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REVIEW

Role of CD44 as a marker of cancer stem cells in head and neck cancer

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Abstract: In recent years, many studies have shown that some types of tumors are characterized by the presence of cells with stem-like characteristics, called cancer stem cells (CSCs). These are considered cells that initiate the tumor and are probably responsible for tumor recurrence. CSCs have the capacity for self-renewal, the potential to give rise to one or more cell types within the tumor, and the ability to drive, in a continuous manner, the proliferation of malignant cells. The failure of current cancer therapies can be attributed to the relative ineffectiveness of drugs against CSCs, which remain viable while retaining their full ability to reproduce the tumor. The development of new strategies is currently hampered by the lack of reliable markers to identify CSCs. One promising surface marker of CSCs in head and neck cancer is the CD44 molecule, which has been shown in preliminary studies to have high specificity, although there are discrepant data because its prognostic value may depend on the specific tumor location. More rigorous studies are needed to investigate the usefulness of CD44 expression in head and neck tumors for possible clinical applicability.

Keywords: CD44, head and neck squamous cell carcinoma, cancer stem cells

Introduction

Emerging studies show that CD44 is an important biomarker of a cellular subpopulation – cancer stem cells (CSCs) – which are capable of self-renewal and have the capacity for initiation, progression, invasion, metastasis, tumor recurrence, and resistance to chemo- and radiotherapy.[1] This cell subpopulation was isolated for the first time by Bonnet and Dick from samples of acute myeloid leukemia.[2] CSCs have also been identified in solid tumors. Al-Hajj et al identified a subpopulation of $CD44^+/CD24^-$ cells with tumorigenic capacity from breast cancer samples in 2003.[3] CSCs were also identified in brain tumors by Singh et al in 2003,[4] in prostate tumors by Collins et al in 2005,[5] in colorectal cancers by Dalerba et al in 2007,[6] in pancreatic tumors by Li et al,[7] and in lung tumors by Ho et al.[8]

In 2007, Prince et al first identified a cellular subpopulation in head and neck tumors expressing the surface marker CD44 with stem-like characteristics; these cells were capable of reproducing when implanted into immunosuppressed mice.[9] In the same year, Harper et al studied the expression of CD44, CD29, and CD133 as presumed markers of CSCs in cell lines derived from head and neck tumors; they found that the greatest expression of CD44 correlated with increased clonogenicity.[10]

CD44

CD44 is a type I transmembrane glycoprotein expressed in several cell types of mesenchymal and neuroectodermal origin.[11] CD44 functions as a major adhesion molecule

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and in the cellular internalization of hyaluronic acid.[12] The interaction between hyaluronic acid and CD44 influences adhesion to components of the extracellular matrix, and it is involved in the stimulation of aggregation, cell proliferation and migration, and angiogenesis.[13] All of these biological properties are essential to normal cell physiology, but in certain conditions they are associated with pathological activities, in particular those of cancer cells.[14]

The bond between hyaluronic acid and the CD44 adhesion molecule may initiate a series of events that begin with modification of adhesion to the matrix and continue with activation of other molecules such as growth factors, degradation of the matrix, angiogenesis, permeation by blood vessels, and extravasation.[15] All of these steps are necessary in the initiation of metastasis.[16] In addition to hyaluronic acid, CD44 binds to fibronectin, the invariant part of the major histocompatibility complex class II,[17] and high-molecular-weight proteoglycans.[18] The heterogeneity of CD44 binding to these ligands reflects the fact that the gene encoding CD44 comprises 20 exons; the first and the last five are constant, and the central ten are subjected to alternative splicing, thus constituting the variable region of the receptor.[19] The most common isoform of the receptor is CD44 standard, which is highly expressed in hematopoietic cells. About 30 receptor variants (CD44v) have been identified, many of which appear to be expressed on tumor cells and arise from alternative splicing at the extracellular proximal portion of the receptor.[20] In pathological conditions such as cancer, the extracytoplasmic domain of the CD44 receptor detaches and is released into biological fluids as a soluble fraction of the receptor CD44sol.[21–25]

