Review Article

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ROLE OF CELL ADHESION MOLECULES IN ORAL CARCINOGENESIS

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ABSTRACT:

Adhesion of like cells is a primary feature of the architecture of many tissues. Cell adhesion molecules are found on all cell surfaces, where they bind to extracellular matrix molecules or to receptors on other cells. They are essential for maintaining the stable structure of stratified squamous epithelium. The major groups of cell adhesion molecules are Syndecans, Cadherins, Catenins, Laminins, Selectins, Integrins and molecules such as CD44. The expression of cell adhesion molecules is normally well regulated-forming, persisting or declining in an ordered fashion for controlled cell proliferation, mobility, differentiation, and survival. However in malignant tumors many of these processes are misregulated leading to the aberrant expression or function of cell adhesion molecules. Altered expression of these molecules has been frequently found in oral squamous cell carcinoma, where loss of cell adhesion molecules expression is often seen in poorly differentiated lesions. This article focuses on the role of various cell adhesion molecules in the carcinogenesis of oral squamous cell carcinoma.

Key Words: squamous cell carcinoma, cell adhesion molecules, syndecan-1, laminin, integrins

INTRODUCTION:

Cell adhesion is critical in tissue morphogenesis and in development and the maintenance of adult organisms. Cell adhesion molecules (CAM's) has the capacity to connect the exterior of the cell with the interior. They form structural linkages between the cell cytoskeleton and the extracellular matrix or between cells, and also function as signaling receptors, transducting signals initiated by cellular interactions which regulate many diverse processes, including cell division, migration, and differentiation. Thus cell adhesion molecules are essential for maintaining the stable structure of stratified squamous epithelium.[1] It is apparent that alterations in cell adhesion can influence almost every stage of cellular transformation. The development of malignant epithelial neoplasms is associated with aberrant expression of cell adhesion molecules leading to disruption

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of cell-to-cell and cell-to-matrix adhesion.[2] Altered expression of these molecules has been frequently found in oral squamous cell carcinoma, where loss of CAM expression is often seen in poorly differentiated lesions.[1] The major groups of CAM's are Syndecans, Cadherins, Catenins, Laminins, Selectins, Integrins and molecules such as CD44.

SYNDECANS

Syndecans are a family of four cell-surface heparan sulphate proteoglycans. The syndecan family is composed of four closely related proteins (syndecans-1 to 4) which are encoded by four different genes.[2] They interact with extracellular matrix components, other cell surfaces, and growth factors, including the basic fibroblast growth factor. Syndecan-1, the prototype member of the syndecan family, is suggested to function as a matrix receptor transducting information between the extracellular matrix and the inside of the cell.[3] Syndecan-1 binds cells via its heparan sulphate chains to a variety of components of the interstitial matrix, including types I, III and V collagen, fibrillar collagen fibronectin and tenascin.[2] In B lymphocytes and stratified squamous epithelia, syndecan-1 is proposed to function as a cell-cell adhesion molecule. Furthermore, it plays an important role in the regulation of cell growth and differentiation during the developmental process. In mature tissues, the expression of syndecan-1 is limited to the epithelial cells, with the exception of B cells and Leydig cells.[4]

Syndecan-1 in Oral Cancer

In vivo, reduction of syndecan-1 expression has been observed in experimentally induced mouse skin tumors and in human squamous cell carcinomas (SCCs). Furthermore, loss of syndecan-1 expression appears to be an early event, since the reduction of syndecan-1 is seen in premalignant lesions of the oral mucosa and the uterine cervix.[3] Similarly reduced expression of Syndecan-1 in dysplastic epithelium was observed by various authors such Kurokawa et al, Jackson LL et al, Kamat SS et al and Lakkam B et al. [5-8] This decrease in syndecan-1 expression occurs in transformed epithelium and is clear when compared to its expression in normal oral squamous cell epithelium. Antonnen et al suggested a decreased expression of syndecan-1 is associated with low histological grade of differentiation and poor outcome in SCC of the head and neck treated with surgery and post-operative radiotherapy.[9] Also the expression of syndecan-1 is known to suppress the level of matrix metalloproteinase (MMP)-9 and to inhibit cell invasion into type I collagen(Muramatsu et al).[10] Mukunyadzi et al suggested that the intensity of syndecan-1 staining within the stroma showed generally an inverse correlation with the degree of tumor cell differentiation. They found that Syndecan-1 expression was not detected in the stroma beneath normal squamous epithelium or adjacent to areas of squamous cell carcinoma in situ. It was concluded that induced expression of syndecan-1 in the stroma surrounding

