Review Article

Structure, function and role of CD44 in neoplasia

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Abstract

CD44 is a group of protein molecules which perform a variety of functions. Their wide range of functions are mainly based on their multiple variations in their molecular structure. Furthermore, they are distributed in various tissues of the human body. They have a unique property of cell adhesion, which can lead to interaction between two different cells or a cell and its pericellular matrix. CD44 as a cell surface adhesive molecule helps in aggregation and migration of tumor cells. CD44 plays an important role in cancer of bladder, liver, lungs, pancreas, etc. Expression profile of CD44 has been seen in the epithelia of the lip, tongue, gingiva, hard palate, floor of the mouth, buccal mucosa and pharynx. The relationship between the expression of CD44 v6 and regional lymph node metastasis has been studied immunohistochemically. The expression of CD44 v6 was apparently downregulated in oral squamous cell carcinoma, but not in normal oral mucosa. Carcinomas expressing lower levels of CD44 v6 exhibited more frequent regional lymph node metastasis. No significant relation was found between the expression of CD44 v6 in primary and metastatic lesions. Still, the precise function of CD44 in the metastatic process and the degree of involvement in human malignancies is yet to be established.

Keywords: Adhesion, CD44, cell surface, metastasis

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INTRODUCTION

CD44 is a multistructural and multifunctional glycoprotein. It is also called as Hermes[1] antigen. It has got functionally distinct standard isoforms such as CD44 standard (CD44s) and CD44 variant (CD44v). CD44s has a molecular mass of 80–85 kDa and is found in a wide range of tissues including the central nervous system, lungs, epidermis, liver and pancreas. CD44v has a very limited distribution and is found on keratinocytes, activated lymphocytes, macrophages and some epithelial cells on the bladder,[2] stomach and uterine cervix. CD44 is a cell membrane molecule, and it was first identified on lymphocytes. It is a cell adhesion protein and is involved in cell–cell and cell–matrix interactions. It is also involved in cell motility, cell migration, cell differentiation, cell signaling and gene transcription. Expression patterns of CD44 as a cell adhesion molecule are being increasingly implicated in disease processes and are candidates for use in diagnostic and prognostic pathology. For example, the organization and function of epithelial cells are maintained by interaction with the underlying substrate, and one of the characteristics of malignancy is the escape from the constraints imposed by the basement membrane.[3] In 1989, Stamenkovic *et al.*[4] found that various carcinoma cell lines and solid tumors expressed CD44 gene. Later, Günthert *et al.*[5] discovered that an isoform of CD44 when inserted into the genetic

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sequence of a nonmetastasizing tumor induced metastatic properties in it. These studies deduced that CD44 was involved in metastatic process, and it led to a large amount of research to understand its possible mechanism of action.

STRUCTURE OF CD44

CD44 is a glycoprotein encoded by CD44 gene located on the short arm of chromosome 11p13. The gene is composed of two sets of exons, that is, constant and variable exons.[2] The genetic sequence can code for a variety of different proteins by selecting specific exons, present within it. One group comprising exons 1–5 and 16–20 are spliced together to form a transcript that encodes the standard isoform CD44s. The other 10 variable exons 6–15 also known as v1–v10 are alternatively spliced and included within the standard exons at an insertion site between exons 5 and 16 [Figure 1]. Molecules containing variable exons or their peptide products are designated CD44v.[3]

The most abundant standard isoform of human CD44 protein (CD44s) contains 363 amino acid (aa) and has a theoretical molecular mass of 37 kDa. The protein consists of three regions as follows: a 72 aa C-terminal cytoplasmic domain, a 21 aa transmembrane domain and a 270 aa extracellular domain. The molecular weight of the standard 37 kDa protein core is increased to 80–100 kDa as a result of glycosaminoglycan side-chain attachment. Glycosaminoglycans are repeating disaccharide units with amino linkage groups that attach the chain to their core proteins. Examples of these side chains include heparan sulfate and chondroitin sulfate. These are large molecules with highly charged sulfate and carboxylate groups.[3]

