Original Paper

# Changes of the extracellular matrix components in the salivary glands pathology

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**ABSTRACT** The aim of this study is to highlight the state of knowledge on quantitative and qualitative changes and the distribution of the various components of extracellular matrix in salivary glands chronic pathology as well as in benign and malignant tumors of salivary glands. Thus, we analyzed the results of several studies in recent years that have followed these changes in matrix structures (in particular collagen, laminin, fibronectin, tenascin, glycosaminglycans and proteoglycans), the specificity of these changes associated with certain pathological pro-cesses; and how these elements can be an effective tool for therapeutic intervention.

**KEY WORDS** *extracellular matrix, tenascin, fibronectin, collagen*

## Introduction

Extracellular matrix is a complex network related with the ever-forming cells and the environment in which they migrate, develop and interact. This stru cture plays an important role to support and sustain the cell, it is a reservoir of substances secreted by these cells and a mediator for cellular interactions. Due to its variability in composition and functionality the extracellular matrix is a major factor in embryogenesis, tissue healing and also in the growth and development of benign or malignant processes

Epitelio-mesenchymal interactions are essential for initiating, developing and main-taining the salivary gland branching system and therefore, at this level, the extracellular matrix is not a passive medium but by the important activity of its components it is essential for the morphogenesis and cell differentiation and is involved in pathological processes of the salivary glands, as demonstrated by numerous studies.

*Conjunctive tissue growth factors, matrix metalloproteinases and tissue inhibitors of metalloproteinases factors* are involved, due to their role in the turnover of extracellular matrix, in the process of fibrosis of various organs. It was studied the activity of these components in *chronic obstructive sialdenitis* of the submandibular gland. Fibrogenesis develops as a result of an imbalance between extracellular matrix synthesis and matrix degradation. Some research showed the activity of these constituents in submandibular gland chronic obstructive sialadenitis. In sialadenitis specimens it was demonstrated immunohystochemically an important periductal increase of epithelial growth factors activity and in the ductal system, in acinar cells and in lymphomonocytic infiltrates in inflamed tissues, an increase of the imunoreactivity of 2,3,9,and 13 metalloproteinases and tissue inhibitors of metalloproteinases compared with the normal salivary gland. The exact aethiopathology and mechanism of atrophy of the glandular cells and lymphocitic infiltration associated with an increase of extracellular matrix in this disease are unknown, but pathological changes of glandular parechyma and the progredient character of the inflamatory progression cannot be explained merely by the secretory congestion and overpresion in the salivary ducts (Teymoortash A, Mandic R, 2004).

Fibrosois in *chronic sclerosing sialadenitis* is associated with an increase quantity and an abnormal distribution of *tenascin* from linear periductal deposition in normal salivary gland to band-like deposition of tenascin found in the fibrous tissue around collecting ducts and around extremely atrophic acini in sialadenitis (Epivatianos A, Iodanidis F et al, 2011).

Important changes in acinar and ductal morphology and function together with important extracellular matrix remodelling are detectable in the salivary glands of patients with *Sjorgen syndrome*. Some studies have demonstrated the effect of matrix metalloproteinases on matrix proteins, basement membrane and stroma of labial salivary glands in Sjorgen syndrome, in the same time was analized the integrity of the acini and ducts as well as the glandular function. It was found an increase of protheolityc activity on basal membrane proteins *(laminin* and *collagen IV*) and on stroma proteins (*collagen I* and *III* and *fibronectin*); the most obvious

alteration is to fibronectin, laminin and collagen I V. Ultrastructural analysis of the basal membrane, ducts and acini showed that, due to the action of metalloproteinases, there are significant alterations to the disappearance of the extracellular matrix. Also it was noted an important decrease in salivary flow (Goicovich E, 2003).

*Irradiation* for head and neck malignant pathology damaging the salivary glands leads to loss of function and fibrosis. Immunohystochemical analysis of extracellular matrix proteins might give a more precise insight into the irradiation damage of glands. Collagen I is a major component of the extracellular space and it was studied the distribution pattern of collagen I in submandibular glands of mice post irradiation up to 60 Gy at 6 and 12 month. In the normal gland collagen I was identified with homogeneous and low distribution around the ductal epithelium and in pericapsular and interseptal spaces. It was a statistically significant increase in the amount of collagen I , in the same location but with an irregular distribution from a 20 Gy exposure to a maximum imunoreactivity at 60 Gy exposure. The significant increase in quantity and the abnormal disposure of different matrix components may explain the postirradiation fibrosis and apoptosis; the extracellular hypoxic environement induces cellular changes (Friedrich RE, Bartel-Friedrich S,2003).

*Hyaluronic acid* is an important component of the extracellular matrix whose production and degradation are dynamic processes. Various studies have shown that the malignant processes are often associated with the increasing amount of extracellular hyaluronic acid.

