REVIEW

Role of ERM Proteins in Oral Carcinogenesis - An Insight

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Abstract:

The ERM proteins are a group of three related proteins (ezrin, radixin and moesin) which play a major role in maintaining structural stability and integrity of the cell cortex by coupling transmembrane proteins to the actin cytoskeleton. They also aid in signal transduction between the intracellular and extracellular compartments of the cell. These proteins determine the cell survival, cell migration, cellular adhesion and regulation of membrane protrusion thereby playing a key role in pathological events such as cancer cell invasion and metastasis. Altered expression of ERM proteins contributes to carcinogenesis and metastasis. This article provides an insight on the role of ERM proteins in oral carcinogenesis.

Key words: ERM proteins, Oral Carcinogenesis, Ezrin, Radixin, Moesin.

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INTRODUCTION

The ERM proteins are a group of three related proteins (ezrin, radixin and moesin) which possess band Four point one (4.1) as a common origin.[1] These proteins interact with the plasma membrane through a common FERM (Four point one, ERM) domain.[2] The ERM proteins are located in cellular structures such as filopodia, lamellipodia, apical microvilli, ruffling membranes, cleavage furrow of mitotic cells, retraction fibres, and adhesion sites, where the plasma membrane interacts with F-actin.[3] ERMs contribute for maintaining structural stability and integrity of the cell cortex by coupling transmembrane proteins to the actin cytoskeleton.[1] They also play a role in intracellular scaffolding that aid signal transduction between the intracellular and extracellular compartments of the cell as well as interacting with other membrane phospholipids.[4] Thus, ERMs are involved in the regulation of several cellular processes such as reorganization of actin cytoskeleton, membrane dynamics, cell survival, cell migration, cellular adhesion and regulation of membrane protrusion or in pathological events like cancer cell invasion and metastasis.[4-6] Altered expression of particular ERM proteins can contribute to carcinogenesis and metastasis. For example, ezrin plays a role in the development of metastasis[7] and moesin in oral squamous cell carcinoma.[8-10]

Discovery of ERM Proteins

Ezrin was the first ERM protein to be identified. It was isolated from chicken intestinal epithelial brush borders in the year 1983 and was named after the founder of Cornell University, Ezra Cornell.

Radixin was isolated from hepatocyte cell junctions of rat. It is found to be localized in the cytoplasmic surface of adherens junctions in many cell types. In Latin, the word radix means root or foundation.

Moesin is a membrane-organizing extension spike protein that was isolated from bovine uterus as a potential heparan sulfate-binding protein.[11]

Structure of ERM proteins

ERM proteins contain an amino (N)-terminal FERM domain with a four point 1, ezrin, radixin, and moesin which associates with membrane proteins, a central helical domain, and a carboxy (C)-terminal domain that binds to filamentous actin.[6] X-ray crystallography showed that FERM domain consists of F1, F2 and F3, which is also referred to as A, B and C subdomains respectively. They are fold and joined together to form a cloverleaf structure.[4,5] The FERM region is closely flanked by a central α–helical domain which has coiled coils[4] and mediate interaction with protein kinase A (PKA).[12] The carboxylic terminal tail consists of the F-actin binding site through which ERMs interact with the actin cytoskeleton.[13] In all the ERM family members, distinct domains within the N-terminal head and C-terminal tail which is known as N-and C-ezrin-radixin-moesin association domains (N-ERMAD and C-ERMAD respectively) mediates homotypic and heterotypic head-to-tail interaction.[4,14,15]

ERM Proteins in Cell Migration

ERM proteins are involved in cell migration by stimulation of the membrane receptors by various ligands.[2] Ezrin is involved in the dissociation of cell-cell contacts, formation of membrane extensions and also promotes cell motility. Ezrin is also believed to play a role in the control of actin polymerization.[16,17]

ERM proteins convey signals to the actin cytoskeleton to regulate cell migration through membrane receptors. It is believed that phosphorylation of ERM proteins will recruit regulators of actin polymerization.[2]

ERM Proteins in Tumor Invasion and Metastasis

ERM proteins play a role in tumor progression. The expression of ERM proteins, their phosphorylation status and subcellular localization are key factors which indicate their role in tumor progression. An increased expression of ezrin in the metastasis of human carcinomas from different origins has been observed through proteomic profiling and immunohistochemical analyses.[18-20] Protein profiles of patients with pancreatic cancers revealed an increased expression of moesin and radixin in the patients who had lymph node metastasis and a change in ezrin phosphorylation was also observed.[18] Expression of moesin in normal squamous cell and in squamous cell carcinomas of tongue and lymph nodes revealed that, moesin is present in the basal layer of normal tissues and seen at the membrane and cytoplasm in tumor cells of squamous cell carcinoma and lymph nodes.[19] The switch in localization of ezrin from the basal layer to the cytoplasm or to the membrane in a non-polarized manner is considered to correlate with lymph node metastasis. Thus, the abnormal cellular localization of ERM proteins can affect the regulation of

several functions in tumor cells. The translocation of ERM proteins from the membrane to the cytoplasm can alter the signal transmission elicited by growth factors or disturb the anchoring of membrane receptors and adhesion molecules in tumor progression.[2]

