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Gene Section
Review

CD74 (CD74 molecule, major histocompatibility complex, class II invariant chain)

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Abstract

Review on CD74, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: DHLAG, HLADG, II, Ia-GAMMA

HGNC (Hugo): CD74

Location: 5q32

DNA/RNA

Description

The CD74 gene consists of 9 exons, different transcripts results in four protein variants.

Transcription

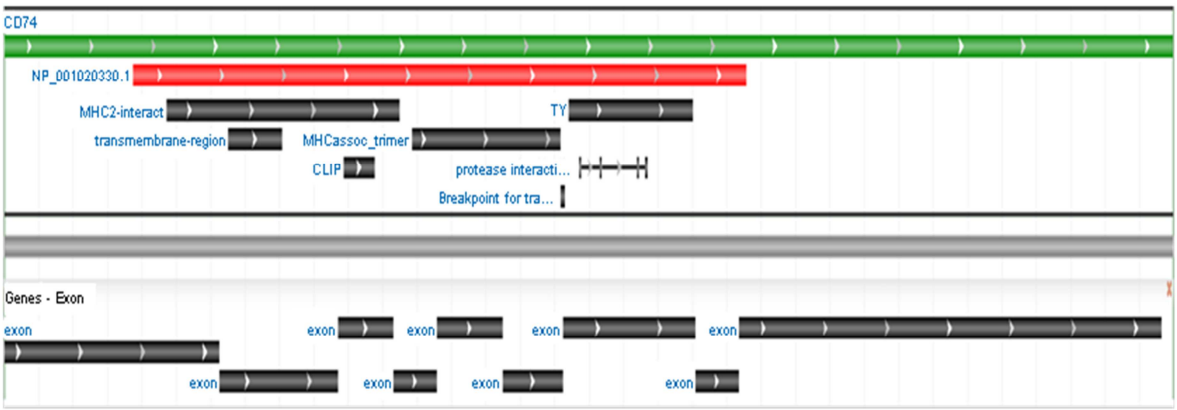
CD74 gene is processed into 4 different in-vivo know transcripts resulting from two different translation initiation sites and alternative splicing (Borghese and Clanchy, 2011; UniProt Consortium, 2013):

P43 - The longest isoform. Contains a longer cytoplasmic tail due to the use of an alternative translation initiation site, and a THY domain from alternative splicing.

P41 - Similar to the P43 isoform but does not contain the longer cytoplasmic tail.

P35 - Similar to the P43 isoform but does not contain the THY domain.

P33 - Does not contain not the longer cytoplasmic tail and not the THY domain.



Transcript structure of human CD74 (Geer et al., 2010).

Schematic representation of a monomeric CD74, isoform p33.

Protein

Description

CD74 is a non-polymorphic type II integral membrane protein. The most common isoform is p33, which is 296 aa long and has a molecular weight of 33 kDa. The protein consists of three parts, a 46 aa long N-terminus cytoplasmic tail, 26 aa long transmembranal domain and a 224 aa long luminal region. CD74 assembles to homotrimers immediately after synthesis.

Expression

CD74 is mainly expressed in antigen presenting cells, endothelial cells and neuroglia cells.

Localisation

Trimers of CD74 are expressed in the endoplasmic reticulum (ER), in association with MHC α and β chains. The complex is transported to the trans-Golgi and then diverted from the secretory pathway to the endocytic system and ultimately to acidic endosome or lysosome-like structures called MHC class II compartments (MIIC or CIIV). A small proportion of CD74 is modified by the addition of chondroitin sulfate (CD74-CS), and this form of CD74 is expressed on the cell surface (Stumptner-Cuvelette and Benaroch, 2002).

Function

CD74 function has two main functions:

1) MHCII chaperon

MHC class II molecules are heterodimeric complexes that present foreign antigenic peptides on the cell surface of antigen-presenting cells (APCs) to CD4+ T cells. MHC class II synthesis and assembly begins in the endoplasmic reticulum (ER) with the non-covalent association of the MHC α and β chains with trimers of CD74. Three MHC class II α β dimers bind sequentially to a trimer of the CD74 to form a nonameric complex $(\alpha\beta CD74)_3$, which then exits the ER (Roche et al., 1991). After being transported to the trans-Golgi, the αβCD74 complex is diverted from the secretory pathway to the endocytic compartments. Once in the endocytic compartments, CD74 is proteolytically processed. CD74 lumenal domain undergoes a stepwise proteolytic cleavage, which results in a short class II-associated Ii chain peptide (CLIP), which remains in the MHC class II peptide grove (Neefjes et al., 1990; Roche and Cresswell, 1991; Stumptner-Cuvelette and Benaroch, 2002). The final step for MHC class II expression requires interaction of αβCLIP complexes with another class II-related αβ dimer, called HLA-DM. Binding of this molecule excludes the residual CLIP peptide, rendering the αβ dimers ultimately competent to bind antigenic peptides, which are mainly derived from internalized antigens and also are delivered to the endocytic pathway (Denzin and Cresswell, 1995; Ghosh et al., 1995). Thus, CD74 was thought to function mainly as MHC class II chaperone, which promotes ER exit of MHC class II molecules, directs them to endocytic compartments, prevents self-peptide binding in the ER and contributes to peptide editing in the MHC class II compartment (Matza et al., 2003).