tumor cells of invasive head and neck squamous cell carcinoma is a frequent event. The increased stromal syndecan-1 expression, coupled with its loss from the surface of carcinoma cells, may contribute to tumor cell invasion and the development of metastases. [11]

CADHERINS

Intercellular adhesiveness is mediated by a family of glycoproteins named Cadherins. Designated by their tissue distribution, several subclasses of classical cadherins exist, including the epithelial E-cadherin (E-cad; also named L-Cam, uvumorulin, Arc-1, and cell-CAM 120/80), placental P-cadherin (P-cad) and neural-cadherin, non-epithelial cadherin or cadherin-2 (N-cad). These molecules are believed to be involved not only in mediating intercellular adhesion, but also in facilitating transduction of signals that influence several important biologic processes, including cellular motility, proliferative activity, and apoptosis. [12] E-cadherin, a predominant member of this family, is involved in the adherens type of intercellular junctions of keratinocytes, P-cad is detected on the cell-cell contact surface of basal keratinocytes. The expression of P-cad in epithelial tissues appears to identify cell populations with proliferative activity, and its expression decreases as cells undergo differentiation.[13] The cell adhesion molecule E-cad is a transmembrane glycoprotein responsible for homotypic binding and morphogenesis of epithelial tissues, and plays a critical role in cell-to-cell adhesion. Based on the extensive studies on the E-cad expression in many forms of human cancers, it is deemed that partial or complete loss of E-cad expression is a frequent phenomenon in various types of cancers.[14]

P cad as described earlier is cell adhesion molecule, which is only expressed in the basal and suprabasal cell layers of the normal oral epithelium. P-cad was described originally in mouse placenta but has also been found in epithelial tissues, including lung epithelia, basal cells of the skin, and myoepithelial cells of the mammary gland. [15] N-cadherin is predominantly seen in neural tissues fibroblasts, skeletal muscle and endothelial cells. The reduction or loss of E-cadherin and the gain of N-cadherin expression, referred as the cadherin switch, are considered as a hallmark of Epithelial Mesenchymal Transition. [16]

Cadherins in Oral Cancer

Tanaka et al suggested immunohistochemical investigation of E cad is of value for the purpose of diagnosing the presence of metastasis. [17] Also least differentiated tumors showed a reduced expression of E-cad in later stages, and these tumor cells are said to acquire invasive phenotype (Bagutti et al).[18] The exact mechanism involved in the variable expression of E-cad is unclear. Recently Kaur et al noted that the loss of the cell adhesion and E-cad plays an important role in progression of OSCC, that is, down regulation of its expression is associated with de-differentiation and metastasis.[19] Wang et al demonstrated

