

# The Role Played by Growth Factors TGF- $\beta$ 1, EGF and FGF7 in the Pathogeny of Oral Pseudoepitheliomatous Hyperplasia

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**ABSTRACT:** Pseudoepitheliomatous hyperplasia is an epithelial proliferation that develops in the dermis or lamina propria. It is a lesion associated to another pathology, which appears as a response to a great variety of infectious, neoplastic, inflammatory or traumatic stimuli. The etiopathogeny of this lesion is not clear yet. Therefore, we performed an immunohistochemical study on a group of 20 cases of pseudoepitheliomatous hyperplasia cases associated with inflammatory and neoplastic conditions, by investigating TGF $\beta$ 1 (Beta growth and transformation factor), EGF (Epidermal growth Factor), and FGF7 (Fibroblast growth factor) expressions during in its development. The TGF- $\beta$ 1 expression was recorded in all the layers of the oral hyperplastic epithelium, going from the basal to the superficial layers, but with a different immunoreactive pattern, according to the region. Our study showed the absence of EGF immunoexpression in the carcinomatous proliferation areas associated to pseudoepitheliomatous hyperplasia and an almost exclusive presence in the hyperplasia lesions associated with inflammatory conditions (in about 30% of the investigated lesions) of a expression varying from poor to moderate for EGF. According to our investigations, we observed the presence of an immunolabeling for FGF7 in 80% of the investigated cases of pseudoepitheliomatous hyperplasia, a maximum of intensity being observed within the cases associated with inflammatory conditions.

**KEYWORDS:** pseudoepitheliomatous hyperplasia, immunohistochemistry, TGF- $\beta$ 1, FGF7

## Introduction

Pseudoepitheliomatous hyperplasia is a reactive benign lesion characterized by the epithelium hyperplasia as “tongue-like” projections in the dermis or lamina propria, sometimes having a pseudoinvasive aspect [1,2,3]. The lesion was also called pseudocarcinomatous hyperplasia [1,3]. In time, this entity was also reported as: “invasive acanthosis”, “verrucous epidermis hyperplasia” and “carcinomatoid hyperplasia”.

This lesion develops as a response to a great diversity of infectious, neoplastic, inflammatory or traumatic stimuli [2,3], being associated to different pathologies. Zayour and Lazova (2011) grouped the etiopathogenic conditions associated to pseudoepitheliomatous hyperplasia into 4 large categories: infectious, neoplastic, dermatoses with chronic irritations and inflammations, and various other pathological processes [4].

The association of pseudoepitheliomatous hyperplasia with multiple etiopathogenic conditions suggests the involvement of various intra-cellular signaling within the pathogeny of

these lesions, which is why we proposed to investigate the role played by markers TGF $\beta$ 1 (Beta growth and transformation factor), EGF (Epidermal growth Factor), FGF7 (Fibroblast growth factor) in the development of hyperplasia.

## Material and Method

An immunohistochemical study was performed on the material collected from a group of 20 patients, the histopathological samples coming from the cases of the Pathology Department within the Clinical Emergency County Hospital of Craiova, being represented by paraffin blocks from which there were first cut seriate sections for confirming the pathology and then for immunohistochemistry analysis. Tissue samples were taken from the patients admitted to the Oro-Maxillo-Facial Surgery Clinic within the Clinical Emergency County Hospital of Craiova, between 2012 and 2014. Every patient included in the study gave his/her written consent to participate in this study, the whole protocol being subjected to the corresponding ethical procedures. The patients included in the study were aged between 26 and

86 years old, the average age being of 46 years old. The patients were mainly males, the men-women ratio being of 3:1. Topographically, 10 lesions of pseudoepitheliomatous hyperplasia were located in the tongue, 6 in the jugal area and 4 in the gums. 7 lesions were associated with inflammatory conditions, 10 with oral squamous carcinoma and 3 with granular cell tumor.