2) CD74 as cell surface receptor

A small proportion of CD74 is modified by the addition of chondroitin sulfate (CD74-CS), and this form of CD74 is expressed on the cell surface (Matza et al., 2003; Naujokas et al., 1993). This cell surface expression of CD74 is not strictly dependent on class II MHC (Henne et al., 1995; Starlets et al., 2006), and numerous non-class II positive cells express CD74 where it can serve as a receptor for the initiation of different signaling cascades (Maharshak et al., 2010; Stumptner-Cuvelette and Benaroch, 2002). The cytokine, macrophage migration inhibitory factor (MIF), was found to be the natural ligand of CD74. MIF binds to the extracellular domain of CD74 with high affinity ($KD = 1.40 \times 10^{-9}$ M) and initiates a signaling cascade (Leng et al., 2003). CD74 forms a complex with CD44, which is essential for the MIF-induced signaling cascade (Gore et al., 2008; Shi et al., 2006).

In murine B cells, CD74 expression is directly involved in shaping the B cell repertoire by regulating mature B cell survival (Gore et al., 2008; Matza et al., 2003; Shachar and Flavell, 1996; Starlets et al., 2006). MIF binding to CD74 induces a signaling pathway that involves the Syk tyrosine kinase and the PI3K/Akt pathway (Gore et al., 2008; Starlets et al., 2006), induction of CD74 intramembrane cleavage, and the release of the CD74 intracellular domain (CD74-ICD) (Matza et al., 2002; Schneppenheim et al., 2013). CD74-ICD translocates to the nucleus where it induces activation of transcription mediated by the NF-κB p65/RelA homodimer and its co-activator, TAFII105, resulting in regulation of transcription of

genes that control B cell proliferation and survival (Gore et al., 2008; Matza et al., 2001; Starlets et al., 2006). MIF was found to regulate cell entry into the S-phase in a CD74 and CD44-dependent fashion, by elevating cyclin E levels, resulting in cell proliferation. In addition, this cascade augments Bcl-2 expression, further supporting cell survival (Cohen et al., 2012; Gordin et al., 2010; Gore et al., 2008; Lantner et al., 2007; Sapoznikov et al., 2008; Starlets et al., 2006). Thus, the MIF binding to CD74/CD44 complex initiates a pathway, resulting in proliferation of the mature B cell population, and their rescue from death.

Implicated in

Chronic lymphocytic leukaemia (CLL)

Prognosis

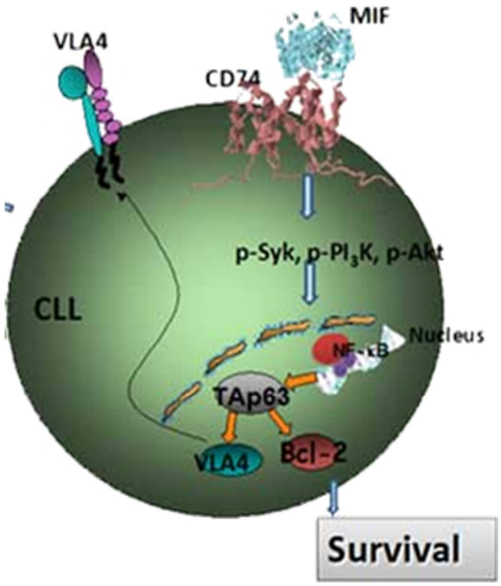
CD74 and its ligand, MIF, were shown to play a pivotal role in the regulation of CLL cell survival. CLL cells markedly upregulate both expression of their cell surface CD74, and their MIF production. Stimulation of CD74 with the MIF ligand (as well as with an agonistic antibody) initiates a signaling cascade leading to IL-8 transcription and secretion in all CLL cells, regardless of the clinical status of the patients. Secreted IL-8 induces the transcription and translation of the anti-apoptotic protein, Bcl-2, and thus regulates an anti-apoptotic pathway. Blocking of CD74 (by milatuzumab), or of MIF or IL-8 results in dramatic downregulation of Bcl-2 expression, and augmentation of apoptosis (Binsky et al., 2007).

