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Review

CD44: functional relevance to inflammation and malignancy

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Summary. CD44 is a principal cell surface receptor for hyaluronan, a major component of extracellular matrices. Cells are surrounded by and encounter matrix *in vivo*, which in turn serves a variety of cell functions through the direct adhesion via their receptors. CD44 communicates cell-matrix interactions into the cell via "outside-in signaling" and has an important role in biological activities. The interaction of CD44 with fragmented hyaluronan on rheumatoid synovial cells induces expression of VCAM-1 and Fas on the cells, which leads to Fas-mediated apoptosis of synovial cells by the interaction of T cells bearing FasL. On the other hand, engagement of CD44 on tumor cells derived from lung cancer reduces Fas expression and Fas-mediated apoptosis, resulting in less susceptibility of the cells to CTL-mediated cytotoxicity through Fas-FasL pathway. Thus, although the CD44-mediated signaling differs among cells and circumstances, we here propose the functional role of CD44 in inflammatory processes and tumor susceptibility and the rational design of future therapeutic strategies including the exploitation of CD44-mediated pathway in vivo.

Key words: CD44, Recirculation/Recruitment, Adhesion Molecules, Inflammation, Cancer

CD44, a major receptor for hyaluronan

CD44

Cells are surrounded by and encounter *in vivo* extracellular matrix components and the engagement of cell surface receptors by the matrices always occurs in various cells in the tissue. Extracellular matrices, thereby, serve a variety of cell functions through the direct adhesion via their receptors. The major component, found in almost all types of extracellular matrix, is hyaluronan and the best known cell surface receptor for hyaluronan is CD44 (Underhill et al., 1987; Aruffo et al., 1990).

CD44 is a 90-kDa transmembrane glycoprotein widely distributed on T cells, granulocytes, monocytes, fibroblasts, keratinocytes and epithelial cells and is involved in various cell adhesion events, including lymphocyte migration, hematopoiesis and tumor metastasis (Lesley et al., 1993; Naot et al., 1997; Pure and Cuff, 2001). Coding lesion of CD44 is on the short arm of human chromosome 11 and multiple mRNA transcripts arise from the alternative splicing of 12 of the 20 exons. The standard and predominant form of CD44 is designated CD44H (hematopoetic) and consists of the link protein-homologous extracellular domains (exons 1-5 and 16), the transmembrane domain (exon 18) and the cytoplasmic domain (exon 20). CD44H is constructed with about 37 kDa of core peptide and post-translationally added n-linked and o-linked oligosaccharides. The distal extracellular domain is the primarily responsible region for the binding of hyaluronan. Although several cell surface hyaluronan-binding proteins have been identified, including CD44, RHAMM, IVd4 and the Liver Endothelial Cell clearance receptor, the most common is CD44 (Kincade et al., 1997) (Fig. 1).

Several isoforms are designated as CD44v (variant) and they arise by the alternative splicing of exons 6-15, also named variant exons v1-v10, resulting in an increased size of CD44, from 85 to 250 kDa and modulation of its functions (Naot et al., 1997). This cytoplasmic domain, 70 amino acids, possesses a capacity for interaction with cytoskeletal proteins and the potential for intracellular signaling (Okamoto et al., 2001).

Hyaluronan

The best known ligand for CD44 is hyaluronan. Hyaluronan is a high molecular weight (about 2,000

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kDa) linear repeating glycosaminoglycan, which consists of 2,000-25,000 disaccharides of ß-D-glucuronyl acid and ß-D-N-acetylglucosamine and is found in almost all types of extracellular matrices (Lee and Spicer, 2000). Fibroblasts are known to mainly synthesize hyaluronan in response to stimulation with cytokines, such as IL-1ß and TNF-α.