The immunohistochemical study utilized primary antibodies raised in mouse or rabbit against human epitopes (Table 1). The serial 4 $\mu$ m-thick sections were subjected to microwaving in citrate buffer for antigen retrieval, endogenous peroxidase inhibition by incubating them for 5 minutes in 3% oxygenated

water, and blocking of non-specific antigen-binding sites with skimmed milk. The sections were subsequently incubated with the primary antibody overnight at 4°C, followed by a wash in a Tween-Phosphate buffer solution. The primary antibodies were then amplified with a LSAB (Labelled Streptavidin-Biotin2 System, Dako, Redox, Romania code K0675), and the result of these reactions was visualized with the 3,3'-diaminobenzidine tetrahydrochloride (DAB) chromogene (Dako, 3467).

The images were captured using Nikon Eclipse 55i microscope (Nikon, Apidrag, Bucharest), equipped with a video camera with a 5-megapixel cooling system and the Image-Pro Plus software.

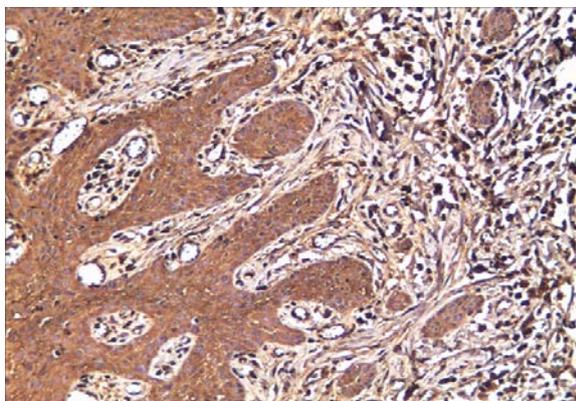
**Table 1. Antibodies used in the study of oral pseudoepitheliomatous hyperplasia**

Antibody	Clone/Manufacturer	Dilution	Antigen retrieval	Positive control
TGF $\beta$ 1	3C11/ Santa Cruz Biotechnology	1:250	Citrate, pH 6	Kidney
EGF	Polyclonal / SDIX	1:100	Citrate, pH 6	Salivary gland
FGF7	Polyclonal / Sigma-Aldrich	1:40	Citrate, pH 6	Appendix

## Results

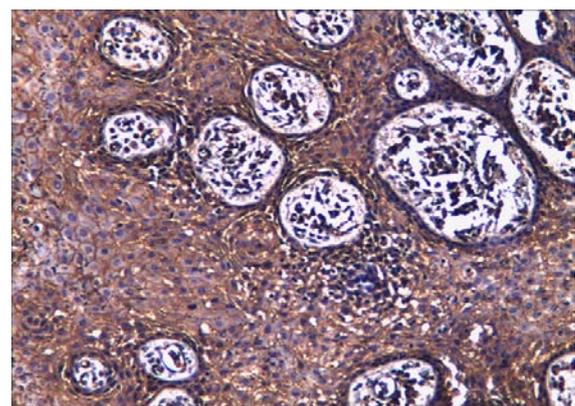
### Expression of TGF- $\beta$ 1

In the lesions of pseudoepitheliomatous hyperplasia we observed the existence of two different types of immunoreaction for the TGF- $\beta$ 1 factor. Thus, in the spinous layer, from the acanthosis areas, the reaction pattern was a membranous and pericellular, the expression being more important in the superficial layers. In the epithelial elongated growths that descend deeply in the lamina propria, the immunoreaction pattern mainly became a cytoplasmic one (Fig. 1).



**Fig. 1. Pseudoepitheliomatous hyperplasia-positive TGF- $\beta$ 1 reaction with cytoplasmic pattern in the epithelial apices. IHC-TGF- $\beta$ 1 staining (brown), x100**

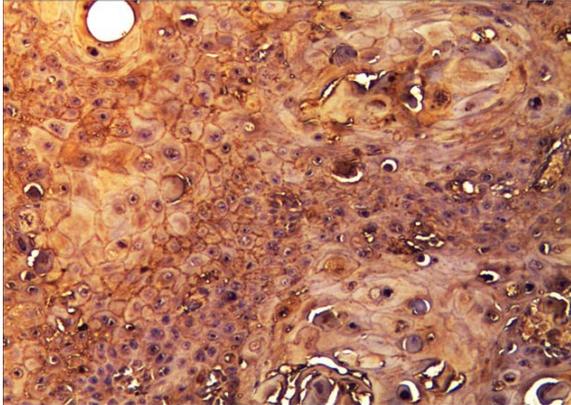
This type of immunoreaction was present more frequent especially in the cases of pseudoepitheliomatous hyperplasia associated with inflammatory conditions. In these cases, there was also present an intense cytoplasmic expression in the vascular endothelial cells and in the inflammatory cellular elements from the underlying lamina propria of these lesions (Fig. 2).



