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DENTAL FOLLICLE: ROLE IN DEVELOPMENT OF ODONTOGENIC CYSTS AND TUMOURS

Dental Folikül: Odontojenik Kist ve Tümörlerin Oluşumundaki Rolü

Amila BRKİĆ[1]

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ABSTRACT

Dental follicle is ecto-mesenchymal derived component of the tooth germ, adjacent to the crown of unerupted tooth. It has many roles during tooth development and eruption. During the impacted tooth surgery, pericoronal and dental follicular tissues are enucleating. However, in rare cases they are submitting for histopathologic evaluation, although it is known, that these tissues are responsible for the occurrence and development of pathologic conditions, such as infections, odontogenic cysts, and tumors.Dental follicle was the subject of many immunohistochemical studies, which have shown a proliferative potential of the dental follicle cells justifying a profilactic removal of the impacted teeth.

According to review of relevant literature, the aim of this article is to describe and discuss importance of dental follicle in oral and maxillofacial surgery.

Kerwords: *Dental follicle, dentigerous cyst, impacted tooth, stem cells*

ÖZ

Dental folikül diş germini ektomezenkimal bağ dokusundan oluşturan, dişin kronun etrafında olan ve diş gelişiminde ve sürmesinde önemli rol oynayan yapıdır. Gömük7 diş operasyonu sırasında, perikoronal ve dental folikül dokuları enükle edilmektedir. Ancak bu dokuları, enfeksiyon, odontojenik kist ve tümör gibi patolojik durumların gelişiminden sorumlu olduğu halde, nadiren histopatolojik incelemeleri yapılmaktadır. Pek çok immunohistokimyasal çalışmalar dental folikülü incelerken, onun proliferatif potensiyelini göstererek, gömük dişlerin profilaktik çekimlerini önermektedir. Konu ile ilgili literatüre göre, bu derlemenin amacı dental folikülün oral ve maksillofasyal cerrahisinde önemli rol olduğunu göstermektir.

Anahtar kelimeler: *Dental folikül, dentigeröz kist, gömük diş, kök hücreler*

[1] Sarajevo University, School of Dentistry, Department of Oral Surgery, Sarajevo, Bosnia and Herzegovina.

Introduction

Dental follicle (DF) is ecto-mesenchymal derived component of the tooth germ. It is adjacent to the crown of impacted tooth, and has many roles during tooth development and eruption (1-3). Histologically it is composed of fibrous tissue, nests of odontogenic epithelium and reduced enamel epithelium (1, 3). Occurrence of the dental follicle starts in the period of the cup stage tooth's development by condensation of the ectomesenchymal cells surrounding the enamel organ and limiting the dental papilla. The enamel organ will produce enamel, the dental papilla will produce dentin and pulp, and the dental follicle will produce all the supporting structures of a tooth (1, 2). It means that the dental follicle is a source of stem cells, which can develop to fibroblasts of the periodontal ligament, cementoblasts, osteoblasts of the alveolar bone, adipocytes and neurons. This observation is consistent with the hypothesis of the presence of Mesenchymal Stem Cells (MSCs) with osteoblastic potential in DF (4).

Dental Follicle Stem Cells

The first isolated stem cells from the dental follicles of the impacted third mollars, were found out by Morsczeck et al. in the 2005. These cells were fibroblast-like cells (5). In one of our previous studies, using an universal kit that recognizes all p63 protein-isoformes, from which ΔNp63 is involved in adult stem/progenitor cell regulation, we have found out that the expression of p63 is stronger in dental follicle cells of completely impacted teeth, than it was in case of the dental follicles of partially impacted teeth. Theconclusion is that the these results might be a consequence of bigger number of stem cells in the completely impacted teeth group (6). There is an opinion that dental follicle has influence on stimulation of transforming growth factor beta-1 (TGF-β 1) in extracellular matrix, that helps fibroblasts to be differentiated into the cells of periodontal ligament (1). Transforming growth factor beta-1 (TGF-β 1) is protein encoded by the TGFB1 gene, that performs many functions such as control of cell growth, proliferation, differentiation and apoptosis. Experimental study in vitro has showed that population of the DF stem cells, comparing with population of DF non stem cells, increases in conditions of hipoxia. This might be associated with stimulation of inflammation with cell death and tissue damage occurring under severe and prolonged hypoxia (7). Schiraldi et al. (8) reported that dental follicle stem cells comparing with the dental pulp stem cells show greater migration and differentiation activity, thus ensuring a quick and appropriate periodontal tissue recovery.

