 expression was found in the progression from low- to high-grade invasive cancer tissues	IHC	[95]
	High levels of CD74 were detected in 23 of 156 (15.0%) curatively resected colorectal cancer tissues	IHC	[96]
	CD74 was increased in dysplastic epithelial cells in 47 of 55 (85%) human colorectal adenomas, with CD74 and MIF protein levels together predicting increasing dysplasia in individual adenomas ($P = 0.003$)	IHC	[97]
Gastric cancer	CD74 was detected in 48 of 126 (38.1%) gastric cancer tissues, and the expression was negatively correlated with the depth of invasion and HLA-DR expression. The patients with detectable CD74 show poor surgical outcomes ($P < 0.05$)	IHC	[98]
		IHC	[99]
	CD74 was detected in 39 of 58 (67.2%) gastric carcinoma tissues, showing significant correlation with the differentiation of gastric carcinoma ($P < 0.05$)		
Breast cancer	The expression of CD74 was significantly more abundant in invasive or metastatic tumors than in ductal carcinoma in situ ($P = 0.02$ and $P = 0.05$, respectively)	SAGE	[100]
	CD74 was detected in 468 of 580 (80.7%) breast cancer tissues, and was related to lymph node metastasis and triple-negative breast cancer ($P = 0.01$ and 0.001). In addition, CD74 expression had a linear correlation with lymph node metastasis and triple-negative breast cancer ($P = 0.02$ and 0.001)	IHC	[101]
	Stat1 and CD74 overexpression is co-dependent and linked to increased invasion and lymph node metastasis in triple-negative breast cancer	LC-MS/MS, IHC	[102]
	CD74 expression was increased in high-grade, invasive urothelial carcinoma of the bladder		[103]
Multiple myeloma	CD74 was detected in 19 of 22 (86.4%) multiple myeloma tissues	IHC	[69]
Pancreatic cancer	CD74 was identified as an overexpressed gene when compared with two SAGE libraries (6 pancreatic cancers vs 11 non-neoplastic tissues), and the expression of CD74 was detected in 15 of 18 (83%) pancreatic ductal adenocarcinoma tissues	SAGE, IHC	[104]
	CD74 was expressed in 52 of 67 (77.6%) pancreatic cancer tissues that was correlated with high perineural invasion ($P < 0.008$)	IHC	[105]
	Moreover, 47 of 68 (69.1%) and 21 of 68 (30.9%) pancreas tissues from patients receiving curative extended resection showed lower (< 70%) and higher (≥ 70%) CD74 expression, respectively. Patients with higher CD74 expression in pancreatic cancer tissues showed a higher rate of lymphatic permeation ($P = 0.04$), perineural invasion ($P = 0.01$), poor prognosis ($P = 0.006$), and poor survival ($P = 0.003$) compared with those with lower expression	IHC	[106]
	Fourteen of 46 (30.4%) and 32 of 46 (69.6%) pancreatic ductal adenocarcinoma tissues showed lower (< 25%) and higher (≥ 25%) CD74 expression, respectively. Patients with higher CD74 expression in pancreatic cancer tissues showed a higher rate of perineural invasion ($P = 0.007$) and poor 3- and 5-yr cumulative survival rates (41% and 62% *vs* 0% and 9%, $P = 0.000$) compared with those with lower expression	IHC	[107]
Cervical squamous cell carcinoma	CD74 expression was significantly higher in CIN than in the normal samples and higher in SCC than in CIN	IHC	[108]
Urothelial carcinoma of the bladder	CD74 was detected in 192 of 342 (56.1%) urothelial carcinoma of the bladder tissues, which is associated with older age at diagnosis (≥ 68 yr, $P = 0.048$), high World Health Organization grade ($P = 0.019$), advanced stages ($P = 0.001$), non-papillary growth pattern ($P = 0.040$), the absence of tumor-infiltrating inflammatory cells ($P < 0.001$), and the presence of tumor-associated inflammatory cells ($P = 0.017$). However, CD74 expression was not related to recurrence-free and overall survivals in primary and subgroup analyses	IHC	[103]
Non-small cell lung cancer	A case report found a mutation in CD74-ROS1 that is associated with acquired resistance to crizotinib.	FISH, RT-PCR	[109]
	CD74 was detected in 57 of 70 (81.4%) non-small cell lung cancer tissues	IHC	[110]
	CD74-ROS1 fusion transcript was detected in 5 of 1073 (0.5%) non-small cell lung cancer tissues	RT-PCR	[61]
	CD74-ROS1 fusion transcript was detected in 4 of 556 (0.7%) non–small cell lung cancer tissues	IHC	[111]
	CD74-ROS1 fusion transcript was detected in 1 of 114 (0.9%) non–small cell lung cancer tissues	RT-PCR	[56]
	CD74-ROS1 fusion transcript was detected in 2 of 208 (1.0%) never-smokers with lung adenocarcinoma tissues	RT-PCR	[112]
	CD74-ROS1 fusion transcript was detected in 2 of 447 (4.5%) never-smokers with lung adenocarcinoma tissues	Transcriptome sequencing	[113]
	Two CD74 polymorphisms, rs2748249 and rs1560661, are associated with hematologic toxicity in patients with non–small cell lung cancer after platinum-based chemotherapy	BeadChip	[114]

CD74: Cluster of differentiation 74; MIF: Migration inhibitory factor; RCC: Renal cell cancer; IHC: Immunohistochemistry; RT-PCR: Reverse-transcription polymerase chain reaction; SAGE: Serial analysis of gene expression; LC-MS/MS: Liquid chromatography–mass spectrometry/ mass spectrometry; FISH: Fluorescence *in situ* hybridization.