General role of ERM Proteins in Carcinogenesis

ERM proteins play a major role in three events that are responsible for cancer induction, which are cell adhesion, migration and epithelial migration.[2,1,5] As discussed earlier the mislocation of ERM proteins are responsible for tumor progression.[2] The overexpression of ERM proteins accounts responsibility for cancer progression in epithelial cancers of breast, lung and prostate. When the epithelial cells undergo oncogenic mutations, they begin to lose their cellular contacts and undergo change in cell polarity or morphology, thereby developing a mesenchymal phenotype that facilitates the proliferation of cells into the lumen of the glandular acini. Disruption of these layers leads to invasion into the surrounding tissue and subsequent spread to secondary sites around the body. The roles of the different ERM proteins are as follows.[21]

Ezrin

Overexpression of ezrin disrupts cell to cell contact, promotes survival of cancer cells, migration and invasion of cancer cells to the surrounding tissue. Ezrin is upregulated by oncogenic transcription factors such as Myc and the downregulation of tumour suppressor factors. This results in the disruption of cellular contacts through interaction of ezrin with Fes kinase, which promotes PKC- and CD44-induced cell migration, and decreases b-catenin levels as well as increases cell survival through activation of PI3K.

Radixin

Radixin induces Rac1-mediated cell migration through inhibition of Vav. Moesin upregulation, through ROCK- and PKC-dependent phosphorylation. It allows cells to become more motile and to change polarity. It also promotes RhoA- induced cell migration.

Moesin

Moesin also interacts with CD44. The upregulation of moesin displaces the tumour suppressor NF2, promoting CD44-mediated cell migration and also induces the translocation of b-catenin to the nucleus.[5]

ERM Proteins in Oral Carcinogenesis

The sixth most common cancer in the world is the head and neck cancer.[22,23] About 50% of the tumors occur in the oral cavity and among them 90% are diagnosed as oral squamous cell carcinoma (OSCC).[24] Despite the many advances in diagnostic and therapeutic techniques[25], the 5- year survival rate of OSCC patients has not showed any significant improvement over the last three decades 5 and remains below 50%.[26] One of the main reasons for the decreased survival rate of OSCC is the lack of biological markers that demonstrate the molecular behavior. These biological markers help to assess the aggressiveness of the disease and evaluate the prognosis more accurately,[27] thereby help to provide treatments targeted at individual patients. The prognosis of patients is not solely determined by the anatomic extent and the histopathological differentiation of the tumor but also by its molecular features.[28,29] Molecular markers improve our understanding of carcinogenesis in OSCC patients.[30]

In the past many tumor suppressor genes, cell adhesion molecules, oncogenes, cell proliferation markers and angiogenic markers were presented as prognostic and predictive tools for OSCC.[30,31] The epithelial growth factor receptor (EGFR), matrix metalloproteinases (MMPs) and p53 were considered as reliable markers for prognosis in OSCC.[32] The overexpression of EGFR, as a part of the cell cycle acceleration and proliferation molecules, showed significant correlation with poor prognosis in OSCC patients. Matrix metalloproteinases modify the cell adhesion and matrix degradation. Poor prognosis of OSCC showed significant correlation with high expression of MMP-7, MMP-9, MMP-13 and MMP-14.[31,32] The p53 biomarker belongs to the tumor suppression and apoptosis biomarker group and it is one of the most studied biomarkers so far.[31] A high expression of cyclin D1 and EGFR, was significantly associated with poor survival rate in patients with OSCC.[31] To clarify the role of p53 in the prognosis of OSCC, randomized prospective trials or meta-analysis with individual data is necessary.[32] Several studies state that the localization, particularly at the invasion front of the tumor plays an important role along with the expression and quantitative analysis.[32]

In 2011, Oliveira and Ribeiro-Silva showed that the results for the analyzed tumor markers were discrepant and concluded that it is necessary to identify better molecular biomarkers for OSCC. Ezrin, a member of the ERM protein family is a promising novel marker.[7] It is believed to play a key role in tumorigenesis and metasta-

sis and has a significant influence on prognosis, in several different types of cancer, including carcinoma of head and neck region, esophagus, breast, endometrium, cutaneous and uveal melanoma and soft tissue sarcoma.[33] Ezrin was initially identified as a substrate for tyrosine kinase in intestinal microvilli to stimulate proliferation.[34] It is grouped together with radixin and moesin as ERM proteins because of their high homology.[34]

