The liberation of CD44

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CD44 was once thought to simply be a transmembrane adhesion molecule that also played a role in the metabolism of its principal ligand hyaluronan. Investigations of CD44 over the past ∼20 yr have established additional functions for CD44, including its capacity to mediate inflammatory cell function and tumor growth and metastasis. It has also become evident that intricate posttranslational modifications of CD44 regulate the affinity of the receptor for its ligands. In this review, we focus on emerging evidence that functional fragments of the cytoplasmic and ectodomain of CD44 can be liberated by enzymatic modification of cell surfaces as well as of cell-associated matrix. Based on the evidence discussed, we propose that CD44 exists in three phases, as a transmembrane receptor, as an integral component of the matrix, and as a soluble protein found in body fluids, each with biologically significant functions of which some are shared and some distinct. Thus, CD44 represents a model for understanding posttranslational processing and its emerging role as a general mechanism for regulating cell behavior.

Cell surface adhesion receptors anchor cells to their surroundings, regulate cell mobility, and provide cells with critical sensors of their environment. Cell adhesion molecules are subject to regulation at multiple levels, including transcription, alternative RNA splicing, and posttranslational modifications such as phosphorylation, glycosylation, and sulfation. Proteolytic processing has also emerged as a key mechanism underlying the regulation of several cell surface adhesion molecules, including members of the selectin and cadherin families.

CD44 is a broadly distributed transmembrane glycoprotein that plays a critical role in a variety of cellular behaviors, including adhesion, migration, invasion, and survival. CD44 mediates cell–cell and cell–matrix interactions in a large part through its affinity for hyaluronan (HA),* a glycosaminoglycan constituent of extracellular matrices, but also potentially through its affinity for other ligands such as osteopontin, collagens, and matrix metalloproteinases (MMPs). A soluble form of CD44 has been detected in the circulation and other body fluids. In this review, we focus on the mounting evidence that limited proteolysis liberates functional fragments of both the cytoplasmic (intracellular) domain as well as the extracellular domain of CD44. Furthermore, we review recent evidence that CD44 released from cells can accumulate as an integral component of cell-associated matrices. We also address the issue of the derivation of soluble CD44 that accumulates in the fluid phase under pathologic conditions that are associated with increased proteolytic activity and matrix remodeling. Based on current evidence, we propose that CD44 can exist in three distinct physical phases, as a transmembrane cell surface receptor, an integral component of the matrix, and in a fluid phase, each with the potential for being functionally significant (Table I).

Structure and function of transmembrane CD44

CD44 is encoded by a single gene, but multiple isoforms of CD44 are generated by alternative RNA splicing. The gene for CD44 contains 20 exons, 12 of which are expressed by the most common form of CD44, referred to as standard or hematopoietic CD44. The nonvariant exons encode for an extracellular domain, a transmembrane domain, and an intracellular domain. Isoforms of CD44 are generated by the insertion of alternative exons (V1–V11) at a single site within the membrane-proximal portion of the extracellular domain (for reviews see Naor et al., 1997; Ponta et al., 2003). The predominant 72–amino acid cytoplasmic domain can also be replaced by an alternatively spliced shorter form. Differential posttranslational modifications, including glycosylation and the attachment of glycosaminoglycans, generate additional structural diversity of CD44.

The regulation of the affinity of cell adhesion molecules is prerequisite for regulating cell–cell and cell–matrix interactions mediated by broadly expressed receptors that are exposed

*Abbreviations used in this paper: CD44-ICD, intracellular domain of CD44; HA, hyaluronan; MMP, matrix metalloproteinase; sCD44, soluble CD44.

Table I. **Potential mechanisms for the generation and function of cell surface, matrix-associated, and fluid phase CD44**

Form of CD44	Potential mechanisms of generation	Known and proposed functions
Transmembrane	Synthesized as type-I integral transmembrane protein	1. Cell–cell adhesion 2. Cell–matrix adhesion 3. Signal transduction 4. Pericellular matrix assembly 5. Hyaluronan metabolism
Matrix-associated ectodomain	1. Shedding of transmembrane form 2. Secretion of alternatively spliced form	1. Pericellular matrix assembly 2. Integral component of ECM 3. Agonist/antagonist of transmembrane form
Fluid phase	1. Shedding of transmembrane form 2. Secretion of alternatively spliced form 3. Enzymatic liberation from matrix	Agonist/antagonist of transmembrane- and matrix-associated forms
Intracellular cytoplasmic domain	Presenilin-dependent cleavage of truncated transmembrane form	Regulation of transcription after nuclear translocation