In addition, stimulation of CD74 with its natural ligand, MIF, initiates a signaling cascade that results in upregulation of TAp63, which directly regulates CLL survival. TAp63 expression also elevates the expression of the integrin VLA-4, particularly during the advanced stage of the disease. Blocking of CD74, TAp63, or VLA-4 inhibits the in vivo homing of CLL cells to the bone marrow (BM). Thus, CD74 and its target genes TAp63 and VLA-4 facilitate migration of CLL cells back to the BM, where they interact with the supportive BM environment that rescues them from apoptosis (Binsky et al., 2010).

Multiple myeloma (MM)

Prognosis

CD74 expression was observed in 19 of 22 cases of multiple myeloma, with most expressing moderate to high levels in the majority of malignant plasma cells (Burton et al., 2004). CD74, expressed in MM, was evaluated as a target for immunotherapy with milatuzumab (a humanized anti-CD74 antibody). In a multicentre dose escalation study, 25 patients with advanced MM received milatuzumab doses of 1.5 (N = 8), 4.0 (N = 9), 8.0 (N = 4) or 16.0 mg/kg (N = 4) administered twice weekly x 4.



CD74 activation by MIF up regulates cell survival and VLA-4 expression.

They had a median of 5 prior treatments (17 post ≥ 1 stem cell transplantation) and were refractory (N = 7) or relapsed (N = 18) with generally short-lived responses to last treatment (median 4.0 months). After increasing prophylactic medications and slowing administration, infusions were well tolerated (National Cancer Institute-Common Terminology Criteria v3 toxicity Grades 1-2) with no dose-limiting toxicity at higher doses. Only one patient developed borderline positive human anti-milatuzumab antibody titres of uncertain clinical significance. Although milatuzumab was rapidly cleared from circulation with little serum accumulation and low trough levels, B-cell levels were moderately decreased with treatment (median decrease, 34%). Disease stabilization and evidence of pharmacodynamic activity support further development for use in combination with other agents or as a drug conjugate (Kaufman et al., 2013).

Mantle cell lymphoma (MCL)

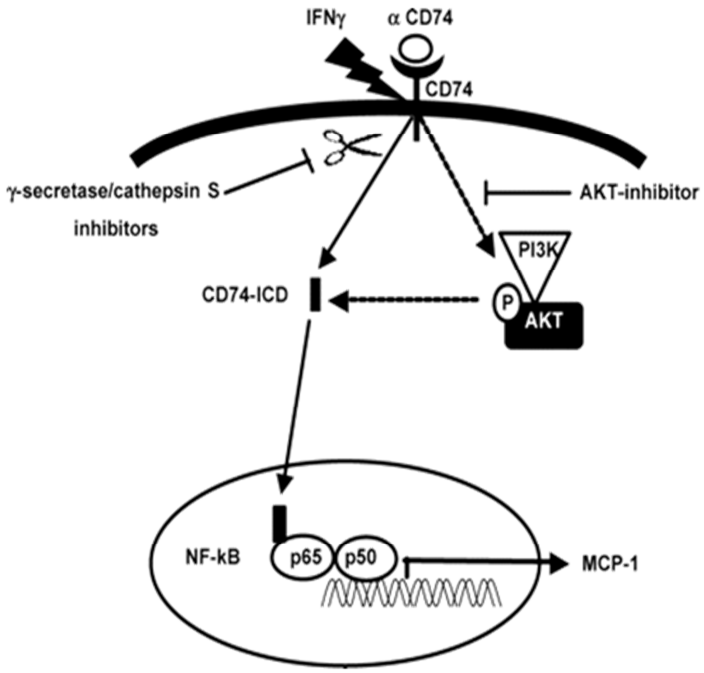
Prognosis

CD74 is expressed on MCL. The combination of milatuzumab and rituximab has preclinical in vitro and in vivo activity in MCL (Alinari et al., 2011). Treatment of MCL cell lines and primary patient tumor cells with immobilized milatuzumab resulted in statistically significant enhanced cell death (Alinari et al., 2012).

Non-Hodgkin lymphoma (NHL)

Prognosis

Preclinical studies of the humanized anti-CD74 mAb hLL1 have shown that it is an effective therapeutic agent that may be of significant value for treatment of NHL (Stein et al., 2007).



Schematic representation of the potential mechanisms by which CD74 is involved in MCP-1. induction.

Invasive carcinoma of the bladder

Prognosis

CD74 expression is increased in high-grade, invasive carcinoma of the bladder.

Its expression was significantly associated with older age at diagnosis (Choi et al., 2013).