Low molecular weight hyaluronan (1.6-10 x 10^3) is present in inflamed tissue and tumor-bearing tissue. Activated hyaluronidase digests hyaluronan there, which leads to the accumulation of a fragmented form. We, and others, suggest that high molecular mass hyaluronan inhibits cellular functions, whereas low molecular fragments have a stimulatory effect, inducing cytokine production of synovial fibroblasts and angiogenesis (Fujii et al., 1999a,b; Savani et al., 2001).

Adhesion of CD44-hyaluronan and signaling

The function of CD44 as a signaling molecule has been emerging. CD44 has an extensive cytoplasmic domain and communicates cell-matrix interactions into the cell via outside-in signaling. We and others reported that stimulation of CD44 with monoclonal antibodies (mAbs) or hyaluronan transmits the signal into the cell, which leads to activation of T cells and cytokine or chemokine release from monocytes and synoviocytes (Fujii et al., 1999 b; Pure and Cuff, 2001). CD44, thereby, plays a major role in multiple physiological functions including cell-cell adhesion, cell-matrix interaction, lymphocyte recruitment to inflammatory sites, and tumor metastasis, through the adhesion to hyaluronan.

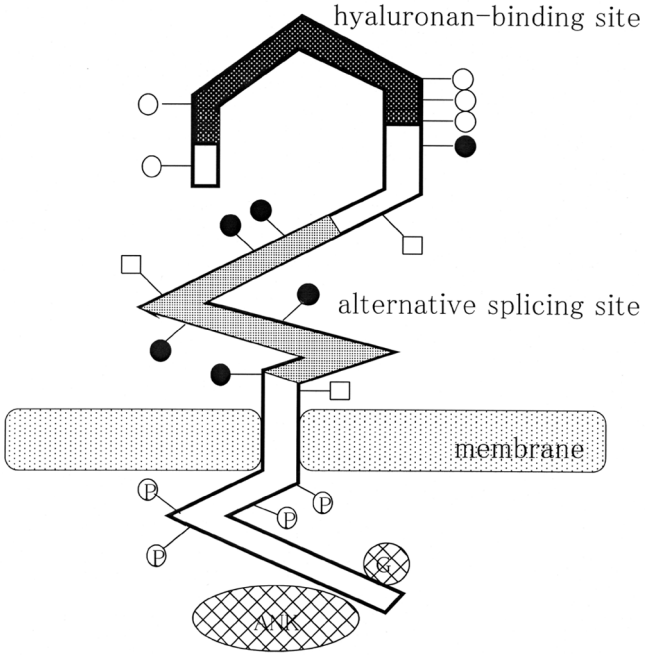

Fig. 1. Structure of CD44. CD44 consists of a link protein-homologous extracellular domain, the transmembrane domain and the cytoplasmic domain (exon 20). The extracellular domain possesses hyaluronan-binding sites and alternative splicing sites and is post-translationally modified with N-linked (open circle) and O-linked (closed circle) oligosaccharides and chondroitin sulfate (open square). The cytoplasmic domain exhibits protein motifs that indicate a capacity for interaction with cytoskeletal proteins such as ankylin (ANK) and the potential for intracellular signaling (P).

Functional significance of CD44 for inflammation

Engagement of CD44 induces IL-6 and VCAM-1 on rheumatoid synovial cells

Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving synovial membranes of multiple joints, characterized by hyperplasia of synovial cells, neovascularization and infiltration with $CD4^+$ T cells. RA synovium is a typical model of inflammation, and CD44 is predominantly expressed in RA synovium, compared to osteoarthritis (OA) (Fig. 2). CD44 is found on the surface of lymphocytes and synovial cells, in proportion to the intensity of inflammation. Crosslinking of CD44 on RA synovial cells using a specific mAb and 2nd crosslinker Ab highly augments IL-6 production and its mRNA transcription. Furthermore, stimulation of CD44 activates transcription factor AP-1 and CRE, followed by the IL-6 production (Fujii et al., 1999b).