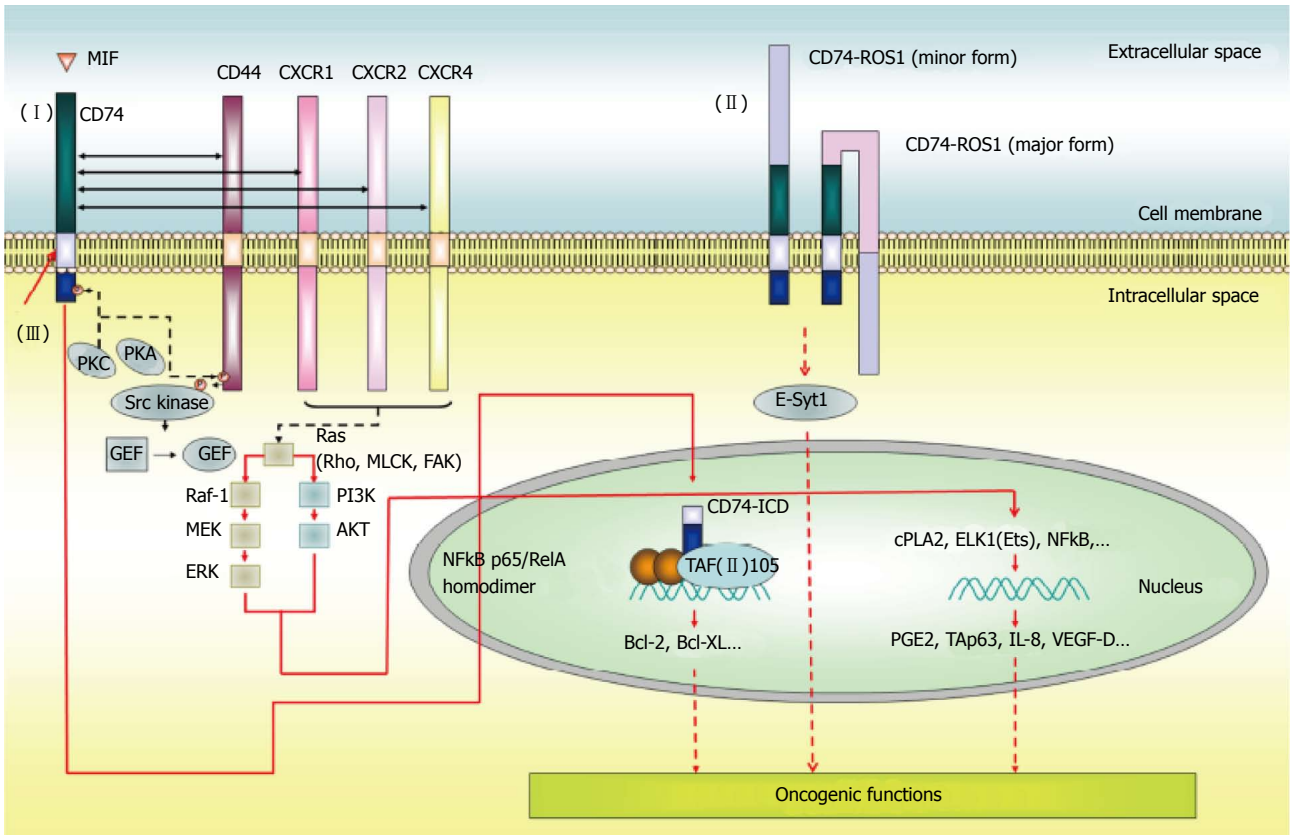

Figure 3 The function of cluster of differentiation 74 in the cancer development. (Ⅰ) Membrane associated-CD74 is involved in modulating the expression of a variety of genes which involved cell proliferation, invasion and survival through interacting with CD44, CXCR1, CXCR2 or CXCR4 followed by activation of the signaling cascades in a MIF-dependent manner. (Ⅱ) After MIF stimulation, CD74 releases its intracellular domain, CD74-ICD. The CD74-ICD translocates from cytoplasm into nucleus and functions as a transcription modulator. (Ⅲ) The CD74-ROS1 fusion protein with one (minor form) or two (major form) transmembrane regions and one kinase domain, promotes novel invasiveness pathway through the phosphorylation of the extended synaptotagmin-like protein, E-Syt1. MIF: Macrophage migration inhibitory factor; CXCR: Chemokine (C-X-C motif) receptor; PKA: Protein kinase A; PKC: Protein kinase C; GEF: Guanine nucleotide exchange factor; Ras: Ras oncogene; Rho: Ras homolog family member; MLCK: Myosin light chain kinase; FAK: Focal adhesion kinase; Raf-1: RAF proto-oncogene serine/threonine-protein kinase; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; NF-κB: Nuclear factor-kappaB; TAF(II)105: Transcription initiation factor TFIID 105 kDa subunit; ROS-1: C-ros oncogene 1; E-Syt1: Extended synaptotagmin-like protein 1; Bcl-2: B-cell lymphoma 2; Bcl-XL: B-cell lymphoma-extra large; cPLA2: Cytosolic phospholipase A2; ELK1: Member of ETS oncogene family; Ets: V-ets erythroblastosis virus E26 oncogene; PGE2: Prostaglandin E2; Tap63: Tumor protein p63; IL-8: Interleukin 8; VEGF-D: Vascular endothelial growth factor D.

dation of CD74-ICD[67]. Figure 3 illustrates the function of CD74 in cancer development.

CD74-TARGETED CANCER THERAPY

The high expression of CD74 in cancer cells in comparison with their normal counterparts provides a potential cancer-selective antitumor strategy. As mentioned above, oncogenic CD74-ROS1 represents a potential tumor-specific target against which next-generation kinase inhibitors might be developed. However, whether additional substrates co-exist with CD74-ROS1 or other unidentified CD74 fusion proteins, and whether other coreceptors participate in CD74-dependent transformation remains to be determined.

A monoclonal antibody, LL1, which binds to and rapidly internalizes cell surface CD74 into lysosomes[68], increases the survival of mice bearing xenografts[69]. Recent studies have also highlighted the efficacy of a humanized anti-CD74 monoclonal antibody derived from LL1, named milatuzumab, in the treatment of lymphoid malignancies[70,71], non-Hodgkin lymphoma[72], chronic lymphocytic leukemia[73], and mantle cell lymphoma[74]. A phase I multicenter, dose-escalation trial of monotherapy with milatuzumab in advanced multiple myeloma has been evaluated[75]. In addition, because the CD74 antibody enters lysosomes rapidly and at high concentration, it could be conjugated to a drug, and then used to target tumors expressing cell surface CD74. Successful preclinical examples include antibodies conjugated with radioisotopes[76,77] and doxorubicin[78,79], as well as combined therapy using milatuzumab and FTY720, a CD74 stimulator[80]. However, further selectivity must be developed, since such antibodies could potentially bind to all antigen-presenting cells.