Gastrointestinal carcinoma

Prognosis

Expression of CD74 within gastrointestinal carcinomas showed a statistically greater expression than in the normal tissue counterparts. CD74 expression was observed in 95% of pancreatic carcinomas with the majority of cases presenting a mostly intense, diffuse labeling pattern.

The results suggested a trend towards greater expression within the higher-grade carcinomas. Colorectal and gastric carcinomas gave similar results with 60% and 86%, respectively, positive for CD74 with an intense, diffuse staining pattern. For PanIN lesions there was greater expression of CD74 within higher grade, PanIN-3 lesions, whereas the colonic adenomas showed no such trend, but overall, a higher frequency and intensity of CD74 labeling than was observed within the colon carcinomas. These findings are supportive of a role for CD74 in the development and maintenance of gastrointestinal neo-plasia, and provide a rationale for development of therapeutic agents that are able to block CD74 function, specifically within the tumor cell (Gold et al., 2010).

Non-small cell lung cancer

Prognosis

CD74 was found to be expressed on non-small cell lung cancer (NSCLC) cells (Ioachim et al., 1996). CD74 immunoreactivity was present in the stromal cells in most tumors.

However, in many tumors the malignant cells themselves also strongly expressed CD74 (McClelland et al., 2009).

Thymic epithelial neoplasms

Prognosis

Sixty-four thymic epithelial neoplasms (27 cases of benign thymoma, 20 cases of invasive thymoma, and 17 cases of true thymic carcinoma) were studied for neoplastic epithelial cell expression of CD74 and MHC class II molecules by immunohistochemical staining of paraffin-embedded tissue.

Neoplastic epithelial cells in 88% of thymic carcinomas (15/17), 70% of invasive thymomas (14/20), but only 33% of benign thymomas (9/27) were immunoreactive for CD74.

A subset of CD74-positive neoplasms was positive for MHC class II as well, with higher relative rates of dual positivity in more aggressive neoplasms. In addition, specific histologic subtypes of thymic epithelial neoplasms displayed differing patterns of CD74 positivity. Based on these findings, CD74 and MHC class II are useful markers for the classification of thymic epithelial neoplasms (Datta et al., 2000).

Pancreatic cancer

Prognosis

Pancreatic ductal adenocarcinoma (PDAC) is still one of the most fatal cancers. Sixty-eight patients receiving curative extended resection combined with preoperative chemoradiation and postoperative chemotherapy for primary PDAC were selected. Immunohistochemistry using anti-CD74 antibody on paraffin-embedded tissue samples was performed, and cases were divided into two groups according to the ratio of CD74-positive cells: expression level I, CD74-positive cells or=70%. The correlation of CD74 expression level with clinicopathological features and overall survival was evaluated. Forty-seven (69.1%) and 21 (30.9%) patients showed level I and II CD74 expression, respectively. Patients with level I CD74 expression had a significantly better survival rate than those with level II (P = 0.003). Among the patients with pathological tumor-node-metastasis stages I and II, those with level I CD74 expression showed a significantly better prognosis than those with level II (P = 0.006). CD74 expression proved as a useful prognostic indicator for PDAC treated with multimodal therapy (Nagata et al., 2009).

Atherosclerosis

Prognosis

Overexpression of CD74 has been reported in atherosclerotic plaques. Stimulation of CD74 with an anti-CD74 antibody, which binds the CD74 extracellular domain, induces the expression of the NF-κB-regulated gene MCP-1, a small cytokine that belongs to the CC chemokine family. MCP-1 recruits monocytes, memory T cells, and dendritic cells to the sites of inflammation (Martín-Ventura et al., 2009).

Alzheimer

Prognosis

CD74 has been found to be upregulated in the microglia and neurons of Alzheimer's patients and can interact with the amyloid precursor protein, potentially inhibiting the production of amyloid-β.

HIV

Prognosis

HIV-1 gp41 binds directly to CD74 in HIV-1-infected cells, leading to ERK1/ERK2 MAPK activation and enhanced HIV-1 infection (Zhou et al., 2011). The cytoplasmic region of HIV-1 Vpu also was found to interact with the 30-amino-acid cytoplasmic tail of CD74. Human monocytic U937 cells infected with wild-type or Vpu-defective HIV-1 showed that Vpu down-regulated the surface expression of MHC class II molecules (Hussain et al., 2008).

Gastric ulceration

Prognosis

The pathogenic bacterium, Helicobacter pylori, was shown to bind to CD74 on gastric epithelial cells. Upon H. pylori binding to CD74, NF-κB activation occurs resulting in the production of proinflammatory cytokines, including IL-8. IL-8 plays a major role in the proinflammatory immune response to H. pylori infection, and the interaction of H. pylori with the gastric epithelial cells might be of critical importance in the immune response to this infection and the development of gastric ulceration (Beswick et al., 2005).

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