Hyaluronan is the major extracellular matrix of RA synovium and is synthesized by synovial fibroblasts in response to stimulation with cytokines, such as IL-1_ and TNF-α (Engstrom-Lurent, 1997). Synovial cells are, thereby, surrounded by and encounter *in vivo* hyaluronan mainly through CD44. Low molecular fragments of hyaluronan effectively increase IL-6 production via binding to CD44 on the cells, compared to a native high molecular weight one. These results indicate that the engagement of CD44 by fragmented hyaluronan occurs in synovial cells in RA synovium, resulting in IL-6

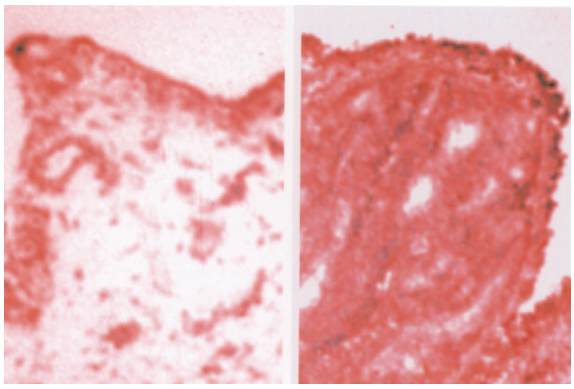

Fig. 2. CD44 in rheumatoid synovium. Shown is expression of CD44 in synovium of osteoarthritis (left panel) and rheumatoid arthritis (right panel). Immunohistochemical studies of CD44 were done using CD44 mAb NIH44-1. x 100

production from the cells during pathological processes of RA synovitis (Fujii et al., 1999b).

CD44 crosslinking also augments VCAM-1 mRNA transcription within 2 hours of stimulation and VCAM-1 expression on RA synovial cells within 6 hours. CD44 stimulation and cytokine stimulation require clearly different kinetics, as CD44 functions much faster than cytokines such as IL-1ß and TNF-α, when they induce VCAM-1 expression. Hyaluronan fragments also effectively increase VCAM-1 expression via binding to CD44 on the synovial cells, compared to native hyaluronan. Furthermore, CD44 engagement on synovial cells results in doubling the integrin-dependent adhesion rate to activated T cells, relative to control. Thus, the stimulation of CD44 by mAb or fragmented hyaluronan upregulates VCAM-1 expression on RA synovial cells and increases cell adhesion to T cells (Fujii et al., 1999a).

CD44 induces apoptosis of synovial cells

Rheumatoid synovium is an extreme characteristic comprised of two diverse phenomena of RA synovial cells, intractable proliferation and growth arrest of the cells, and the mechanisms altering its balance lead to the pathogenesis of RA (Pap et al., 2000; Sundy and Haynes, 2000; Tanaka et al., 2000b). Recent reports indicate that Fas-mediated apoptosis of synovial cells is a specific phenomenon for RA synovitis, because it is observed in RA, but not in OA and that anti-Fas mAb accelerates apoptotic change of the RA synovial cells (Kobayashi et al., 1999; Muller-Ladner and Nishioka, 2000).

We propose that engagement of CD44 induces Fas-mediated apoptosis of RA synovial cells because: 1) CD44 and Fas are similarly localized in RA synovium in vivo and expressed on cultured synovial cells in vitro; 2) CD44 crosslinking on RA synovial cells upregulates Fas and Fas mRNA transcription, more than stimulation with IL-1α and TNF-ß does; 3) Fas-mediated apoptosis of RA synovial cells is markedly augmented by the CD44 cross-linking on the cells, and 4) fragmented hyaluronan effectively augments Fas-mediated apoptosis compared with native hyaluronan (Fujii et al., 2001).

In vivo, synovial cells are surrounded by and encounter hyaluronan through CD44, indicating that the engagement of CD44 by matrix always occurs in RA synovium. Thus, our results imply that in vitro culture steps without extracellular matrix may introduce major biases; in vitro synovial cells having less amounts of Fas using cultured synovial cells may protect themselves against FasL-bearing T cell recognition, although, in vivo, synovial cells which express Fas as highly as CD44 shown in immunohistochemical examination and express VCAM-1 induced by CD44 efficiently fall into Fas-mediated apoptosis induced by FasL-bearing T cells.