Tooth Eruption

Dental follicle is responsible for the eruption pathway and later eruption of the tooth, regulating osteoclastogenesis and osteogenesis (1). In this period, it reaches its maximum weight; collagen content increases by 25% and proteoglycans by 45% (1, 9). Studies suggest that osteoclast precursors, which are mononuclear cells, are present into the dental follicle. Bone resorption and formation of the eruption pathway start after differentiation into osteoclasts, the multinucleate cells (10, 11). During trauma, DF might be disrupted or lost, which leads to blocking an eruption process and ankylosis of the involved tooth, as a consequence of the loss of periodontal ligaments (1, 9).

Hyperplastic Dental Follicle

Radiographically, dental follicle presents pericoronal radiolucency 2 to 2.5 mm in width. The size can help determine the difficulty of the extraction, thus if the dental follicle is wide in size (almost cystic), which is in the case of younger patients, less bone must be removed, making tooth easier to be extract (12). Otherwise, if the follicular space is narrow or non-existed, the difficulty of procedure increases including the time required for the procedure (12). Radiolucency of more than 2.5 mm is suggestive of a pathologic DF and development of a dentigerous cyst and other pathologies including odontogenic keratocysts and ameloblastoma. However, according to Slater's (13) radiographic follicular space until 4 mm, if the dental follicular tissue grossly measures 4 mm in thickness, it is not a characteristic of a pathologic lesion, but a hyperplastic (thickened) DF; hence, there is no space for fluid-filled pathologic cavity, which is the way of development of a dentigerous cyst. Hyperplastic (thickened) dental follicle, an enlarged follicular sac, presents a radiographic follicular space until 4 mm, with no space for fluid-filled pathologic cavity, which is the way of development of a dentigerous cyst (13). This abnormality of the dental follicle is responsible for delayed or arrested tooth eruption. The study of Kim et al. (14) have shown that hiperplastic dental follicles show a reduction of expression of matrix metalloproteinases (MMP-1 and MMP-3), important for root development and tooth eruption (14). Rare form of hyperplastic follicle is multiple calcifying hyperplastic dental follicle (MCHDF), first described by Sandler et al, which is characterized by numerous calcifications and rests of odontogenic epithelium (15, 16). Differential diagnostic, this lesion may be mistaken with central odontogenic fibroma, because of fact that both lesions have connective tissues, rests on odontogenic epithelium and calcifications (15). Because of mentioned, a correct diagnosis should be based on clinical, radiographic and histological findings. It is interesting that by reports, multiple calcifying hyperplastic dental follicle shows sex predominance to male and occures mostly in the lower jaw (15, 17).

Role in Development of Odontogenic Cysts and Tumors

Due to odontogenic components, which have shown a proliferative potential, dental follicle might be a source of development of different odontogenic cysts and tumors. Studies associated with pathologic changes of dental follicular tissues before two decades ago were mostly based on radiographic and histopathologic examinations. This explains the influence of chronic inflammation as the iritant which stimulate the proliferation of epithelial cells. According to Saravana and Subhashraj (18), the presence of squamous epithelium in the lining of a tissue, that surrounds the crown of an unerupted or impacted tooth, defines progression from dental follicle to dentigerous cyst. The most common pathologies associated with dental follicle are dentigerous cyst, keratocystic odontogenic tumor and ameloblastoma (6, 19, 20). However, cases of carcinomas, such as primary intraosseous carcinoma and the other tumors including sarcoma and fibromixoma were described too (21-24). Moure et al. (25), are in opinion that arrangement and distribution of collagen fibers in dental follicle tissue may also play an important role in development of

pathologic conditions. The results of their study showed that collagen in dental folicle and dentigerous cyst without inflammation have similar morphological characteristics. On the other hand, dentigerous cyst with inflammation and keratocystic odontogenic tumor exhibited comparable collagen organization, showing loose arrangement and presence of distinct layers (25). It is interesting that many authors have reported that the pathologic transformations are more common in male than female patients, in their 20- 30 years of age and the mandible is more common affected than maxilla (6, 20). Comparing the impacted tooth position and incidence of pathologic transformations in the dental follicle tissue, it was found, that the dental follicles, associated with vertical and mesioangular positions of the impacted lower third molars, are most prone to pathologic changes (26-28). However, report by Knutsson et al. (29) suggests that dental follicles of horizontally positioned impacted third molars are most commonly associated with pathologic changes. According to Pell&Gregory's classification (12), Simşek-Kaya et al. (28) reported that pathological changes were significantly higher in Class B when compared to Class C of impacted teeth.

