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THE REST CELLS IN PERIODONTAL REGENERATION - A REVIEW

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ABSTRACT

The major goal of periodontal therapy is periodontal regeneration including regeneration of alveolar bone, cementum and periodontal ligament fibres. Recapitulation of embryology shows the importance of Hertwig's epithelial root sheath (HERS), involved in cementogenesis and root formation. The remnants of these cells are found in normal periodontal ligament as the epithelial cell rests of Malassez (ERM). The cells of ERM are known to retain the functions of HERS by expression of various proteins and growth factors. These cells have stem cell characters and known to express stem cell related genes and thus lead to the hypothesis that they can contribute to true periodontal regeneration. This article reviews about the embryology and morphology of ERM. It intends to describe the functional roles of ERM not only in maintaining the periodontal ligament homeostasis but also in contributing to periodontal regeneration.

Keywords: Hertwig's epithelial root sheath, Epithelial cell rests Malassez, cementogenesis, stem cells, growth factors.

INTRODUCTION

Regeneration of periodontium rather than repair of lost tissues is the major goal of any periodontal therapy. Regeneration is the reproduction or reconstitution of a lost or injured part with form and function of lost structures restored.¹ Periodontal regeneration involves cementogenesis, osteogenesis, and formation of the periodontal ligament fibres. But current treatment strategies like non-surgical therapy, or surgical procedures with guided tissue regeneration or the use of growth factors, a complete periodontal regeneration remain clinically unpredictable. To achieve a complete regeneration, recapitulation of the processes of embryogenesis and morphogenesis becomes essential. The most important structure implicated in the development of periodontium is the cells of Hertwig's epithelial root sheath. HERS initiates

cementoblast differentiation and thus is known to be involved in the development of root and also in the formation of the attachment apparatus. After completion of the root formation, these cells remain quiescent as rest cells. These rest cells have been the subject of interest from the earliest days of periodontal research. Originally described as 'restes de l'organe de l'email' (Rests from the enamel organ) by Serres in 1817, are named as epithelial rest cells of Malassez in 1885 as a credit for his work on the cells and their distribution². These cells form part of normal periodontium and are considered as cells with no known function. Recent researches show that these cells retain the functions of HERS and play an important role in periodontal regeneration. This article briefs about the development, structure of the epithelial rest cells of Malassez, and intends to describe their

part in the maintenance of periodontal health and their putative roles in periodontal regeneration.

Development of the Epithelial Cell Rests of Malassez

Root development begins when the formation of anatomical crown is completed. The cervical margin of the enamel organ forms the cervical loop which consists of inner and outer enamel epithelium. The mitotic activity in the cervical loop initiates root formation. The cells divide to produce apical elongation of its double layer of epithelial cells. This structure is referred to as the Hertwig's epithelial root sheath, and it is the vehicle that is directly responsible for inducing the formation of root. As the first layer of dentin is formed, the HERS starts disintegrating and form fenestrations. Through these fenestrations, mesenchymal cells from the surrounding dental follicle enter and contact the newly formed dentin. These mesenchymal cells then differentiate to form cementoblasts forming cementum.

Once the root formation is completed, the remains of the Hertwig's root sheath is represented by the Epithelial cell rests of Malassez.^{2,3,4}

Structure

The epithelial cell rests of Malassez (ERM) were originally described as small circular aggregates of cells in routine sections and are usually close to the cementum. In oblique sections of the periodontal ligament, these epithelial cell rests can be seen as a network, similar to a fishnet, surrounding the root.⁵ The question of continuity or otherwise is important. If the network is continuous, covering the whole root, it shows that it could play some local physiological role in the functioning of the periodontal ligament. On the other hand, if the continuous network were absent over the ligament it rules out any possible role contributing to the local physiological functioning of the periodontal ligament.

They are comparatively close in the gingival region; more prominent in the mesial side of

molars than distal side. Eventhough the cell rests may persist throughout life, they decrease in prominence with age. The mode of distribution also varies with age. In first two decades, the ERM are more common in apical third of the periodontal ligament and in old age, the distribution is such that - 53% is found in cervical third, 26% in middle third and only 21% in apical third.⁶ Yamasaki and Pinero described three morphological subtypes of these cells as - Resting epithelial rests of Malassez, Proliferating epithelial rests of Malassez, Migrating epithelial rests of Malassez.⁷ This classification shows that cells of ERM are not resting but can get activated and subsequently proliferate on some stimuli like inflammation or any other environmental changes.