continuously to their ligands. Most primary cells express CD44 but in a low affinity state that does not exhibit a capacity to bind to HA. Cellular activation can induce a transition of CD44 to a high affinity state that mediates binding to HA. Transition from the "inactive" low affinity state to the "active" high affinity state of CD44 on leukocytes can be induced by the ligation of antigen receptors, and on leukocytes and epithelial and other mesenchymal cells by soluble factors including cytokines (Levesque et al., 1997; Cichy and Puré, 2000; Brown et al., 2001). A variety of mechanisms have been implicated in the transition from inactive to active forms of CD44, including variant exon usage, receptor oligomerization, glycosylation, and sulfation (for review see Ponta et al., 2003). However, to date, no data are available to indicate how these posttranslational modifications alter either the configuration of the receptor, its three-dimensional structure, or its molecular interactions with other moieties to modify the affinity of the receptor for HA. Functional activation of CD44, as opposed to regulation of receptor solely at the level of transcription, presumably provides for more efficient recruitment of CD44–HA interactions in mediating cell–cell and cell–matrix interactions as required, for example, after exposure to an inflammatory stimulus. In contrast to normal primary cells, many tumor-derived cells express CD44 in a high affinity state with capacity to mediate constitutive binding to HA (for review see Naor et al., 1997). In addition to being a receptor for HA, CD44 can interact with several ECM proteins, such as fibronectin and collagens, growth factors, cytokines and chemokines, as well as metalloproteinases (for reviews see Naor et al., 1997; Ponta et al., 2003), but less is known about the regulation of the interactions of these ligands with CD44.

Transmembrane CD44 serves multiple roles, including mediating the metabolism of HA (Kaya et al., 1997), in the regulation of tumor invasiveness and in the modulation of inflammatory cell function. Alterations in CD44 expression and structure have been documented in many types of cancer and are related to tumor dissemination (for reviews see Naor et al., 1997; Ponta et al., 2003). Moreover, targeted deletion of CD44 prevented dissemination of some tumors (Weber et al., 2002). Most of the known effects of CD44 on cell adhesion, migration, and metastasis are intimately associated with its capacity to promote cell attachment to HA (for review see Naor et al., 1997). Recent findings suggest that CD44 might also promote metastasis through its association with other molecules. For example, CD44 provides a

docking site for MMP-9 on the surface of melanoma and carcinoma cells (Yu and Stamenkovic, 1999) and thus can indirectly contribute to pericellular proteolysis to regulate tumor cell motility, growth factor activation, angiogenesis, as well as survival mechanisms. Furthermore, it was recently demonstrated that CD44-mediated localization of MMP-9 to the surface of some tumor cell lines results in the activation of TGF-β and promotion of tumor invasion and angiogenesis (Yu and Stamenkovic, 2000). Interestingly, increased levels of soluble CD44 (sCD44) have been detected in plasma from patients with some tumors (Okamoto et al., 2002). This may reflect the increase in proteolytic activity and matrix remodeling that is associated with tumor growth and metastasis.

CD44 does not appear to play a critical role in the immune system under homeostatic conditions. However, inflammation is associated with increased expression of cell surface CD44 on hematopoietic cells. Activation of T cells augments CD44-mediated HA binding and contributes to targeting of T cells to inflammatory sites (DeGrendele et al., 1997). Based on the detection of elevated numbers of circulating T cells expressing activated CD44 in conditions of chronic inflammation, it has been suggested that functional activation of CD44 on lymphocytes may contribute to chronic inflammatory diseases (Estess et al., 1998). A critical role for CD44 in inflammation is supported by studies using anti-CD44 antibodies and CD44-deficient mice. Administration of anti-CD44 antibodies to mice retarded cutaneous delayed-type hypersensitivity (Camp et al., 1993) and protected mice against experimental arthritis (Mikecz et al., 1995). In addition, anti-CD44 antibodies protected mice from the pathology associated with acute infection with *Toxoplasma gondii* (Blass et al., 2001). Although minimal defects were noted in unchallenged CD44-deficient animals (Schmits et al., 1997), inflammatory responses in CD44-deficient mice are significantly altered compared with wild-type mice. For example, the extent of atherosclerotic lesions in hypercholesterolemic (apolipoprotein E–deficient, apoE$^{-/-}$) mice that were also deficient in CD44 was markedly reduced when compared with apoE$^{-/-}$ mice expressing CD44 (Cuff et al., 2001). Reduced atherogenesis was associated with the inhibition of macrophage recruitment and inhibition of macrophage and vascular smooth muscle cell activation in atherosclerotic lesions. Furthermore, the deletion of one particular isoform, CD44v7, protected against experi-

