

Expression and Significance of Cadherins and Its Subtypes in Development and Progression of Oral Cancers: A Review

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ABSTRACT

Cadherins are a family of transmembranous glycoproteins responsible for calcium-dependent intercellular adhesion. Absence or loss of function of E-cadherin leads to the disappearance of epithelial characteristics of the cells and generates higher invasiveness for extracellular matrices. That is why cadherin expression is considered to be a decisive indicator for differentiation, aggressive behaviour, high proliferation, metastasis, poor prognosis and invasiveness of human carcinoma cells. In this review, the role of cadherin expression was focused on, both in development and carcinogenesis, paying particular attention to mechanisms involved in its down-regulation. The elements common to this process in both physiological and pathological situations was analysed, particularly in relation to one of the most common malignancy, oral squamous cell carcinoma.

Keywords: Cancer biomarkers, Cancer metastasis, Cell-cell adhesion, Desmosomes, Oral squamous cell carcinoma, Prognosis

INTRODUCTION

At specific sites on the contacting cell membranes, where cells come into contact with one another and sometimes, with the extracellular matrix, specialized junctions are formed. These specialized junctions are classified into several different categories as follows [1]

1. Occluding (tight) junctions (zonula occludens).
2. Adhesive junctions.
 - a. Cell-to-cell: i. Zonula adherens; ii. Macula adherens (desmosome)
 - b. Cell-to-matrix: i. Focal adhesions; ii. Hemidesmosomes
3. Communicating (gap) junctions.

Ultra-structurally, intercellular junctions typically consist of three components: a transmembrane adhesive protein, a cytoplasmic adapter protein, and a cytoskeletal filament, which differ on the basis of type of junctions. In occluding or tight junctions (where intercellular space essentially is obliterated), transmembrane adhesive proteins are responsible for keeping the opposing cell membranes in close contact [1].

Adhesive junctions keep the cells together, anchor cells to the extracellular matrix and have a role in cellular signalling. Their cytoplasmic components triggers changes in cell shape or motility by interacting with skeleton, may also interact with certain tumour suppressor molecules, or they may act as nuclear transcription factors or coactivators [1,2].

In case of zonula adherens, part of adhesive junctions, E-cadherin is the principle transmembrane protein with alpha and beta catenin as cytoplasmic adapters, and actin filaments as the cytoskeletal component. Cytoplasmic proteins associated with the zonula adherens like p120 catenin, associate with E-cadherin in stabilizing the junction. Principle cadherins in the desmosome, are desmoglein and desmocollin, interact with those from the adjacent cell and result in a dense line in the middle of the intercellular space at the desmosome. Cell-matrix junctions differ from cell-cell adhesive junctions on the molecular level, though both have a similar structural organization [1].

Catenin family includes cytoplasmic adapter proteins that interact with cytoplasmic domain of the trans-membrane cadherin molecule, cytoskeleton, proteins including kinases, and with tumour suppressor molecules that are associated with adhesive junction [1].

Genetic abnormalities of functional or cytoskeletal proteins or presence of any autoimmune disease leads to alteration or disruption in cell-cell and cell-matrix junctions. These junctions have roles in the differentiation, development and function of normal cells, tissues, organs [1].

Cadherins are calcium dependant molecules, 120 kD glycoprotein that mediate homophilic (like- to-like) cell-cell adherence and differentiation. It is a family of cell surface glycoproteins of 723-747 amino-acids that act as intercellular adhesion molecules by calcium dependant homophilic binding and maintains epithelial structure, epithelial cell organization, integrity and polarization [2]. Cell adhesion molecules (CAMs) have been categorised into three gene families, the integrins, the immunoglobulin superfamily, and the cadherins, all of which have been implicated in metastasis [3,4].

One of the most common malignancies now-a-days is oral cancer, which is histologically characterized as oral squamous cell carcinoma which is epithelial in origin. Thereby cadherin molecule family has an important role to play in tumour differentiation, nodal invasion and distant metastasis, which are traditionally implicated as prognostic markers for overall patient health and treatment outcome. In this review, we have discussed role of this family of molecule in local and distant spread of the tumour and their prognostic significance.

REVIEW OF LITERATURE

Cadherin function covers different aspects of tissue morphogenesis, including cell recognition and sorting, boundary formation and maintenance, coordinated cell movements, induction and maintenance of structural and functional cell and tissue polarity. Diversity in structure and the large size of the cadherin family enables many types of cell interactions required for tissue morphogenesis in complex organisms [1, 2].

To make the review more informative and concise, we have sub-divided this part of the article under following headings.

Role of Cadherins during Embryogenesis and Development

During development, the behaviour of cadherin not only assists in properly positioning of cells but they are also responsible for the separation of the different tissue layers, and for cellular migration. Cadherin subtypes are expressed at the highest levels in

distinct tissue types during development. For example, E-cadherin is not only present at the morula stage of embryogenesis, but also expressed in all epithelia and is important for establishing and maintaining apico-basal polarity (Takeichi 1988; Honjo et al., 2000). During the next stage, the development of the neural plate, N-cadherin (neural cadherin) is expressed and there is a decrease in E-cadherin. Finally, during the development of the notochord and the condensation of somites, E- P- and N-cadherin expression increases [2,5,6].

