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The Prognostic Influence of CD44 in Oral Squamous Cell Carcinoma

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Abstract

Oral Squamous Cell Carcinoma (OSCC) is the most frequent malignant tumor of the oral cavity, exhibiting a heterogeneous behavior. Because the mortality rate for this tumor has essentially remained unchanged over the last few decades, the need exists for more reliable prognostic factors in OSCC. The objective of this review was to examine the relevance of CD44 expression on the prognosis of OSCC patients through a critical analysis of the most significant current scientific literature on this subject. We found that most investigations of CD44 expression in OSCC over the years have demonstrated some prognostic influence, although there were significant differences among the studies. Certain studies have also demonstrated that CD44 may be an important biomarker of Cancer Stem Cells (CSCs) in OSCC. However, as with the discrepancies regarding the true prognostic value of CD44 in OSCC, some studies have indicated that CD44 might be limited in the identification of oral CSCs. Thus, according to our findings, additional and more standardized research should be conducted to validate the CD44 molecule as a reliable biomarker of prognosis and of CSCs in OSCC.

Keywords: Oral cancer; CD44; Cancer stem cells; Prognosis

Introduction

Oral Squamous Cell Carcinoma (OSCC) is the most frequent malignant tumor of the oral cavity with a mortality rate that has essentially remained unchanged over the last few decades. For this reason, the discovery of more reliable prognostic biomarkers to guide therapeutic planning in OSCC has garnered considerable interest [1,2].

The transmembrane glycoproteins of the CD44 family are the major human cell surface receptors for hyaluronate, which also bind extracellular matrix proteins and certain growth factors, and act in a diverse range of physiological and pathological processes such as cellular adhesion, migration, angiogenesis, certain lymphocyte functions, and in the dissemination of malignant cells [3-7].

The CD44 gene is unique for all the various isoforms of the protein, and includes at least 19 exons. Exons 1-5 and 16-19 are spliced together to form a transcript known as CD44s isoform, whereas exons 6-15 are variable, generating several isoforms of the CD44 molecule [8]. Thus, the CD44 family consists of a standard form of CD44 (CD44s) and an alternative splice variant (CD44v). The association of the CD44 family with metastasis formation and prognosis in several tumors has been controversial, particularly in oral cancer, and remains inconclusive [3,7].

Recent studies have demonstrated that malignant neoplasms are organized as hierarchical tissues containing differentiated cells with a small subpopulation of proliferating and undifferentiated cells, the so-called cancer stem cells (CSCs) [9]. The CSC theory postulates that only a specific subset of cancer cells within a tumor exhibits stem cell characteristics (e.g., the ability to self-renew and to proliferate extensively), which can sustain growth and promote the recurrence and metastasis of malignant neoplasms [10,11]. In head and neck squamous cell carcinomas (HNSCCs), the CSCs have been previously observed to occur in low percentages, and it has been demonstrated that they can be characterized according to CD44 expression levels [10,12].

Due to conflicting results that have been recently published regarding the influence of CD44 expression on OSCC prognosis, the purpose of the present manuscript was to review the relevance of CD44 expression on prognosis in OSCC patients through a critical analysis of the most significant current scientific literature on this topic.

CD44 Does Not Significantly Influence OSCC Prognosis

The CD44 proteins are commonly found in epithelial tissues and were previously established to be important regulatory factors in normal squamous epithelium for processes such as cellular adhesion and cell–cell interaction [13]. Although this protein has been previously associated with infiltration and metastatic dissemination when expressed in neoplastic squamous epithelium [14-16]. Controversial results have been reported with numerous investigations that demonstrate conflicting findings for OSCC [17-21]. According to Bloor et al. [17] and Mascolo et al. [20], is appears unlikely that CD44 expression has value as a prognostic marker in OSCC.

These findings underscore the fact that certain studies have indicated that CD44 does not influence OSCC prognosis and that these discrepant results in this field require additional clarification and research with improved standardization of the methods used among the studies.

CD44 Significantly Influences OSCC Prognosis

Over the years, most studies of CD44 expression in OSCC have demonstrated some prognostic influence [2,22-24]. Interestingly, earlier investigations found that the reduced expression of CD44 was a significant predictor of poor prognosis in most OSCC studies [22,23,25,26]. On the other hand, current studies on this subject have indicated a poor prognosis in OSCC associated with strong CD44 expression [2,19,27,28].