Numerous studies have highlighted the connection between CD44, hyaluronic acid, and the PI3K–Akt system, whose stimulation leads to phosphorylation of Akt (also known as protein kinase B). p-Akt is positively involved in the processes of cell survival and in the development of resistance to chemotherapy.[26] Activation of this enzyme triggers a series of reactions, all of which increase cell proliferation and survival through the transformation of phosphatidylinositol-4,5-bisphosphate, located in the cytoplasmic membrane, to phosphatidylinositol-3,4,5-triphosphate, which activates the effector molecule Akt. Akt is a Ser–Tyr kinase whose active form p-Akt phosphorylates a number of proteins involved in cell proliferation (Figure 1). For example, Akt is involved in the maintenance of cell metabolism in growth-limiting conditions through adenosine triphosphate production via glycolysis; increased cellular uptake of glucose by glucose transporter type 4; mammalian target of rapamycin phosphorylation, which increases the synthesis of cyclin D; intracellular activation of transcription factors such as S6 kinase and apoptosis through BAD phosphorylation/inactivation; and reduction in proapoptotic gene transcription through phosphorylation of AFX, FKHR, and FKHRL1.[27,28]

Alteration in the T lymphocyte-mediated immune response can change the expression of CD44 and its role in lymphocyte homing. CD44 is also involved in the transport of circulating lymphocytes to lymph nodes and in lymphocytic–epithelial interactions, through which it modulates lymphocyte adhesion and activation.[29] These roles form the basis of the idea that CD44 plays an important role in lymph-node metastasis and in the potential carcinogenicity of certain forms of T-cell leukemia and lymphoma. The proposed pathway involves promoting the survival of T cells by increasing their resistance to apoptosis induced experimentally by corticosteroid treatment or ultraviolet rays through a p53-dependent mechanism involving the inhibition of DNA fragmentation.[30]

Clinical studies

Currently, researchers continue to study the biological characteristics of the surface CD44 molecule as a marker of cancer stem cells (Allegra and Trapasso, unpublished data, 2012). However, there are conflicting findings about the clinical significance of CD44 expression.

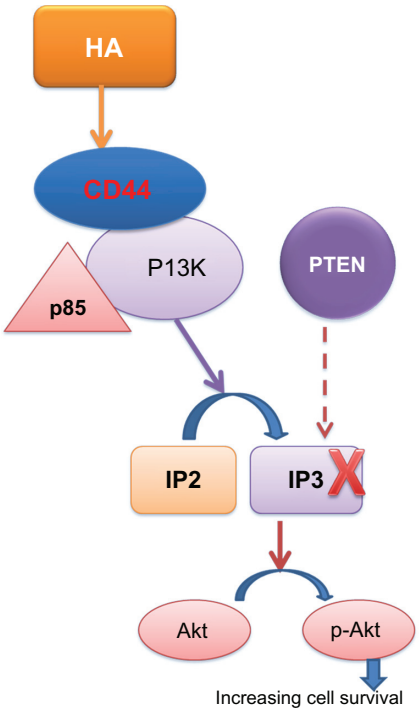

Figure 1 Increasing cell survival mediated by CD44.
Abbreviation: HA, hyaluronic acid.