**Fig. 2. Pseudoepitheliomatous hyperplasia-positive TGF- $\beta$ 1 reaction in the vascular endothelial cells and inflammatory cellular elements in the underlying lamina propria. IHC-TGF- $\beta$ 1 staining (brown) x100**

In the pseudoepitheliomatous hyperplasia lesions associated with oral squamous carcinoma, strictly in the carcinomatous proliferation areas, TGF- $\beta$ 1 expression was higher than in the hyperplasia lesions. The

expression of carcinomatous cells was a membranary and diffusely cytoplasmic one (Fig. 3), the cytoplasmic positivity being also present in the tumor stromal cells.

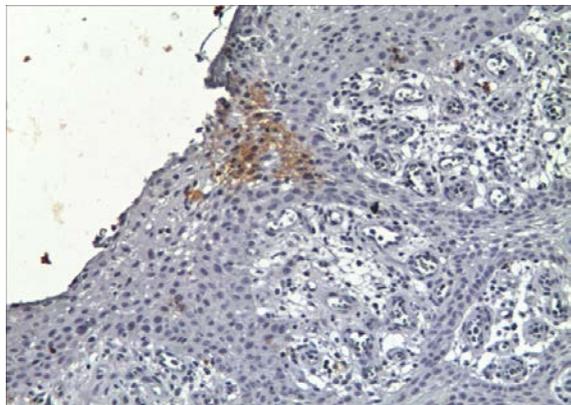


**Fig. 3. Pseudoepitheliomatous hyperplasia-membranary and cytoplasmic positive TGF- $\beta$ 1 reaction in the carcinomatous proliferation areas associated with oral squamous carcinoma. IHC-TGF- $\beta$ 1 staining (brown) x100**

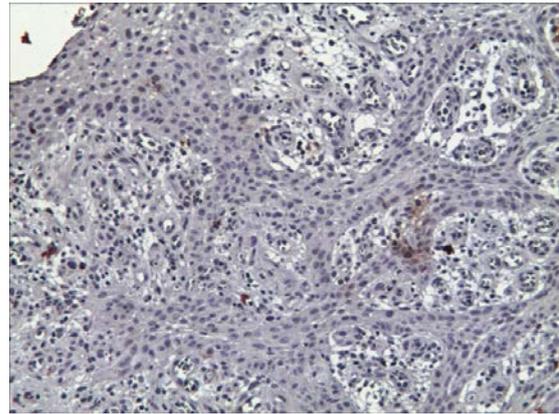
### Expression of EGF

In the immunoreactive cases, the reactions for EGF was present in the spinous layer, commonly in the superficial part of the hyperplastic lesions (Fig. 4) and more rarely in the epithelial cusps and within the lamina propria (Fig. 5). The immunoreaction pattern was a granular cytoplasmic one.

In the cases associated with oral squamous carcinoma we did not observe the presence of the EGF immunoexpression in the carcinomatous proliferation areas. Still, both in the lamina propria from the hyperplasia lesions, as well as in the tumor stroma or in the lamina propria of the lesions associated with inflammatory conditions, we observed a variable expression for EGF in the fibroblasts and in some of the present inflammatory cells.



**Fig. 4. Pseudoepitheliomatous hyperplasia-moderately positive EGF reaction in the spinous layer of the superficial area of the lesions. IHC-EGF staining (brown) x100**



**Fig. 5. Pseudoepitheliomatous hyperplasia-poorly positive EGF reaction in the epithelial networks of the sublesional lamina propria. IHC-EGF staining (brown) x100**

### Expression of FGF7

We observed the presence of immunolabeling for the FGF7 growth factor in the areas of pseudoepitheliomatous hyperplasia (80% of the lesions).