reduced expression of E cadherin in the invasive tumor front when compared with superficial/center area which correlated with poor prognosis.[14] Gao et al found that cytoplasmic rather than membrane staining of E-cadherin was a prominent aberrant tumour-related alteration, and that this expression was mainly present in moderately and poorly differentiated tumours.[20] Studies on the expression of E cad and P Cad on OSCC suggested that that down-regulation of E-cad and P-cad is a common malignant event in OSCC progression, and correlates closely with the prognosis.[13,15] The reduced expression of these adhesion molecules in tumor invasion suggests that these cells can detach easily. The dissociation of cancer cells from each other may enable the carcinoma cells to invade the stroma and cause metastasis. [15] In OSCC, the nuclear pattern of N-Cadherin expression was particularly observed in dedifferentiated cancer by Domenico et al. They suggested the pattern of cadherin expression might constitute a useful diagnostic and prognostic tool in the evaluation of tumors and for determining the histogenesis of tumour cells. Moreover, they found a statistically significant correlation between N Cadherin expression and grade, and a statistical trend for stage.[21] Pyo et al evaluated the immunoreactivity of E-, P- and N-cadherins (cad) in oral squamous cell carcinoma and correlated their expression with clinicopathological features and clinical outcome. They found that reduced E-cad expression and the aberrant N-cad expression are closely associated with each other in oral cancer cases, and suggested that cadherin switching from E. cad to N. cad may play a critical role in cancer development and metastasis.[22]

CATENINS

Catenins are intracellular proteins that link the cytoplasmic domains of cadherins to the cytoskeleton to promote its biological functions. The intracellular domain of E-cadherin is linked to the actin cytoskeleton through its interaction with its cytoplasmic-binding partners α, β, and γ-Catenins. α-Catenin is involved in the regulation of actin cytoskeleton and cell-cell adhesion, which when altered could contribute to cancer progression. β-Catenin is a multifunctional adaptor protein involved in cadherin-mediated cell–cell adhesion and in responses to the activation of several signal transduction pathways. β-Catenin plays a role in cell-cell adhesion by controlling cadherin-mediated cell adhesion at the plasma membrane and by mediating the interplay of adherens junction molecules with the actin cytoskeleton. β-catenin also serves as a pivot between the roles of cell adhesion and gene transcription.[23] γ-Catenin is a cytoplasmic protein structurally and functionally related to β-catenin.[13]

Catenins in Oral Cancer

Laxmidevi et al and Zaid showed that down-regulation of β-catenin was significantly correlated with lack of differentiation in oral squamous cell carcinoma. Reduced membranous

expression and predominant cytoplasmic localization were prominent among higher-grade tumors, suggesting stabilization of β-catenin and its role as a signaling molecule.[24,25] Likewise, Lo Muzio demonstrated an inverse relationship between the location of β-catenin expression within the cells and the degree of OSCC differentiation, such that reduced membranous expression was associated with less differentiation. More interestingly, a diminished expression of this molecule was also found in the invasive front of OSCC grade 2, and less significantly in OSCC grade 1, thus supporting the idea that the loss of β-catenin expression is causative of poor clinical outcomes.[26] Similarly Tanaka et al observed a reduced expression of *α*-catenin and *β*-catenin in SCC's with regional metastasis suggesting that immunohistochemical investigation of these proteins is of value for the purpose of diagnosing the presence of metastasis.[17] Närkiö-Mäkelä et al demonstrated that reduced expression of γ-catenin was associated with poor differentiation of OSCC, with neck lymph node metastases, and, more importantly, with poor disease-specific survival. They found that the loss of γ-catenin expression contribute to metastatic properties of OSCC and concluded that evaluation of the expression pattern of γ-catenin may be useful for predicting outcome in patients with OSCC.[27]

LAMININS

The interface between the epithelium and the connective tissue is a matrix named the lamina or basal membrane, a thin but resistant layer that has an important role in controlling cell behavior. It is composed of type IV collagen, heparan sulphate, fibronectin, entactin and laminin. Laminin is a large heterotrimeric extracellular glycoprotein composed of α, β, and γ subunits that is involved in cell adhesion, cell migration, proteolytic activity, cell proliferation, and tumor and metastatic growth.[28] Laminin 5 (α3, β3, γ2) is a typical component of epithelial basement membrane and is considered as a biochemical equivalent of the anchoring filaments fixing basal keratinocytes to the basement membrane.[29] The ability of malignant neoplasias to destroy the basal membrane has been correlated with its invasive potential and the loss of continuity of laminin expression and collagen IV.[30]