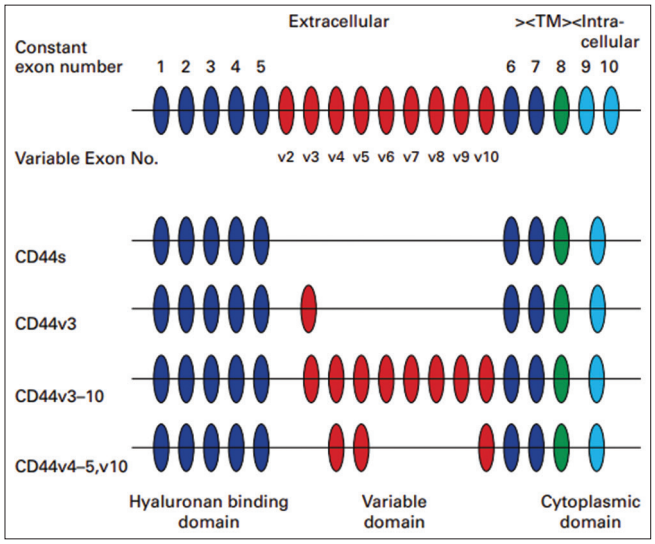

Figure 1: Genomic structure of CD44 with isoforms[2]

CD44 is a transmembrane molecule, most of which is sited extracellularly [Figure 1]. The carboxy-terminal end of the protein chain is intracellular and forms part of the cytoplasmic domain, and it is encoded by exon 10 or alternatively exon 9. The transmembrane segment is encoded by one exon (exon 8). The extracellular part of the molecule consists of variable domain and the amino-terminal domain. Variable domain is also known as middle domain. The variable domain is where differing isoforms express their characteristic variant protein, encoded by the variant exons v2–v10 (between exon 5 and exon 16). Amino-terminal domain is hyaluronan-binding domain. Cytoplasmic domain interacts with the cytoskeleton of the cell. Cytoplasmic domain is also required for distributing CD44 to specific areas of the cell. It also increases the longevity of the molecule.[2]

DISTRIBUTION OF CD44

CD44s was first identified on lymphocyte. After that, it was found on various tissues, for example, central nervous system, lungs, epidermis, pancreas, intestines, kidneys, urinary bladder and cervix. CD44v is located on keratinocytes, lymphocytes, macrophages and epithelial cells on the bladder, stomach and cervix.[6,7] CD44 expression within an epithelial tissue can vary between layers and also between cells. Dall *et al.* reported that CD44 v6 expression was limited to the stratum basale and stratum spinosum of normal uterine cervical squamous epithelium. Korabiowska *et al.*[8] reported that CD44 was not expressed in normal melanocytes and nevi, although the surrounding keratinocytes express CD44 v3–v10. In the oral cavity, CD44s is strongly present in the gingival tissue, tongue and esophagus. CD44 v6, CD44 v7, CD44 v8 and CD44 v9 are also present in the tongue and gingiva.[2]

FUNCTIONS OF CD44

CD44 molecule has a wide range of functions such as cellular adhesion (aggregation and migration), hyaluronate degradation, lymphocyte activation,[9] lymph node homing, myelopoiesis, lymphopoiesis, angiogenesis,[10] and release of cytokines because of its varied structure and distribution in body tissues. CD44 functions are mainly dependent on cellular adhesion and thus mediating the aggregation of cells. This adhesion can lead to interaction between two different cells or between a cell and its pericellular matrix. Functional diversity is achieved by the alternative splicing of the pre-mRNA, and the fine-tuning of ligand binding can be achieved by posttranslational modification. The balance of interactions between cell surface molecules and between those molecules and the extracellular matrix

will determine the positional address and the migrational status of specific cell types.

CELL–CELL AND CELL–MATRIX ADHESIONS BY CD44

CD44s protein is involved primarily in the maintenance of three-dimensional organ/tissue structures. Epithelia undergoing proliferation and cells under repair, upregulate CD44 as well as hyaluronic acid (HA) production. They also enable the attachment to a structural scaffold during expansion.[11,12] HA accumulates in angiogenesis, wound healing and embryonic cell migration.[10,13] CD44 molecules can also mediate the aggregation of cells. This can be achieved through multivalent HA binding by CD44 on adjacent cells or through interCD44 binding through attached glycosylation moieties. HA-dependent binding can cause aggregation of macrophages, lymphocytes and fibroblasts. CD44 has got other ligands such as hyaluronate, chondroitin, collagen, laminin and fibronectin.