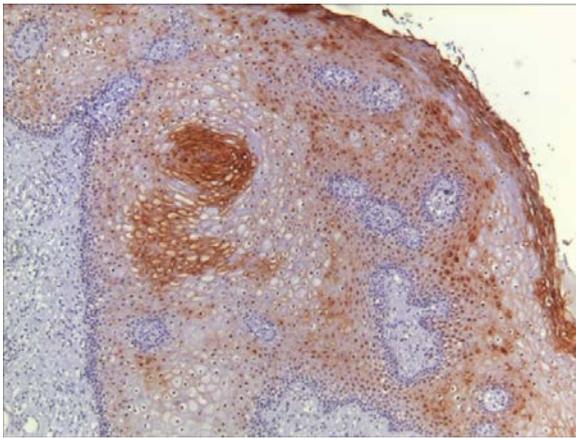
The most intense immunoexpression was observed in the spinous layer, namely in the lower and upper layers of the spinous layer, especially the superficial layer (Fig. 6).

In the lower layers, the expression was much more prominent in the acanthosis areas. The immunoexpression pattern was mainly a membranous and nuclear one. The nuclear expression was present in almost the entire thickness of the lesion epithelium, except for the basal and parabasal layer.

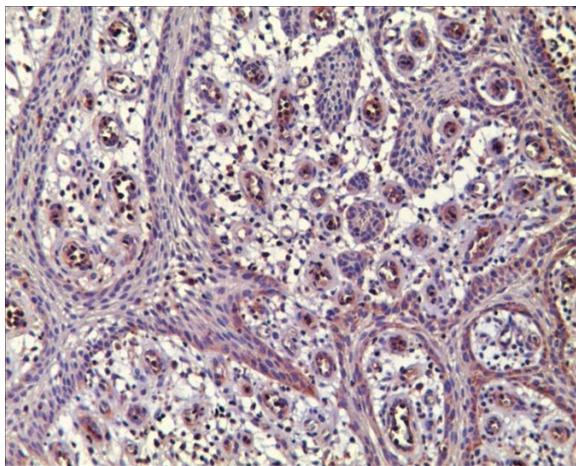
The immunoexpression was also evident in the sublesional lamina propria, namely at cytoplasmic level in the fibroblasts, vascular endothelial cells and some of the inflammatory cells present at this level (Fig. 7).

In the cases associated with oral squamous carcinoma, the FGF7 expression was also observed in the carcinomatous proliferation areas, still with a much lower intensity than in the pseudoepitheliomatous hyperplasia areas (Fig. 8).

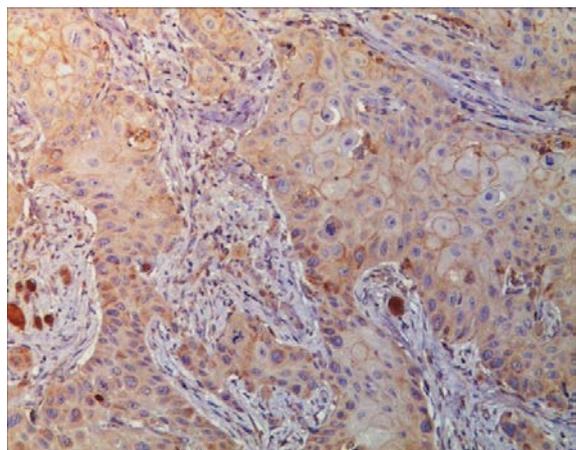
The reaction pattern was a mainly membranous one. Still, an expression comparable with the one from the hyperplastic lesions was observed in the tumor stroma of fibroblasts, macrophages and endothelial cells of the tumor vessels.



**Fig. 6. Pseudoepitheliomatous hyperplasia-intensely positive FGF7 reaction in the cells of the spinous and superficial layer. IHC-FGF7 staining (brown) x40**



**Fig. 7. Pseudoepitheliomatous hyperplasia-positive FGF7 reaction in the fibroblasts, vascular endothelial cells and some of the inflammatory cells in the sublesional lamina propria. IHC-FGF7 staining (brown) x100**



**Fig. 8 Pseudoepitheliomatous hyperplasia associated with oral squamous carcinoma-cytoplasmic positive FGF7 reaction in the tumor stromal fibroblasts and macrophages, and a poor membranary reaction in the carcinomatous cells. IHC-FGF7 staining (brown) x100**

## Discussion

Not until now there were clarified the etiopathogeny and molecular mechanisms on which pseudoepitheliomatous hyperplasia etiopathogeny is based.