mental colitis (Wittig et al., 2000). Targeted disruption of CD44, in contrast, resulted in impaired resolution of the inflammatory response after bleomycin-induced lung injury, resulting in death (Teder et al., 2002). CD44 deficiency under these conditions resulted in excessive accumulation of HA in bronchoalveolar lavage fluid, impaired clearance of apoptotic neutrophils, and a defect in TGF-β activation. Together, these data suggest that CD44 is pivotal to the progression of inflammation and fibrosis.

Potential mechanisms for shedding of CD44 from the cell surface

sCD44 has been detected in serum, lymph, arthritic synovial fluid, and bronchoalveolar lavage (Katoh et al., 1994, 1999; Shi et al., 2001). Malignant disease and immune activation and inflammation are often associated with increased plasma levels of sCD44, whereas immunodeficiency correlates with low plasma levels of sCD44. These findings indicate that release of CD44 correlates with enhanced local proteolytic activity and matrix remodeling and have generated interest in CD44 as a potential biomarker for tumor growth and metastasis and immune activation and inflammation. Expression of an alternatively spliced form of CD44 lacking the transmembrane and cytoplasmic domains of the receptor has been described, providing a mechanism for the de novo synthesis of sCD44 (Yu and Toole, 1996). However, the major mechanism invoked in the production of sCD44 involves proteolytic cleavage of cell surface CD44 (Okamoto et al., 1999). CD44 is released from cells constitutively, but enhanced release can be induced by phorbol esters, a calcium ionophore, ionomycin (DeGrendele et al., 1997), cytokines (Ristamaki et al., 1997), as well as bacterial- and leukocyte-derived proteinases (Cichy et al., 2002; Lazaar et al., 2002). Release of sCD44 is also likely to be ligand inducible, as antibody cross-linking of CD44 leads to release of sCD44 (Camp et al., 1993; Shi et al., 2001). Concomitant with CD44 shedding, cytoskeletal reorganization occurs (Shi et al., 2001). Pharmacological disruption of actin assembly reduced CD44 shedding, whereas activation of Rho family GTPases, which regulate actin filament assembly, enhanced CD44 cleavage (Shi et al., 2001). Shedding of CD44 has also been reported to be induced by Ras, an oncoprotein involved in cell motility and migration. The effect of Ras on CD44 processing appears to be mediated by members of the Rho family of GTPases (Kawano et al., 2000). Taken together, these data suggest that shedding of CD44 is controlled by Ras and Rho GTPases (Cdc42 and Rac1), possibly via regulation of the actin cytoskeleton.

Endogenous metalloproteinases and serine proteinases have been implicated in the shedding of CD44 based on abrogation of its release by selective pharmacologic inhibitors. In contrast, selective inhibition of serine proteinases in some cell systems augments the release of CD44, suggesting that serine proteinases may control the activity of another class of enzymes involved in the processing of CD44 (Okamoto et al., 1999). Cell surface localization as well as activation and inhibition profiles suggest that the ADAM (a disintegrin and metalloprotease) family of enzymes may be involved in CD44 shedding, but at least one particular ADAM family member, TACE (TNF-α converting enzyme), has been ex-

cluded as playing a role in the processing of CD44 (Shi et al., 2001). Membrane type 1 and membrane type 3 metalloproteinases (MT1-MMP and MT3-MMP, respectively), on the other hand, have been shown to be capable of mediating the processing for CD44. Coexpression of CD44 and either MT1-MMP or MT3-MMP, but not MT2-, MT4-, and MT5-MMPs, resulted in shedding of CD44 in human breast carcinoma cells (Kajita et al., 2001).

