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, glycosaminoglycans and proteoglycans), the specificity of these changes associated with certain pathological processes; 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 structure 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 maintaining 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 sialadenitis 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 immunohistochemically 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 immunoreactivity of 2,3,9, and 13 metalloproteinases and tissue inhibitors of metalloproteinases compared with the normal salivary gland. The exact aetiology and mechanism of atrophy of the glandular cells and lymphocytic infiltration associated with an increase of extracellular matrix in this disease are unknown, but pathological changes of glandular parenchyma and the prodigent character of the inflammatory progression cannot be explained merely by the secretory congestion and overpresion in the salivary ducts (Teymoortash A, Mandic R, 2004).

Fibrosis 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 Sjögren syndrome. Some studies have demonstrated the effect of matrix metalloproteinases on matrix proteins, basement membrane and stroma of labial salivary glands in Sjögren syndrome, in the same time was analyzed the integrity of the acini and ducts as well as the glandular function. It was found an increase of proteolytic 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. Immunohistochemical 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
dispose of different matrix components may
explain the postirradiation fibrosis and apoptosis;
the extracellular hypoxic enironement 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 pleomorh 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 interactions 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 tenasin 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. tenasin 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 tenasin 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 therapeutic means.

References


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