Laminins in Oral Cancer

De Souza et al demonstrated that there was decreased immunohistochemical expression of laminin in the basal membrane of high malignancy grade OSCC. They suggested that this structural change may affect basal membrane dynamism and favor tumor invasion.[31] Studies by Tosios et al, Mostafa et al and Shruthi et al showed a decreased distribution of laminin from Well Differentiated Squamous Cell Carcinoma (WDSCC) to Moderately Differentiated Squamous Cell Carcinoma (MDSCC) to Poorly Differentiated Squamous Cell Carcinoma (PDSCC). They interpreted that WDSCC cases showed more laminin expression in basement membrane

around the tumor islands and less loss of continuity compared to MDSCC and PDSCC cases suggesting a greater enzymatic degradation of basement membrane components in MDSCC and PDSCC than WDSCC. The loss of structural basement membrane laminin and the presence of laminin in the tumor cells of PDSCC cases suggest that laminin helps in tumor invasion. It was thus concluded that expression of laminin in the basement membrane may be a useful parameter to evaluate tumor histologic differentiation and aggressiveness.[32,33,34] Kannan et al reported a gradual increase in the frequency of laminin discontinuity from normal epithelium to hyperplastic, dysplastic and SCC.[35] Santos García et al found discontinuity in laminin expression in dysplastic lesions that progressively increased for in situ and microinvasive carcinomas, being higher in OSCCs.[36]

SELECTINS

Selectins are a family of type 1 single-chain transmembrane proteins found on platelets, leukocytes, lymphocytes, and endothelial cells.[1] The family is composed of E-selectin, P-selectin, and L-selectin, adhesion molecules that are crucial for binding of circulating leukocytes to vascular endothelium during the inflammatory response to injury or infection.[37] L-(lymphocyte) selectin is constitutively expressed on essentially all blood neutrophils and monocytes, on the majority of blood-borne T and B-cells, on a subset of natural killer cells, and on immature hematopoietic cells. P (Platelet) and E (endothelial cell) selectins are expressed on activated platelets and stimulated endothelial cells. E selectin expression is limited to endothelium, principally endothelium responding to inflammatory stimuli.[38] Although selectins are not normally expressed by oral epithelial cells, expression of E-selectin has been found on inflamed gingival epithelial cells.[37]

Selectins in Head and Neck Cancer

Renkonen et al analyzed the expression of E- and P-selectins and their sialyl-Lewis(x) (sLe(x))- and/or sialyl-Lewis(a) (sLe(a))-containing ligands in head and neck tumors. Results showed that epithelial expression of sLe(x) and sLe(a) glycans was higher in benign than in malignant lesions in both epithelial and lymphoid tumours. On the other hand, endothelial expression of sLe(x), sLe(a), E- and P-selectin was lower in benign than in malignant lesions in both epithelial and lymphoid tumours. Thus the study suggested that the altered epithelial and endothelial expression of sLe(x) and sLe(a)glycans acting on selectin ligands is linked to the development of head and neck tumours.[39] Elevated circulating levels of E-selectin have been reported in oral SCC and may represent a marker of disease presence.[1]

INTEGRINS

Integrins are a family of heterodimeric, cation-dependent cell membrane adhesion molecules which mediate cell-cell and cell-matrix interactions. They play a fundamental role in the maintenance of tissue integrity and in the regulation of

cell proliferation, growth, differentiation and migration.[40] Integrins consists of an α subunit and a β subunit. To date, 18 α and eight β subunits have been identified and these can associate in numerous different combinations with different ligand specificities. Integrin β1 can bind to various ECM components depending on its α subunit partner: the heterodimers α2β1, α3β1 and α5β1 bind preferentially to collagen, laminin and fibronectin, respectively. The intracellular tail of integrin β1 is linked to the actin cytoskeleton via association with proteins such as talin, α-actinin and vinculin.[41] Integrin β1 is crucial for cell motility in a number of contexts; it is required for efficient keratinocyte wound healing in vivo.[40] Stratified squamous epithelium expresses integrins of the β1, β4, and αv families. Integrins have also been shown to play a role in keratinocytes migration, matrix metalloproteinase expression, and formation of basement membrane.[1]