Various studies state that ezrin plays an important role in the growth and metastatic spread of OSCC and their expression reported in head and neck squamous cell carcinoma.[35,6]

An insight on the role of ERM Proteins in Oral Carcinogenesis

In normal cells, ERM proteins tend to exist at the cytoplasm in a dormant state and at the membrane in an active functional state.[6] In normal oral squamous epithelium, moesin is localized mainly at the membrane and redistributes to the cytoplasm in SCC. The intracellular localization of moesin is considered to be a prognostic indicator and cytoplasmic moesin is associated with metastasis and poor survival.[9]

In nonproliferating squamous cells ezrin normally localizes to the membrane. However, in SCC, cytoplasmic ezrin serves as an independent prognostic factor.6 Merlin is considered as a tumor suppressor member of the ERM proteins. It has a membrane localization and an anti-metastasis activity.[36] Willin is a newly identified member of the ERM family. In head and neck SCC, willin is seen localized to the nucleus.[37] Thus in a normal oral mucosa, the pattern of ERM protein expression in differentiating epithelium is as follows - moesin in the basal layer, willin in the parabasal layer, and ezrin in more differentiated cells.[6]

Research suggest that ezrin and moesin are potential biomarkers for predicting survival in head and neck SCC.[6] Based on a study conducted by Li et al. (2015) the knockdown of moesin in oral squamous cell carcinomas cell lines and a significant reduction in migration and invasion was observed. Also, moesin silencing showed an increased cell-cell adhesion. In cell spreading assay, moesin inhibition reduced filopodia formation, thereby indicating the role of moesin in cytoskeletal modifications. This indicates that the weak expression of moesin could be related to higher survival rates in oral squamous cell carcinoma patients. Hence moesin is considered as a prognostic marker for oral squamous cell carcinoma.[38] Immunohistochemical expression of moesin in oral squamous cell carcinomas were observed. Cytoplasmic moesin expression was observed in many tumors. The keratin pearls and some areas with more differentiated neoplastic cells showed weak/negative moesin immunoexpression.[39]

Reason for moesin localization

Membranous expression of moesin in the basal and parabasal layer cells of normal oral epithelia is an expression pattern that is consistent in normal epidermis and in esophageal epithelium. The basal layer and parabasal layer of cells form the proliferative pool of a normal oral epithelium. In OSCC samples, the moesin expression is seen predominantly in the cytoplasm.[9] Moesin shuttles between the juxtamembrane and cytoplasm. It is inactivated and released from the juxtamembrane to the cytoplasm by intramolecular association between N- and C-terminal domains.[40] This conformational dormancy is then reversed by appropriate stimulation, such as exposure to phospatidylinositol 4,5-biphosphate[41] or phosphorylation of Thr-558.[42] The activated moesin travels underneath the cell membrane as a cross-linker between the membrane and cytoskeleton. The cytoplasmic moesin expression in OSCC cases is that the equilibrium between membrane and cytoplasm is shifted to the cytoplasm by a decrease of activating signals or increase of inactivating signals. Also CD44 which is a major receptor for hyaluronan, is shed with moesin from the cell surface to the cytoplasm by proteolytic processing.[9] A study indicates that membrane-type 1 matrix metalloproteinase (MT1-MMP) cleaves CD44 at the membrane-proximal domain; both wild-type CD44 and MT1- MMP are required for promotion of tumor cell migration and invasion.[43] In normal epidermis and squamous cell carcinoma, the similarity of expression patterns between moesin and CD44 was observed; in squamous cell carcinoma[44], the diminution of membranous labeling of moesin and CD44 standard was accompanied by an observed increase of cytoplasmic labelling.[45] Ezrin was demonstrated to coprecipitate with E-cadherin and β-catenin in colorectal epithelial tumor cell lines.[46]

CONCLUSION

ERM proteins play different roles in tumor development and progression. They take part in a number of signalling pathways that are crucial for cancer progression like - RhoGTPases, PI3K/Akt, Wnt/b-catenin, CD44 and RTKs -such as EGFR and HGFR.[23] The role of Meosin and Ezrin

as potential prognostic biomarkers in OSCC has been observed. However, the fundamental impact of Radixin in OSCC and other oral cancers have not been established yet. Further studies are needed to demonstrate the role of radixin in oral squamous epithelium. Also more information regarding the activation mechanisms and interaction and/or regulatory partners of the ERM proteins is required to strongly reinforce their specific roles in different in oral cancers, and their possible use as relevant prognostic markers.

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