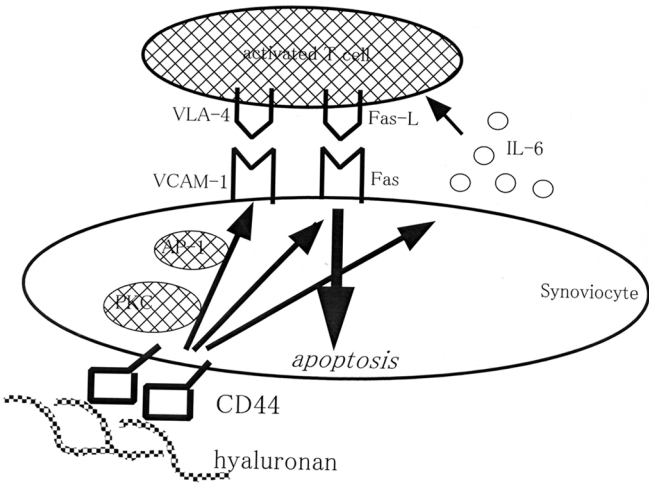

Fig. 3. Functional role of CD44 on synovial cells in RA synovitis. Interaction of CD44 and degraded products of hyaluronan induces expression of VCAM-1, Fas and IL-6, which results in augmentation of Fas/Fas-L-mediated apoptosis of synovial cells by the adhesion with T cells.

Relevance of CD44 to RA synovitis

CD44 is involved in the pathogenesis of RA synovitis in the following characteristics: 1) the involvement of cell surface functional molecules per se (here, CD44) and in the induction of other functional molecules (here, Fas and VCAM-1) on the same cell; 2) interaction of CD44 and degraded hyaluronan play an important role in biological activities, such as induction of apoptosis; 3) CD44-mediated signaling might be different from a cytokine-mediated one in regulating Fas expression and Fas-mediated apoptosis; and 4) CD44 further augments Fas/Fas-L-mediated apoptosis of synovial cells by augmenting the adhesion of synovial cells with T cells through up-regulation of VCAM-1 on synovial cells (Fig. 3).

Although T cells are known to play a central role in an initiation of RA synovitis (Tanaka et al., 1998a), the significance of T cell functions for persistent inflammation is unclear. In SCID mouse model of RA, depletion of T cells rather amplifies synovial cell proliferation, the growth of pannus and subsequent degradation of bones (Sack et al., 1999). Thus, T cells might rather restrain synovial hyperplasia in chronic RA and support amelioration of proliferation of synovial cells, whose CD44 is engaged by surrounding hyaluronan, by adhering to T cells and by being affected by T cells through FasL/Fas pathway. Alternatively, soluble Fas, soluble VCAM-1/ICAM-1 and soluble CD44 might be involved in susceptibility of the RA synovial cells to T cell-mediated apoptosis, by reducing interaction between these cells and by interrupting the Fas-FasL pathway (Kobayashi et al., 1999). The rational design of future therapeutic strategies for RA synovitis may thereby include the exploitation of CD44 and the Fas death pathway in order to directly reduce growth of synovial cells i*n vivo*.

The role of CD44 in malignancy

The role of CD44 in extravasation of tumor cells during metastasis

Many studies document the prevalence and diagnostic/prognostic value of CD44 and its variant isoforms in human cancers. However, the precise function of CD44 in tumor has not been fully established (Schmits et al., 1997; Sneath and Mangham 1998). Metastatic spread requires a series of interactions between the tumor cells, non-tumor cells and the surrounding matrices. The theoretical steps of the metastatic process are known as the similarity of leukocyte recruiment into tissues (Tanaka et al., 1998b; Tanaka, 2000a). In this process, tumor cells must make contact and adhere to endothelial cells lining the vessel wall within the target organ using certain adhesion molecules and then transmigrate to the tissue. Integrins LFA-1 and VLA-4 play a central role in leukocyte adhesion to the endothelium and subsequent migration into tissues (Tanaka et al., 1993, 1996, 1997). However, the majority of tumor cells derived from solid cancers including colorectal cancer do not express suitable adhesion receptors, LFA-1 and VLA-4.