This variability of results may be a consequence of the lack of standardization in research on this topic, particularly in relation to the anatomical region [2,3]. According to Kokko et al. [19], significant differences exist regarding the results of CD44 expression and its prognostic influence according to the anatomical location in the head and neck region. Yet, several investigators have grouped certain HNSCCs together with the oral tumors, as well as those of the oropharynx and larynx, which have a different prognosis [6,29,30].

Because the CD44 family consists of a standard form of CD44 (CD44s) and its alternative splice variants (CD44v) [3], it is currently becoming evident that discrepancies in the OSCC ability for recurrence, loco regional or distant metastasis, as well as in the radioresistance of its malignant cells, may be mainly due to the overexpression of a specific CD44 isoform [31].

The low expression of CD44s on tumor cells was significantly correlated with poor prognosis in tongue carcinomas [32], whereas the absence of CD44v expression was associated with a shorter survival time in lip OSSC [26]. On the other hand, Bankfalvi et al. [33] found that the increased immunoexpression of the CD44v9 alternative splice isoform along with a loss of CD44s, v4, and v7 was significantly associated with a poorer clinical outcome in OSCC. In some other cases, the overexpression of CD44v (v3 and v6) appears to reflect the cellular invasiveness and leads to the increased aggressiveness of some HNSCCs, as well as that of OSCCs [34], given that these different isoforms are also associated with lymph node metastasis and chemoresistance [35]. Moreover, an increased expression of CD44 standard and variant isoforms was also confirmed in most oral dysplasias, which also exhibited a selective accumulation of CD44s, v3, v4 and v9 in OSCC at the invasive tumor front [33,36].

CD44 as a Cancer Stem Cell Marker in Head and Neck Cancer

Notably, some studies have demonstrated that CD44 may be an important biomarker of a cellular subpopulation of CSCs in head and neck cancer [10,12,31]. The first evidence that the malignant cells of head and neck carcinomas have a hierarchy of development and contain a subpopulation of cells with self-renewal and differentiation capacities was reported by Prince et al. [10], who also associated the CD44 expression with the CSC immunophenotype. Accordingly, significant resistance to apoptosis has been demonstrated for the CD44-positive cells in HNSCC [37,38] and additional studies have observed an association of CD44 overexpression with certain other putative CSC biomarkers such as CD24 and CD133, which also demonstrate significant prognostic influences in OSCC [2,6].

As with the discrepancies regarding the true prognostic value of CD44 in OSCC, a recent study has indicated that CD44 may be a limited biomarker of oral CSCs in the determination of the CSC immunophenotype [39], whereas other studies have demonstrated that the CD44-negative cells in HNSCC also have stem cell-like traits [40]. Accordingly, Clay et al. [18] also recently suggested that it was unlikely that CD44-positive cells were a pure population of CSCs, highlighting the need to combine such studies with other CSC markers.

As previously discussed, it is well established that CD44, the product of a single gene, exists as several isoforms generated by alternative exon splicing and posttranslational modifications, and that one or more of the CD44 splice-variant isoforms can be differentially expressed in some tumors and may also affect the CSCs identification [41].

Final Considerations

The precise understanding of CD44 regulation mechanisms in OSCC is essential to furthering research on cancer progression and invasiveness, as well as to the acquisition of additional knowledge on tumor prognosis. However, no consensus has still emerged on this subject and the conflicting results reported regarding CD44 immunoexpression in OSCC prognosis and CSC identification can be attributed to factors such as different selection criteria of OSCC patients and variation of different alternative isoforms of CD44 with limited commercially available antibodies directed against them, as well as to the contrasting technical methods used for evaluation, as in the different antibodies and cutoff values selected [2,3,16,28]. To overcome these shortcomings, a novel anti-CD44 monoclonal antibody must be needed, or setting the primer for CD44 to detect wide range of splice variants. Thus, most current investigations regarding the CD44 association with the CSC immunophenotype have demonstrated that additional and better-standardized studies are required to elucidate these hypotheses.

Conclusion

The literature still contains widespread discrepant findings regarding the prognostic influence of CD44 expression in relation to OSCC. Additionally, investigators continue to seek reliable biological evidence of the CD44 molecule as a CSC biomarker in OSCC. Thus, standardized additional studies are needed to validate the CD44 molecule as a reliable biomarker of prognosis and of CSCs in OSCC.

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