The CD44 molecule is also involved in the degradation of hyaluronate. The hyaluronate CD44 complex is internalized and then joined to a lysosomal component, where acid hydrolases act upon it. This is an important function of the CD44 molecule because buildup of hyaluronate can have negative effects, such as in the lungs, where it can interfere with gas exchange.[14]

Proliferating cells express high amounts of CD44. In these areas, hyaluronate concentrations are low, and it has been suggested that localized degradation of hyaluronate leads to a morphological change in the tissue. Proliferating cells showing this expression include cells involved in the repair process, embryonic morphogenesis, organogenesis and angiogenesis.[10,14] In addition, it has also been found that semi-purified fragments of degraded hyaluronate could stimulate the proliferation and migration of endothelial cells and accelerate angiogenesis. Moreover, interestingly, proliferating epithelial cells are rich in hyaluronate.[11]

Smooth muscle cells involved in repair processes have been shown to upregulate both CD44 and the ligand, hyaluronate. Smooth muscle cells establish an autocrine form of stimulation in the repair process.[12] Another ligand, i.e. chondroitin binds to CD44 molecule as hyaluronate. Collagen, laminin and fibronectin bind to CD44 by interaction with the chondroitin sulfate side chains that are linked to the core protein by glycosylation.

The binding of HA can induce gene expression in inflammatory cells. A number of inflammatory genes that can be induced in macrophages by HA oligomers have been identified. These include several members of the chemokine gene family and nitric oxide synthase family of enzymes. HA fragments as small as hexamers are capable of inducing these effects.[15]

Osteopontin is a cytokine secreted by several cell types, and it induces cellular chemotaxis. Osteopontin is another ligand which binds with CD44 and colocalization of CD44 with osteopontin in lymphatic vessels may lead to lymphogenous metastasis. Interaction of CD44 and osteopontin mediates regulation of inflammation, osteogenesis and angiogenesis.[16,17]

CD44 AND LYMPHOCYTE

Many of the functions of lymphocytes are dependent on CD44. Lymph node homing[18] is achieved by a specific interaction between the middle domain of CD44s on lymphocytes and a protein called as mucosal addressin, which is present on the high endothelial cells of Peyer's patches and lymph nodes.[19] Addressin is also known as mucosal vascular addressin cell adhesion molecule. Its task is to determine which tissue the lymphocyte will enter next. Increased surface levels of CD44 proteins are characteristic of T-cell activation after encounter with its cognate antigen.[20] Cell surface CD44 on lymphocytes can mediate the adhesion of lymphocytes to vascular endothelial cells through binding of HA, and its interaction is used for activated T-cell extravasation into the sites of inflammation.[21,22] Targeting of lymphocytes to effector sites by CD44-HA binding is enhanced by the induction of HA synthesis in vascular endothelium by the tumor necrosis factor α and interleukin 1 β. In the same way, the presence of CD44 splice variants appears to be obligatory for the migration and function of Langerhans cells and dendritic cells from the peripheral organs to lymph nodes for antigen presentation.[23] CD44 provides proliferation initiating signals for early progenitors of all three hematopoietic lineages, that is, myelopoiesis, lymphopoiesis and angiogenesis.

CD44 IN NEOPLASIA

CD44 and its binding with HA influence tumor growth and development [Figure 1]. Tumor cells expressing CD44 can adhere to the extracellular matrix through its ligands, including hyaluronan, chondroitin sulfate, fibronectin, laminin, collagen and matrigel.[2] This allows tumor cells to colonize efficiently. The changes in the pattern of expression of a cell adhesion molecule in a tissue environment are likely to disrupt normal

epithelial–mesenchymal interactions, and they contribute to structural and functional disorganization, which is a characteristic of cancer.[3] The functions of uptake and degradation of hyaluronate by CD44 could enable tumor cells to invade hyaluronate-rich tissues. Much effort has centered on the possible involvement of CD44 isoforms in tumor metastasis. Most of the reports suggest that it is CD44s rather than CD44v isoform that is associated with metastatic behavior of the malignant tumors.[24] However, CD44 plays a crucial role in promoting tumor invasion and metastasis by subscribing adhesion of tumor cells to endothelium and fibronectin-enriched matrices. However, there is evidence that CD44 alone is not responsible for metastatic capability.

CD44 AND EPITHELIAL–MESENCHYMAL TRANSITION

Epithelial–mesenchymal transition (EMT) is a tightly regulated and highly conserved cellular process for a cell type changing from an epithelial phenotype to a mesenchymal phenotype. It plays a crucial role not only in the normal embryogenesis and tissue remodeling but also in the progression of various diseases, including inflammation, fibrosis, tumor proliferation, invasion, metastasis, recurrence and drug resistance. EMT is involved in the acquisition of stemness of epithelial tumor cells, which confers cells with aggressive traits and an invasive phenotype that may result in tumor recurrence and metastasis.[25] CD44 also promotes EMT in many cancer types such as colon cancer,[26] gastric cancer, pancreatic cancer, prostate cancer, liver cancer and glioma by upregulating mesenchymal markers and downregulating epithelial markers.