We have reported the following features of CD44 on the colon cancer cells: (1) colon cancer cells highly express CD44; (2) stimulation of cancer cells by CD44 crosslinking or fragmented hyaluronan markedly induces the expression of LFA-1, some of which reveal an activation epitope on the cells; (3) fragmented hyaluronan induces upregulation of activation epitope of LFA-1, which is mediated through protein kinase C; (4) stimulation of CD44 augments LFA-1-mediated adhesion of cancer cells to endothelial cells and facilitates transendothelial migration; (5) stimulation of CD44 also induces expression of HGF receptor c-Met on cancer cells; and (6) HGF further amplifies LFA-1-mediated adhesion of the cells pre-stimulated by CD44-derived signaling (Fujisaki et al., 1999).

Our results indicated that stimulation by CD44 crosslinking or ligation with fragmented hyaluronan induces "outside-in signaling", which consists of a direct pathway via CD44 and an alternate pathway through the induction of c-Met expression via HGF (Fig. 4). Such stimuli augment the expression and trigger the function of integrins via "inside-out signaling" in colon cancer cells, which leads to the amplification of integrin-mediated adhesion to the vessel wall and subsequent transendothelial migration (Tanaka et al., 1999).

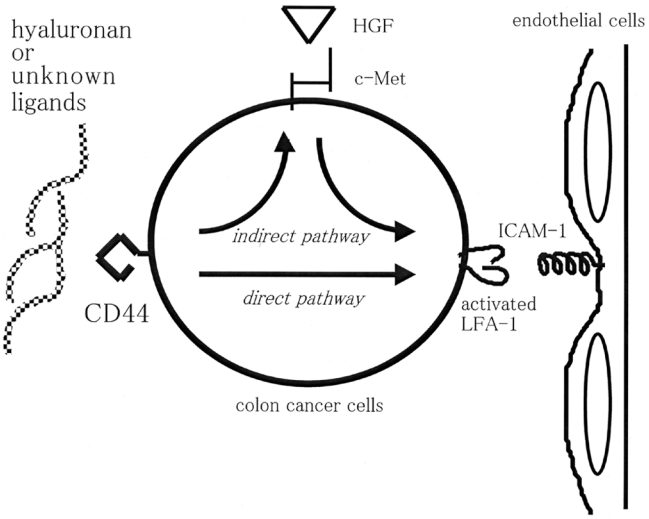

Fig. 4. Functional relevance of CD44 to extravasation of colon cancer cells. Engagement of CD44 by fragmented hyaluronan or unknown ligands induces "outside-in signaling", which consists of a direct pathway via CD44 and an alternate pathway through the induction of c-Met expression via HGF. Such stimuli augment both quantity and quality of integrins of the cells, which leads to amplification of integrin-mediated adhesion to the vessel wall and transendothelial migration.

CD44 reduces Fas-mediated killing of tumor cells

The role of the immune system in preventing tumor growth and the molecular requirements for effective function of cytotoxic T lymphocytes (CTL) is emerging. Although CTL play a major role in the rejection of tumor cells, tumor rejection does not always occur in vivo and tumors often protect themselves against CTL recognition or attack by various mechanisms. Thus, defects in the development or execution of anti-tumor immune responses are commonly observed.