The number of cadherins as well as distinct features of their gene structure permits precise temporal and spatial transcriptional regulation of cadherin subtypes, and variations in protein structure, particularly the cytoplasmic domain, facilitate interactions that result in both specific modulation of cadherin activity and initiation of intracellular signalling cascades in response to adhesion. The extensive transcriptional and post-transcriptional regulation of cadherins suggests that the level of cadherin cell surface expression and the maintenance of linkage to intracellular binding partners modify cadherin activity [7,8].

For the development and function of any organism, ability of cells to interact directly and specifically with other cells and with extracellular matrix is crucial. Cadherins, decrease the interfacial tension at the forming cell-cell contact, thereby promoting contact expansion and they also signal to the actomyosin cytoskeleton to reduce cortex tension and thus interfacial tension at the contact. Thereby they stabilize the capacity of tumour cells to adhere to other tumour cells, host cells or components of the extra cellular matrix that affects their ability to migrate [9].

Role of Cadherins in Neoplasia

Epithelial tissues constantly adapt to physiological stimuli in the surrounding environment by proliferation, apoptosis and cell migration. These processes are pre-programmed temporarily in the genome but they are under the influence of several signal transduction pathways including signal transduction from adhesion receptors such as cadherins. Through catenin, E-cadherin plays a critical role in transducing signals to influence these biologic processes. Thus, they can act as mechanotransduction receptors, coupling the external surface and cytoskeleton of the cell, enabling cells to detect and respond to environmental constraints, as in durotaxis, chemotaxis and haptotaxis, key mechanisms in the control of biological processes [1].

Normal oral epithelium displays an intense pericellular (membranous) distribution of cadherin expression throughout the basal, suprabasal and prickle cell layers. The regulatory mechanisms that control E-cadherin expression under normal and pathological circumstances is the topic of interest because of its involvement in epithelial morphogenesis and homeostasis, and its proven anti-invasive role in carcinoma progression [3]. E-cadherin gene is located in 16q and translational disorders or allelic loss of 16q have been reported as possible mechanisms of abnormal E-cadherin expression in human cancers [2].

Various regulatory mechanisms control cadherin expression at the level of gene transcription and protein trafficking and organization at the cell surface. Cancer development is the outcome of alterations of proteins involved in the E-cadherin-catenin complex. It includes reduction or loss of E-cadherin expression, induced by genetic and epigenetic events (i.e. mutation or reduced transcription of the genes), redistribution of E-cadherin to different sites within the cell, shedding of E-cadherin, and competition for binding sites from other proteins [2].

Role of Cadherins in Oral Squamous Cell Carcinomas (OSCC)

During carcinogenesis, methylation of the E-cadherin promoter is associated with reduced E-cadherin expression, and with disease

progression and metastasis. Chang et al., found that methylation was observed in metastatic cells with reduced expression of E-cadherin in about 67% of nodal metastases of OSCC cases [10,11]. Various studies have been conducted to correlate E-Cadherin expression with histologic grade and the growth pattern of various carcinomas. Their absence or loss of function leads to the disappearance of epithelial characteristics of the cells and generates higher invasiveness. Epithelial-to-mesenchymal transition (EMT) is a term used in cases where loss of characteristic polarity, dis-assemble cell-cell junctions and migration of epithelial cells is seen as in case of tumour metastasis [11,12].

Recent studies have shown the importance of other members of the cadherin family in tumour cell invasion and metastasis. N-cadherin, enhances cell motility of various tumour cell types. All these facts raise the possibility that a 'cadherin switch' from proadhesive, epithelial cadherins (e.g. E-cadherin) to mesenchymal, promigratory cadherins (e.g. N-cadherin) promotes tumour invasion and metastasis [9]. Furthermore, some studies have demonstrated that cadherin switching is necessary for increased motility but simultaneously morphological changes occur that accompany EMT [11-13].

Now-a-days the profile of cadherin is used in diagnostic pathology. Their expression is used to differentiate tumours of similar histology but with distinct subtypes or cell type origin [12,13]. Various immune-histochemical studies, have confirmed that the tumours with preserved epithelial morphology, classified as differentiated type, express high amounts of cadherins, whereas the tumours with scattered morphology or infiltrative growth, classified as undifferentiated type, have reduced amounts of these molecules. Also, well differentiated OSCC expressed E-cadherin often as strongly as normal stratified squamous epithelium, while in poorly differentiated OSCC expression of E-cadherin was lost or cytoplasmic, and in moderately differentiated tumours it was expressed in a heterogeneous fashion. Therefore, E-cadherin is considered as an invasion suppressor and proliferation suppressor molecule. Absent or less expression is mostly seen in tumours larger than 4cms in diameter and tumours in with distant metastasis [9-14].

CONCLUSION

Cadherins are basically polypeptides which undergo modifications to become the proteins. These proteins are responsible for cell-cell adhesion and recognition. Bulk of the protein in cadherin is extra-cellular (outside the cell) while remaining part consists of cytoplasmic and transmembrane component. Cadherin family not only have role in formation of cell-cell adhesions, but also specify cell-cell recognition and sorting, boundary formation in tissues, coordination of multi-cell movements, and the establishment and maintenance of cell and tissue polarity. Cancer development is the outcome of alterations of proteins involved in the cadherin-catenin complex by genetic and epigenetic events. During carcinogenesis, methylation of the E-cadherin promoter is associated with disease progression and metastasis. Absent or less expression is mostly seen in tumours larger than 4 cms in diameter and tumours in with distant metastasis and overall poor prognosis for the patient. Therefore, conventional histopathologic reports supplemented with cadherin profiles can add up interesting diagnostic details and can help clinician to formulate individual treatments protocols as per of patients needs.

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