Consequences of the release of CD44 from the cell surface

The release of CD44 is likely to affect cellular behavior through multiple mechanisms. First, the released ectodomain of the receptor may compete with cell surface CD44 for ligand binding. The ability of sCD44–Ig fusion protein to block HA binding suggests that sCD44 can indeed antagonize the effect of membrane-bound CD44. In fact, sCD44 has been used to disrupt endogenous CD44–HA interactions and thereby promote apoptosis, inhibit MMP-mediated invasion, and inhibit tumor cell proliferation (Yu et al., 1997; Peterson et al., 2000; Yu and Stamenkovic, 2000). Overexpression of sCD44 is believed to displace endogenous HA from its membrane-anchored receptors. The changes in tumor cell growth induced by sCD44–Ig fusion protein were dependent on the ability of sCD44 to bind HA, indicating that sCD44 can act as a competitive inhibitor of endogenous HA–protein interactions (Peterson et al., 2000). However, soluble forms of CD44 can differ in their capacity to bind HA. For instance, the affinity of sCD44 released from lung-derived epithelial tumor cells for HA varies depending on the stimuli used to induce its release (unpublished data). Regulation of the affinity of sCD44 for HA may determine its impact on CD44-dependent processes. Second, cleavage of CD44 might also be a mechanism to disrupt or prevent CD44-dependent cell–cell and cell–matrix adhesion. Third, the cleavage of CD44 may regulate cell migration. Thus, coexpression of CD44 and wild-type MT1-MMP promoted motility of human breast cancer cells, whereas mutants of CD44 lacking the MT1-MMP processing site or pharmacological inhibition of MMP activity led to suppression of cell migration, supporting the concept that cell migration requires cell surface processing of CD44.

CD44 accumulates as an integral component of the matrix

sCD44 was previously assumed to be released into body fluids mainly as the result of proteolytic cleavage of cell surface CD44. However, in vitro, spontaneously released CD44 appears to be at least partially sequestered through its association with the cell-associated matrix, where it can be targeted for further processing by extracellular proteinases and other matrix-modifying enzymes such as chondroitinase (Cichy et al., 2002) (Fig. 1). Release of matrix-associated CD44, as opposed to membrane CD44, may impact differently on the behavioral response of cells to conditions of elevated proteolytic activity and matrix remodeling. For example, liberation of CD44 from the matrix is less likely to trigger the intramembrane cleavage of CD44 and production of the intracellular domain of CD44 (CD44-ICD), which would
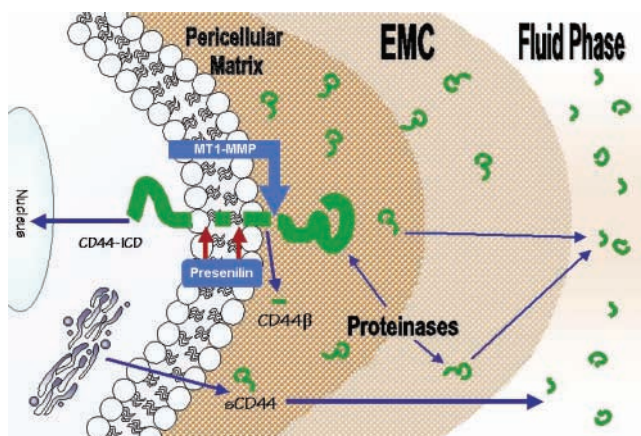
Figure 1. **CD44 exists in three phases: a typical transmembrane receptor, a matrix-associated fragment of the extracellular domain, and as soluble fragments in the fluid phase.** Membrane-anchored CD44 can be cleaved by MT1-MMP at the cell surface and is subject to subsequent dual intramembraneous cleavage by presenilin-1. Presenilin-1–dependent processing of CD44 results in the liberation of a cytosolic fragment, CD44-ICD, that can translocate to the nucleus to control gene transcription. Proteolysis of membrane-anchored CD44 results in the release of CD44 preassembled into complexes with matrix components or the release of the ectodomain that then can accumulate as an integral component of the matrix due to association with other matrix components. Alternatively, transmembrane CD44 may be proteolytically released from the cell surface or synthesized de novo in soluble form. The released ectodomain of CD44 can be retained in the ECM by establishing physical associations with other matrix components such as fibronectin, HA, and collagen. Exposure of the cell-associated matrix to exogenous matrix-modifying enzymes, such as chondroitinase, and leukocyte- or bacterial-derived proteinases generated as the result of infection, inflammation, or tumor metastasis can lead to the enhanced release of sCD44 from the matrix and, in the face of high local concentrations of proteinases, the degradation of sCD44.

be expected to occur if proteinases targeted membrane CD44 (Brown et al., 2000).