In this context, we have postulated that the failure of immune protection, the so-called immune escape mechanism, is due to intrinsic features of tumor cells which do not allow the induction of an effective immune response and that CD44 play a major role in the mechanisms: (1) lung cancer cells express high levels of CD44; (2) engagement of CD44 on the cells by a mAb or fragmented hyaluronan reduces Fas expression; (3) CD44 crosslinking reduces Fas-mediated apoptosis; (4)

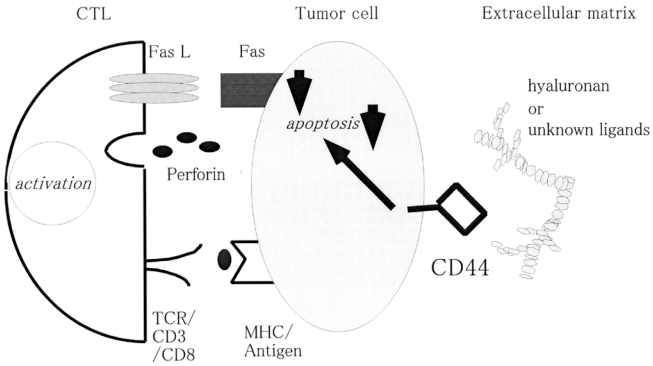

Fig. 5. Functional significance of CD44-mediated signaling for CTL-killing of lung cancer cells. The interaction between CD44 on lung cancer cells and extracellular hyaluronan reduces both Fas expression and Fas-mediated apoptosis of the cells, resulting in less susceptibility of the cells to CTL-mediated cytotoxicity through Fas-FasL pathway.

stimulation of CD44 on lung cancer cells decreases IFN-γ production by autologous CTL; and (5) CD44 stimulation prevents killing of lung cancer cells by autologous CTL (Yasuda et al., 2001a).

Based on these findings, we here propose an alternate immune evasion mechanism, based on the interaction between CD44 on lung cancer cells and extracellular hyaluronan, which reduces both Fas expression and Fas-mediated apoptosis of the cells, resulting in less susceptibility of the cells to CTL-mediated cytotoxicity through Fas-FasL pathway (Fig. 5).

In vivo, tumor cells are surrounded by and encounter extracellular matrix through their receptors, indicating that the engagement of CD44 by matrix protein always occurs in tumor cells. Thus, our results imply that in vitro culture steps without matrix may introduce major biases; in vitro tumor rejection by CTL might be efficiently induced during the interaction of tumor cells and CTL, although, in vivo, tumor cells may protect themselves against CTL recognition and immune evasion mechanisms are acquired by tumor cells through interaction with extracellular matrices (Yasuda et al., 2001b).

Future application and concluding remarks

We propose that CD44 is not only glue between a cell and matrix but communicates cell-matrix interactions into the cell via outside-in signaling and that hyaluronan is far from an inert space filler, but has an important role in biological activities. The interaction between CD44 and hyaluronan results in various adhesion events between cell-cell and cell-matrix. Of interest is that degraded hyaluronan at inflamed sites induces Fas-mediated apoptosis of synovial cells, whereas it reduces CTL-mediated cytotoxicity of tumor cells through Fas-FasL pathway (Fujii et al., 2001; Yasuda et al., 2001a). Thus, such a difference of CD44-mediated signaling might result from the difference of cell types and circumstances such as tumor-bearing tissue and inflamed sites.

It is somewhat startling that CD44-null mice are viable and do not demonstrate any obvious morphological defects (Wielenga et al., 2000), which implies that other proteins may compensate for the function of CD44 but that inhibition of CD44-mediated adhesion and/or signaling might not affect physiological conditions (Pure and Cuff, 2001). Thus, the functional role of CD44 might be emphasized in pathological conditions as discussed, indicating that CD44 might be a suitable target for therapeutic strategies to regulate tumor cells and synovial cells. Recent studies suggest that CD44 receptor-globulin chimera, native hyaluronan and hyaluronan oligomers efficiently inhibit tumor growth, metastasis and invasion in in vivo and in vitro (Lesley et al., 2000; Herrera-Gayol and Jothy, 2001). The rational design of future therapeutic strategies not only for tumor cells but also synovial cells may thereby include the exploitation of CD44 and Fas death pathway in order to directly reduce tumor growth and synovial cell proliferation in vivo.

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