Grunwald and colleagues were among the first to suggest that the lesion may develop from the skin appendix, more exactly from the follicular infundibulum and eccrine glands [1]. The problem of the glandular or follicular origin seems to have been clarified a lot later by Hanly and colleagues, who showed the glandular origin of the hyperplastic lesion, as in the mucous surfaces such lesions develop in the areas rich in minor salivary glands, and, as a consequence, at skin level, this lesion would develop from the eccrine glands [5]. Still, Tuttle and colleagues described 25 cases of basocellular carcinoma with infiltrative and morpheaform variants associated with pseudoepitheliomatous hyperplasias that presented a differentiation pattern of the follicular type [6]. The authors concluded that skin pseudoepitheliomatous hyperplasia could have its origin both at skin level and in skin appendices.

The association of pseudoepitheliomatous hyperplasia with a variety of etiopathogenic conditions suggests the involvement of various ways of intracellular signaling in the pathogeny of these lesions [7]. Thus, a series of studies suggested the intervention of some growth factors in the etiopathogeny of these lesions, namely of EGF and of TGF $\alpha$  (Alpha Transformation and Growth Factor) [8,9,10]. Other authors suggested the intervention of the TNF- $\alpha$  factor and of interferon- $\gamma$  in the genesis of hyperplastic lesions associated with skin leishmaniosis, taking into consideration their sub-expression in the papillary dermis underlying to hyperplastic lesions [11].

## Expression of TGF- $\beta$ 1 in oral pseudoepitheliomatous hyperplasia

TGF $\beta$  and the TGF $\beta$ -similar molecules are members of a large super family of over 40 secreted cytokines, including, alongside TGF $\beta$ , the bony morphogenic proteins (BMPs), activin, nodal, lefty, myostatin, the antimulerian hormone and the growth differentiation factors (GDFs) [12]. These cytokines control numerous biological functions, among which: proliferation, apoptosis, embryo development, stem cell survival, cellular differentiation, cellular migration and immune system regulation [13,14]. TGF- $\beta$  is found as 3 isoforms called TGF- $\beta$ 1, TGF- $\beta$ 2 and TGF- $\beta$ 3, scattered

ubiquitary and that may influence most of the human tissue types.

Strictly regarding the localization in the head and neck, Lu and colleagues showed a super expression of TGF- $\beta$ 1 factor in squamous carcinomas of the head and neck and in their adjacent tissues, in comparison to the level of its expression in the normal tissues at this level [15].

In the normal oral epithelium, almost similar to our results, Karatsaidis and colleagues found an expression for the active form of the TGF- $\beta$ 1 factor only in the granular layer and the upper layers of the spinous layer, the maximum of intensity being recorded in the upper part of the spinous layer [16].

In the study performed by us, the TGF- $\beta$ 1 expression was recorded in all the layers of the hyperplastic oral epithelium, going from the basal one until the superficial layers, still with a different immunoreactive pattern according to the region involved. Thus, in the spinous and superficial layers, the expression was a membranous and pericellular one, the maximum of expression being recorded at this level. In the basal and parabasal layers, the membranous expression was lower and a diffuse cytoplasmic expression was also present. The latter pattern was more highlighted in the elongation areas of the epithelial apices. Moreover, the maximum of expression was observed in the cases of pseudoepitheliomatous hyperplasia associated with inflammatory conditions, the cytoplasmic expression for TGF- $\beta$ 1 being present in these cases also in the vascular endothelial cells and the inflammatory cellular elements of the underlying lamina propria.

### **Expression of EGF in oral pseudoepitheliomatous hyperplasia**

EGF is the main representative of the growth factor family derived from the epidermis, also including the EGF-similar growth factor that binds heparin (HB-EGF), TGF- $\alpha$ , amphiregulin, epiregulin, epigenin, betacellulin, neuregulin-1,2,3 and 4 (NRG1,2,3 and 4) [17]. EGF is a low molecular weight polypeptide that was purified for the first time in the mouse submandibular gland and plays major parts in the proliferation, differentiation and survival of cells [18].

A series of studies showed that EGF modulate the growth and differentiation of various cancer cells, as well as of normal epithelial cells [19,20].