Targeted therapy using small molecules is another developing field. Some small molecules have demonstrated activity against other proteins that associate with CD74, and can thus indirectly block CD74 function[30,81]. Examples are MIF activity modifiers, which prevent MIF binding to CD74. For instance, Ibudilast, a phosphodiesterase inhibitor, blocks MIF activity fol-

lowed by inhibited chemotactic activity of peripheral blood mononuclear cells[82]. (S, R)-3(4-hydroxyphenyl)-4, 5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1) and 4-iodo-6-phenylpyrimidine (4-IPP) function as tautomerase inhibitors that also abolish MIF activity[83]. Ebselen disrupts the formation of MIF trimmers, thereby inactivating the complex[84]. A second set of examples is the cathepsin S inhibitors that prevent antigen presentation and disease progression through inhibiting CD74 degradation. The accumulated CD74 binds to MHC class Ⅱ molecules within endocytic compartments, which are targets for treatment of autoimmune diseases using molecules such as Clik60[85], LHVS[86], and SB-331750[87], and RWJ-445380. Finally, there are CD74 expression modifiers such as Auraptene that suppresses CD74 expression and thus blocks *Helicobacter pylori* adhesion and pro-inflammatory mediator production in C57BL/6 mice[88,89]. However, whether these small molecules will have anti-cancer activity remains to be determined. More specific targeted approaches will emerge from the ongoing screening efforts to find compounds that directly target CD74. Combined with an effective method to deliver the targeting agents efficiently to the tumor, this would be a critical breakthrough for the field.

CONCLUSION

Recent advances in our knowledge of CD74 functions have emerged through discovery of its natural ligand, additional interacting proteins, and elucidation of molecular mechanisms associated with CD74 signaling in immunity and cancer. Normal expression in antigen-presenting cells maintain proper MHC class Ⅱ-restricted antigen presentation and an appropriate immune regulation. However, aberrant expression of CD74 in cells leads to an unbalanced immune system, and possibly also oncogenesis, in a MIF-dependent manner. Despite the natural protective actions of CD74 in the immune system, functional studies from several CD74-focused experimental models show that CD74 inhibition will also likely halt cancer progression and improve patient prognosis. There are ongoing clinical studies into the role of CD74 in diverse diseases, including various types of cancer. Further research into CD74 and its effect on cellular processes, including the complex interactions between CD74 and its binding partners, will undoubtedly translate into clinical benefit for patients.

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