The accumulation of CD44 released from cells as an integral component of the matrix suggests that pericellular and extracellular matrix may be important reservoirs of sCD44. Digestion with bacteria- and phagocyte-derived proteinases liberates sCD44 from the matrix (Cichy et al., 2002). Thus, the disruption of the ECM that occurs in the face of the enhanced proteolytic activity associated with infection, inflammation, and tumor metastasis may liberate matrix-associated as well as transmembrane CD44 and lead to an increase in fluid phase CD44 as manifested by a rise in levels of sCD44 in body fluids under these conditions (Katoh et al., 1994; Okamoto et al., 2002). Moreover, accumulation of CD44 as an integral component of the matrix may provide a protective mechanism for maintaining the integrity of cellular barriers, such as that surrounding airway epithelium, by competing with cell surface CD44 as a substrate for proteinases and by competing for pathogen binding. The composition of the ECM and its organization are major determinants of environmental signaling that controls cell fate. Previous studies demonstrated that the transmembrane form of CD44 plays a role in the assembly of HA-rich pericellular matrices (Knudson et al., 1996). Based on our recent data

demonstrating that CD44 also accumulates as an integral component of cellular matrices after it is proteolytically cleaved from the cell surface (Cichy et al., 2002), it is tempting to speculate that shedding of CD44 may contribute to the organization of the ECM. It is generally well accepted that assembly of the ECM occurs in close proximity to the cell surface. If CD44 is involved in the formation of the matrix at the cell surface, then shedding of CD44 is likely to be associated with the deposition and retention of other CD44-associated molecules into the extracellular milieu. In other words, pericellular matrix, through shedding of surface receptors including CD44, may act as a source of ECM or its nucleation and retention. The broad distribution of CD44, the ability of a wide variety of CD44-positive cells to shed the receptor, and the fact that many cells are characterized by the expression of high levels of CD44 on the cell surface suggest that shedding of this receptor could potentially result in significant deposition of ECM components preassembled into sCD44-containing complexes at the cell surface. A role for CD44 in organizing the matrix after it is released from the cell surface is consistent with the noted homology of the extracellular domain of CD44 with the family of proteoglycans with G1 domains that contain link modules (the HA binding motif).

Proteolysis liberates the intracellular cytoplasmic domain of CD44 from the membrane

Cleavage of the extracellular domain of CD44 can be followed by subsequent proteolysis within the transmembrane domain dependent on presenilin-1, a putative membrane aspartyl protease (Okamoto et al., 2001; Lammich et al., 2002). Several substrates for presenilin-1–dependent activity have been identified, including Notch, E-cadherin, ErbB-4, and β-amyloid precursor protein. All of these type-1 transmembrane proteins have been demonstrated to undergo ectodomain shedding, which appears to be required for the subsequent presenilin-dependent cleavage (Lammich et al., 2002). Presenilin-dependent proteolysis of CD44 has been reported to occur at two sites (Fig. 1): one close to the cytoplasmic border, leading to the liberation of CD44-ICD, and another site within the transmembrane domain, resulting in the extracellular release of the so-called CD44β peptide. The latter is reminiscent of the presenilin-dependent processing of β-amyloid precursor protein leading to the release of amyloid β peptide(s) implicated in Alzheimer's disease (Lammich et al., 2002). Shedding of CD44 may also play a role in regulating gene transcription as the result of the liberation of CD44-ICD (Okamoto et al., 2001). CD44-ICD appears to translocate to the nucleus and promote transcription mediated through TPA-responsive elements, including transcription of CD44 itself, providing a classic feedback mechanism for regulating CD44 expression.

Concluding remarks

The multiple products of a single gene, such as CD44, can take on a variety of forms and functions. Proteolytic processing of CD44 may regulate cell–cell and cell–matrix interactions, and results in the generation of potentially biologically active fragments. Thus, CD44 exists as a typical transmem-

brane receptor, a matrix-associated extracellular domain fragment, and as a soluble fragment of the extracellular domain found in the circulation and other body fluids. In addition, a proteolytic fragment of the cytoplasmic domain of CD44 can be released intracellularly and translocated to the nucleus. Molecular genetic approaches can be used to generate mice expressing sCD44 in the absence of transmembrane CD44, expressing transmembrane CD44 resistant to proteolytic processing, and overexpressing CD44-ICD. Such studies will be required to better understand the role of proteolytic fragments of CD44 in homeostasis and disease. Future studies are also required to determine the extent to which other cell surface receptors are subject to similar processing events.

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