In the study performed by Christensen, there was highlighted the presence of an immunoreaction for the growth factors EGF

and TGF- $\alpha$  in the normal oral mucosa adjacent to oral squamous carcinomas from 55 patients, especially in the cellular layers above the basal layer [21]. In the study performed by Kannan and colleagues, there was shown that the EGF immunoreaction in the oral mucosa was significantly correlated with tumor progression [22].

Shirasuna observed a poor expression and even its absence for the EGF factor, both in the normal oral epithelial mucosa and in the epithelium from the leukoplakia areas or of the squamous carcinomatous proliferation areas. Still, the expression was present as a line in the subepithelial lamina propria, the reaction intensity growing together with the increase of the malignancy degree, the maximum of expression being recorded in the stroma of invasive squamous carcinomas [23].

Somehow similar to these results, our study showed the absence of the EGF immunoreaction in the carcinomatous proliferation areas, in those cases associated with pseudoepitheliomatous hyperplasia. Still, we highlighted the almost exclusive presence in the hyperplastic lesions associated with inflammatory conditions (in about 30% of the investigated lesions) of a reactivity varying from poor to moderate for EGF, with a cytoplasmic pattern, granular in the spinous layer cells and most highlighted in the superficial region of hyperplastic lesions.

### **Expression of FGF7 in oral pseudoepitheliomatous hyperplasia**

FGF7 is one of the 22 members of the polypeptidic growth factors FGF, factors involved in the regulation of the cellular proliferation, migration and differentiation during the vertebrate development, as well as in the homeostasis regulation, of the aggression response and the recovery of the tissues in adult animals [24]. Also known as the keratinocyte growth factor (KGF), it is released by the mesenchymal cells [25].

A series of *in vitro* and *in vivo* studies showed that the FGF7 factor has cytoprotective and regenerative effects over the epithelial tissues exposed to a great variety of toxic substances [26,27,28,29].

FGF7 proved to have mytogenic effects for numerous epithelial cell populations [30,31,32,33]. Moreover, this growth factor increases the migration of normal keratinocytes [34], most probably in association with the lesion healing response [35].

Strictly at oral level, there was proven that the oral fibroblasts are responsible for the FGF7 synthesis [36] and it was suggested that these would be much more potent in the synthesis of this growth factor in comparison to their correspondents at skin level [37]. In an experiment about the effects of fibroblasts and the FGF7 factor over the morphogenesis of reconstructed human oral epithelium, there was proven that the fibroblasts determined the thickness growth of the entire epithelium and the increase of the proliferation rate of basal cells, their presence deeply influencing the epithelial differentiation pattern, and it induced a commutation of the cell death pattern from the spontaneous one that takes place mainly in the basal layer to the one secondarily induced to the terminal differentiation in the superbasal layer [38].

According to our investigations, we observed the presence of an immunolabeling for FGF7 in 80% of the investigated cases of pseudoepitheliomatous hyperplasia, the maximum of intensity being observed in the cases associated with inflammatory conditions. In the pseudoepitheliomatous hyperplasia areas, the pattern of immunoexpression was a mainly membranous and nuclear one in the acanthosis and dyskeratosis areas, and also in the superficial parakeratosis layers, while in the epithelial apices, the expression pattern was a mainly cytoplasmic one in the basal layer cells. The immunoexpression was also highlighted in the lamina propria, especially in the cases associated with inflammatory conditions, the cytoplasmic expression being highlighted in the fibroblasts, blood endothelial cells and some of the inflammatory cells. The immunolabeling intensity was higher in the hyperplasia lesions, in comparison to the expression in the proliferative carcinomatous islands, where the immunoreaction pattern was a mainly membranary one.

## Conclusions

Our study highlighted different expressions for the studied growth factors. While the low EGF expression proves its limited involvement, the presence of and extended expression for TGF- $\beta$ 1 and FGF7 proves a clear involvement in the pathogeny of oral pseudoepitheliomatous hyperplasia.

The existence of certain intense reactions for the studied growth factors (TGF- $\beta$ 1, EGF and FGF7) in the sublesional lamina propria, the expression being more intense especially in the

areas where the epithelial apices deeply descend into the lamina propria, and especially in those cases associated with inflammatory etiopathogenetic conditions, suggests the presence of some epithelial-mesenchymal intricate mechanisms in the genesis of such lesions.

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