A study ‘s objective is the evaluation of the amount of hyaluronic acid and two of it’s receptors (CD44 andHARE) in relation with metastatic potential of salivary *mucoepidermoid carcinoma*. (10 cases of parotid gland, one case of submandibulary gland and one case of minor salivary glands). It has been shown that, in normal salivary gland, the hyaluronic acid is absent on epithelial cells surface while is well represented around tumor cells and metastatic regional lymphnodes (experiments show that primary tumors with lymphatic metastasis have larger amount of hyaluronic acid compared with those located strictly glandular) (Wein RO, McGary CT, 2006).

*Tenascin* is an extracellular matrix protein whose abnormal activity is correlated with *tumor morphogenesis* and also with *local invasiveness and metastatic potential* of malignant tumors. One research compares the distribution pattern of tenascin in 63 cases of pleomorf carcinoma and 20 cases of salivary glands adenocarcinoma versus 10 cases of normal salivary glands. Tenascin is situated around excretory ducts of normal salivary glands. Large amount of tenascin is found around malignant cells particulary in metastatic forms (73%) while in benign tumors tenascin is absent, which supports the hypothesis of qualitative and quantitative changes of tenascin during malignant transformation of pleomorphic adenoma and the correlation between these changes and the evolution of salivary carcinomas (Felix A, Rosa JC et al, 2004).

*Tenascin* and *fibronectin* distribution was studied in 23 cases of *pleomorphic adenomas* comparing the major salivary glands (11 cases)and minor salivary glands (12 cases) by determining antitenascin and antifibronectin antibodies (Patricia Bento, Roseana Freitas et al.2006). There are no significant differences between the two tipes of glands. Fibronectin was mostly found in the fibrous stroma, around the basement membranes and pericapsular. It is noticed that tenascin is best represented in the fibrous and high cellularized stroma has very similar characters to those present in the embryonic stages of normal salivary glands development in which this component of the extracellular matrix plays an important role (Alberts et al, 1994).

Other authors (Soini Z Paako P et al 1992) demonstrate that in the pleomorphic adenoma, epithelial cells release tenascin and secrete glycosaminglycans especially hyaluronic acid and chondroitin sulfate that accumulates between the cells and isolate them from surrounding matrix. The glycosaminglycans have an affinity for tenascin and together they have a major role in epitelio-mesenchymal interractions and in extracellular matrix reorganization and restructuring.

*Hyalinizing clear cell carcinoma* is a recently described low-grade carcinoma of the salivary glands presenting two main histological features: clear neoplastic cells and prominent hyalinized stroma. A study on three cases of this type of carcinoma investigating the stroma components changes using antifibronectin, antilaminin and anticollagen I, III and IV antibodies. *Collagen I* and *fibronectin* are found tumor stroma in all cases studies, *collagen III* and *tenascin* are present in tumor with hight invasiveness degree. Collagen IV and laminin distribution is around tumor cells

but not in the stroma (Felix A Rosa JC, Nunes JF et al 2002)

It was studied the role of the extracellular matrix (ECM) role in morphogenesis and cellular differentiation of salivary gland tumors originating from the intercalated duct.

It is analyzed the presence and distribution of *laminin, collagen IV, fibronectin* and *tenascin* in 34 cases of salivary glands tumors: *pleomorphic adenoma, myoepithelioma, basal cell adenoma, adenoid cystic carcinoma* and *polymorphous low grade adenocarcinoma*

According to this study it is concluded that:

1. *laminin* and *collagen IV* are present in all tumor types as well-organized duct-like structures that separate ducts from the stroma and/or surrounding cell clusters. In pleomorphic adenoma and myoepithelioma were observed fragmentations of the basement membrane and deposition of collagen IV and laminin around fusiforme cells.

2. *tenascin* was found in all tumors types stroma excepting the pseudocystic spaces of adenoid cystic carcinoma(only collagen IV and laminin were located in these spaces). The quantity and distribution of tenascin is variable depending of the tumoral type.

3. *fibronectin* was identified as a thin periductal layer in polymorphous low grade adeno-carcinoma (Raitz R, Martin MD, 2003).

The role of proteoglycans in early recurrence of metastatic potential of the salivary adenoid cystic carcinoma has been demonstrated through a survey in 2009 (Hong S, W Jie et al.) which showed that, by inhibiting the proteoglycans synthesis it was significanntly reduced the cell adhesions and the invasiveness of the malignant cell lines and also the incidence of metastatic disease ( particulary lung metastases).

Knowing the mechanisms controlling the morphogenesis and differentiation of the salivary glands is the first step in understanding their pathology. The identification, the description of qualitative and quantitative pathological changes of extracellular matrix components; distribution and restructuring abnormalities and the hypothesis about the ways in which all these modifications interfere in the salivary glands branching system mechanisms are of great practical importance in order to provide more efficient therapeuthic means.

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