Integrins in Oral Cancer

As with other carcinomas, integrin expression in oral carcinoma varies both between tumours and within different areas of the same tumour. In OSCC there is variable loss or reduced expression of beta 1 integrins and of α6β4, which correlates to loss of basement membrane proteins and is most extensive in poorly differentiated lesions.[42] Downer et al demonstrated that focal or extensive loss of α2β1, α3β1, αvβ5, and α6β4 is common in OSCC especially in poorly differentiated lesions, and loss of α6β4 has been shown to coincide with loss of basement membrane. This provided the evidence that integrin expression correlates closely with tumour invasion and nodal metastasis.[43] Hamidi et al detected αvβ6 expression in oral dysplastic but not hyperplastic lesions, and concluded that transition of normal mucosa to SCC involves the induction of αvβ6.[44] Ramos et al demonstrated that expression of β6(1) increases oral SCC cell motility and growth in vitro and in vivo, negatively affects fibronectin matrix assembly and stimulates the expression and activation of MMP3. They suggested that the integrin αvβ6 is a key component of oral SCC invasion and metastasis through modulation of MMP-3 activity.[45]

CD 44

CD44 family of cell surface glycoproteins consists of standard form of CD44 (CD44s) and alternative splice variants (CD44v), which are post-translationally modified by N- and O-glycosylation and addition of glycosaminoglycan side chains.[46] It is a multistructural and multifunctional cell surface molecule involved in cell proliferation, cell differentiation, cell migration, angiogenesis, presentation of cytokines, chemokines and growth factors to the corresponding receptors, docking of proteases at the cell membrane, as well as in signaling for cell survival. All these biological properties are essential to the physiological activities of normal cells, but they are also associated with the pathologic activities of cancer cells.[47] The high molecular weight isoforms of CD44 are characterized by certain insertions in

the transmembrane domain. Genomic analysis indicated that the CD44 gene has 20 exons and the region encoding the insertion is composed of 10 exons that are alternatively spliced to produce variable isoforms carrying different membrane proximal inserts. The standard form does not include any of the v1 to v10 exons. Multiple CD44 isoforms are expressed by normal stratified squamous epithelia, such as the epidermis and the lining of the oral cavity.[48]

CD 44 in Oral Cancer

Several studies have indicated that the down regulation of CD44 variants, including CD44v9, v4/5 and v6 is associated with tumor metastasis in OSCC. It has also reported that there is a positive correlation between the reduced immunoexpression of CD44v9, metastasis to lymph nodes and poor survival in OSCC of tongue (Satoa S et al).[49] Various studies by Kuo et al, Stoll et al, Kanke et al, Fonseca et al and Ue et al and Hema et al demonstrated that CD44 expression by tumor cells in OSCCs is statistically correlated with tumor.[50-54] The decrease in the intensity of the CD44s levels with the increase n the grade of the tumor suggests reduced cell to cell adhesion, resulting in easy detachment of the cells from a rigid constitution. Low expression of CD44s in OSCC tissues may be an indicator of high metastatic potential and may be related to lymph node metastasis. So decreased expression of CD44 may correlate with poor prognosis.[55]

CONCLUSION:

Over the last decade, our understanding of how tumor cells interact with their environment through expression of cell adhesion molecules has increased dramatically. No single cell adhesion molecule appears to be responsible for the transformation of cells to a malignant phenotype, and expression varies greatly between tumor types, between individual tumors of the same type, and even within a single tumor. Identification of these molecules through various advanced modalities has helped us in determining the prognosis of the diseases and will also aid us in developing newer therapeutic modalities.

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