Joshua et al have studied a lineage-CD44$^+$ (Lin-CD44$^+$) subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma, and they have observed a high frequency of Lin-CD44$^+$ cells correlated with known poor prognostic factors such as advanced T classification and recurrence.[31] In some cases, the overexpression of CD44v (v3 and v6) seems to reflect the cellular invasiveness and leads to increased aggressiveness of tumors in the head/neck, such as in carcinoma of the oral cavity.[32] Understanding CD44 is important to the study of tumor progression and invasiveness because invasive tumors attack the extracellular matrix of surrounding tissues for expanding; the interaction between CD44 and hyaluronic acid plays a decisive role in various cellular pathways.[33,34]

There are clear discrepancies in the interpretation of the expression of CD44 in relation to tumors of various head and neck regions with different biological characteristics. In squamous cell carcinomas of the oral cavity, the evidence seems to indicate that a low expression of CD44 correlates with a greater capacity for metastasis and recurrence, with negative prognostic significance or no significant impact on prognosis.[35,36] There are few studies of oropharyngeal cancer, and the results are inconsistent. Rajarajan et al[37] and Carinci et al[38] found no evidence of expression of CD44 or prognostic significance, whereas Lindquist et al[39] and Kokko et al[36] reported a correlation between high expression of CD44 and poor prognosis. In squamous cell carcinoma of the tongue, the few available clinical trials reported by Fonseca et al showed a relationship between lack of expression of CD44 and lateral cervical lymph-node metastases.[40] This finding is similar to those of Mostaan et al,[41] Rodrigo et al,[42] and Masuda et al,[43] who reported a correlation between the expression of CD44 and low propensity for metastasis and poor prognosis.

Instead, the high expression of CD44 in laryngeal tumors seems to correlate more strongly with a poor prognosis. This contrasts with other locations of head and neck cancer, in which high expression of CD44 correlates with a greater capacity for locoregional or distant metastasis and resistance to radiochemotherapy.[44–46] It is becoming increasingly clear that differences in the ability for locoregional or distant metastasis and radioresistance seem to depend on the overexpression of specific CD44v: Sun et al[47] and Lu et al[48] have shown that high expression of CD44 correlates with a greater tendency to develop metastatic lymph nodes, recurrence, and radioresistance. The different isoforms CD44v3 and CD44v6 seem to correlate with lymph-node metastasis, systemic diffusion, and failure of radiation therapy.[49] The metastatic potential identified by markers of CSCs in tumors of the head and neck was recognized in a study that considered other candidate biomarkers of CSCs such as BMI1 with significant implications for clinical outcomes.[50] For example, in laryngeal carcinoma, high expression of BMI1 combined with the absence of p16 expression implies the presence of lymph-node metastases.[51]

Considering the role of CD44 in the activation of cell replication, its antiapoptotic activity, and its potential as a marker of CSCs in epithelial tumors, we decided to study the role of CD44 standard in head and neck tumors. We studied the levels of CD44 sol in the saliva of patients with tumors of the larynx,[52] starting from the assumption that in the normal upper aerodigestive tract, CD44 is expressed on the basal surface, whereas in the histologically dysplastic epithelium, CD44 is expressed in all layers of the mucosa in more than 90% of cases. This overexpression is also present in 90% of invasive head and neck tumors.[52,53] Our results were encouraging because we found high levels of CD44sol in most patients with laryngeal carcinoma with high specificity compared with controls, and the highest levels of CD44sol were observed in patients with advanced stages of disease. Our and Franzmann et al's results are promising because of their high diagnostic power, and suggest that CD44sol could be a specific diagnostic marker of head and neck cancer.[52,55–57]

These data are superior to those obtained by other studies using various markers with different methods of investigation such as loss of heterozygosity, the methylation-specific markers, telomerase activity, mitochondrial DNA mutations, and recently the multiplexed immunobeaded-based technology.[58–63]

Conclusion

CD44 appears to be a fairly reliable marker of head and neck tumors and to have potential diagnostic value, because its detection is easy and there are clinical benefits in terms of final outcomes. Cruz et al wrote, "The identification of a fraction of cancer stem cells (CSCs) associated with resistance to chemotherapy in most solid tumors leads to the dogma that eliminating this fraction will cure cancer."[64]

Further studies are needed to validate this theory and to consolidate the role of CD44 as a biomarker of CSCs in head and neck cancer.

Disclosure

The authors report no conflicts of interest in this work.

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