Dental follicle was the subject of many immunohistochemical and genetic studies, which were investigated and showed a proliferative potential of the dental follicular cells. Some of the studies trying to explain a mechanism of the odontogenic cells proliferation and neoplastic transformation (30-38) have used different markers such as bcl-2, proliferating cell nuclear antigene (PCNA), mini-chromosome maintenance protein 2 (MCM-2), p53, proliferating cell nuclear antigen (PCNA), epidermal growth factor receptor (EGFR), Ki- 67 and MCM-2 cell proliferation marker. Although many of the markers are "proliferating", some of them are known as the markers of the "apoptosis", which may also have a role in pathogenesis of the dental follicle. It appears that inhibiting apoptosis levels are more probable reason to accumulate cells in odontogenic epithelium of follicle, leading to cystic lesions and odontogenic tumors (3). By results of Matsumoto et al. (30), who found out a weak expression of p53 in dental follicles with reduced and stratified squamous epithelium, and PCNA positive cells in basal and supra basal layers of the same epithelium, dental follicles possess proliferative activity. Biological behavior of dental follicles during the late stage of dental eruption may not be associated with deregulation of apoptosis and/or cell proliferation. Edamatsu et al. (34) is in opinion that apoptosis and cell proliferation of the dental follicle may play a role in the pathogenesis of dentigerous cyst. The results of the author's study have shown that markers of proliferation, such as Ki-67 and apoptosis-relatedfactor as single-stranded DNA (ssDNA), are more expressed in the dental follicles with inflammatory changes than those without these changes, while Ki-67 was more expressed in the epithelium with proliferative rate processes (34). This means that inflammation could reorder the cell turnover of the dental follicle epithelial components. Similar study was performed by Cabbar et al. (35), who were investigated Ki-67 and mini-chromosome maintenance protein 2 (MCM-2) proliferation markers in the dental follicle tissues. The authors concluded that the dental follicle's mesenchymal cell inflammation up-regulate the cell turnover of odontogenic epithelium and lead to proliferation (35). Ki-67 and mini-chromosome maintenance protein 2

(MCM-2) were also the subject of investigation of Güler et al. (38) in their study. The results revealed that almost 50% of dental follicleshad a squamous metaplasia with inflammatory cells, showing a high expression of Ki-67 and MCM-2, thus supporting that inflammation, may stimulate the squamous changes in healthy dental follicle tissue (38). Examinating a malondialdehyde (MDA) in dental follicles of asymptomatic impacted third molars, Tekin et al. (39) found out, that oxidative stress may occur in dental folicles leading to pathologic changes.

The expression of epidermal growth factor receptor (EGFR) may be also an indicator of increased potential for epithelial components of the dental follicle to become odontogenic cysts or tumors (31). However, some previous studies suggest that presence of EGFR in dental folicular cells of the human tooth germ is one of important factors involved in the development stage of the tooth, including eruption process (32, 33).

Although all of the mentioned studies emphasize the importance of proliferative potential and malignant transformation of the dental follicle cells, in practice, there is still no agreed protocol by which the dental follicle and pericoronal tissues, during impacted teeth surgery, would be submitted for histopathologic evaluation. Also, there are different opinions about removal of asymptomatic impacted teeth, especially third molars. Adeyemo (40) reported that incidence of prophylactic extractions vary from 18% to 54%. The study results of Saraçoğlu et al. (37), analyzing a proliferative potential of rests of odontogenic epithelium by evaluating MIB-1 positive cells, suggests, that removal of impacted teeth to prevent the possibility of neoplastic transformation of rests of odontogenic epithelium is not a justifiable rationale.

Assael (41) is in opinion that in patients over the age of 25, impacted teeth should be removed only if there are clinical or radiographic signs of a pathosis, due to the risk of bone loss and slower healing. Simşek-Kaya et al. (28) recommends monitoring and submitting for histopathological analyses of all surgically extracted follicle tissues. Kotrashetti et al. (42) and Brkić et al. (6) are, also, in same opinion for histopathologic evaluation of dental follicular and pericoronary tissues, even in cases when clinically and radiographically these tissues seem "normal". De Oliveira et al. (43) recommended that every asymptomatic, unerupted third molar should be followed up by radiographs, and the follicular tissue, obtained from such teeth, should be sent for a histopathology.

Conclusion

Dental follicle might be a source of development of different odontogenic cysts and tumors, because of odontogenic components, which justifies prophylactic removal of impacted teeth. In cases when clinically and radiographically dental follicle and pericoronary tissues seem normal, histopathologic evaluation is necessary to be performed due to potential pathologic development.

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Corresponding Author:
Amila BRKİĆ
Fra AndjelaZvizdovića 8, 71000 Sarajevo
Bosnia and Herzegovinia
e-mail: amilabrkic@hotmail.com