CD44 IN TUMORS

CD44 plays a crucial role in tumorigenesis and metastatic cascade. Tumors originating from epithelia that normally carry CD44v on their surface remain positive for CD44 and often produce higher concentrations of CD44 transcripts. However, this finding is not uniform. Hudson *et al.* found that squamous cell carcinoma (SCC) arising from stratified squamous epithelium has a reduced expression of one or more of the variant exons that are expressed normally. This reduced expression of CD44v was greatest in the least differentiated regions and in distant metastases.[27] Studies also suggest that some cells do not use CD44 in tumorigenesis or in the production of metastases. In neuroblastoma, Burkitt's lymphoma and melanoma CD44v are often absent.[28] Givehchian *et al.* discovered that squamous cell carcinomas arising from the lung retain the CD44 expression profile of the normal respiratory epithelium, whereas all other types of lung cancers showed a significantly reduced or absent expression of either CD44s or CD44v.[29] Higashikawa *et al.* found that all the colorectal adenocarcinomas they examined overexpressed high-molecular-weight CD44 transcripts including the v6 exon.[30] Studies involving CD44 expression in breast carcinoma have indicated that expression could be regulated by hormones. Increase in the expression of estrogen and progesterone receptors showed a positive correlation with CD44 v6.[31] Using immunohistochemistry, Sinn *et al.* showed a higher expression of CD44 at the tumor–stroma interface and that all regional lymph node metastases were homogenously positive for CD44v.[32] Preliminary studies on carcinoma of the prostrate indicate altered expression of CD44 in these tumors.[33] De Rossi *et al.* found that CD44s was overexpressed in appropriately half of their cases of B-cell chronic lymphocytic leukemia, although CD44 v5 and CD44 v6 expressions were usually found to be normal.[34] A study of pancreatic carcinomas and CD44 expression revealed that the variant CD44 v6 is found in normal ductal cells as well as in cancer specimens.[35] Ermak *et al.* showed that CD44 v6 and CD44 v7 are coexpressed in a tightly coupled manner in thyroid cancers.[36] Sliutz *et al.* showed that ovarian tumor samples exhibited a more complex pattern of CD44 expression than normal ovarian tissue and proposed that this expression is reflected in its serum concentration.[37] Wang *et al.* discovered that certain sarcomas have higher incidence of CD44s expression such as epithelioid sarcoma and angiosarcoma, whereas liposarcoma and clear cell sarcoma have lower expression of CD44.[38]

CD44 IN ORAL CANCER

Many studies have been conducted to study the expression of CD44s and CD44 v6 in oral SCC and in its metastatic lymph nodes. Kunishi *et al.* studied CD44 v6 immunohistochemically in 38 cases of SCC.[39] Carcinomas expressing lower levels of CD44 v6 exhibited more frequent regional lymph node metastasis. CD44 v6 showed no statistically significant relationship to the degree of differentiation of carcinoma. No significant relation was found between the expression of CD44 v6 in primary and metastatic lesions. Kosunen *et al.* studied CD44 expression in 138 cases of SCC and found that irregular staining of CD44 in tumor cells was associated with poor tumor differentiation and higher clinical stage.[40] Irregular staining of CD44 correlated with a decreased survival, although increased CD44 expression was consistent with a longer survival. It can be assessed that a loss of cell adhesion related to a decreased expression of CD44 may be determinant of survival in those patients.

CONCLUSION

How an organism can achieve multiple functions from a single gene is best studied by CD44 family of transmembrane proteins. Numerous studies reveal complex roles for the CD44 family of proteins in physiological and pathological processes. The multifunctional aspect of CD44 cell adhesion molecules is achieved by the balance of a number of variable parameters that the cell uses in the expression of this gene. These include the amount of total CD44, alternative splicing choices, the balance of many types of posttranslational modifications and the active/inactive HA-binding state of the cell surface protein. The principal physiological functions of CD44 are in the aggregation, migration and activation of cells, and these occur through the adhesive qualities of the molecule. Question remains open for the precise function of CD44 in the metastatic process and the degree of involvement in human malignancies.

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Conflicts of interest

There are no conflicts of interest.

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