Protein expression by ERM

Different types of proteins are expressed by ERM and these can be broadly classified as cytokeratins and neuropeptides. Studies with immunohistochemistry demonstrate the expression of cytokeratins in ERM. Cytokeratins 1, 2, 5, 6, 7, 8, 10, 11, 16, 18 and 19 are specifically identified in humans which confirm the epithelial phenotype of these cells.⁸ They express a number of neuropeptides that includes calcitonin gene-related peptide, substance P, vasoactive intestinal peptide, tyrosine receptor kinase A and parathyroid hormone related protein.⁹

ERM also express matrix macromolecules like, glycosaminoglycans, hyaluronic acid, dermatan sulphate, chondroitin sulphate and type IV collagen; fibronectin, laminin and laminin-5; and proteins that are more commonly associated with mesenchymal tissues like osteopontin (OPN), bone sialoprotein (BSP) and osteoprotegerin.¹⁰

Growth factors like granulocyte-macrophage colony-stimulating factor (GM-CSF), epidermal growth factor, bone morphogenetic proteins, enamel matrix proteins (EMP) amelogenin and enamelin¹¹ and various cytokines like interleukin-1 α , interleukin-6, interleukin-8 and β defensin

(BD-1), prostaglandins E and F ^{12,13} are found to be expressed by ERM.

Putative roles of ERM in periodontium

Initially it was supposed that ERM were either quiescent or involved only in generating diseases like periapical cysts, marginal periodontitis or periodontal pockets. This view has been changed with the evidence of expression of various proteins by these cells. Now it is believed that these cells have some putative roles in:

1. Regulation & maintenance of the periodontal ligament space
2. Prevention of root resorption & alveolodental ankylosis
3. Maintenance of homeostasis in periodontium
4. Induction of acellular cementum formation
5. Cementum repair and regeneration
6. Stem cells and periodontal regeneration.

Maintenance of the periodontal ligament space and prevention of ankylosis

Several studies show the relationship between periodontal ligament homeostasis and cell rests of Malassez and their role in maintenance of the periodontal ligament space.

The meta-analysis in the evolution of Hertwig's epithelial root sheath showed that only in mammalian dentition no ankylosis is seen. This is because the root sheath is continuous along the root surface and so their remnants.¹⁴

Loe and Waerhaug did tooth transplantation experiments and noted that ankylosis did not occur after tooth transplantation in areas where periodontal ligament was vital with rest cells. It resulted in ankylosis, in areas where the ligament was dried or physically removed before reimplantation. They concluded that normal periodontal ligament was established only in areas where the vitality of the rest cells was maintained.¹⁵

Usually dental traumas cause ankylosis due to the destruction of ERM cells. During orthodontic treatment ankylosis does not occur. This is

because ERM cells are not destroyed. They participate in the induced tooth movement and increase the production of Epidermal Growth Factor (EGF), prostaglandins and stimulate bone resorption while maintaining periodontal ligament space.^{16,17}

Maintenance of the periodontal ligament homeostasis

Maintenance of the periodontal ligament homeostasis is mainly accomplished by the expression of proteins like epidermal growth factor, hyaluronidase, prostaglandins. Epidermal growth factor stimulates osteoclastogenesis and thus induces bone resorption. It also stimulates mitosis in many cell types like epithelial cells, fibroblasts, endothelium, chondrocytes, smooth muscles and hepatocytes and plays an essential role in tissue repair. There is constant release of EGF by ERM cells that will induce resorption of the alveolar bone surface, thus ensuring the preservation of the periodontal ligament space within a range of 0.20 and 0.40 mm ¹⁷ (i.e., 0.25 mm on average).

Cementogenesis and cemental repair

The fact that ERM can express a number of cementum-related proteins, (osteopontin and bone sialoprotein) associate them in cementogenesis and cemental repair. These proteins are found to be expressed by cementoblasts along the root surface.

Both BSP and OPN are expressed by cells related to the formation of mineralized tissues, like bone and cementum while OPN is also expressed by cells within the newly forming periodontal ligament. It shows that BSP is localized in cementum and bone while OPN is distributed in the periodontal ligament, cementum and bone.^{18,19}

OPN has been found to be involved in the regulation of ectopic crystal formation, i.e., in controlling the extent of hydroxyapatite crystal nucleation and/or growth. OPN has been stated to inhibit apoptotic events, like those associated with

inflammation.²⁰ This ability suggests that they may have some significance in the regulation of cells during cementogenesis and during wound healing.²¹

BSP acts as an adhesion molecule, maintains applicable cells and acts as an initiator of mineralisation at the root surface. The temporal and spatial expression during cementum formation and bone formation is consistent with its role in promoting mineral formation.²²

Role of ERM in periodontal regeneration

Periodontal regeneration involves interaction of several cell types, including gingival fibroblasts (GF), periodontal ligament fibroblasts (PDLF), cementoblasts and osteoblasts, macrophages and endothelial cells.

The current treatment modalities mostly are involved in the repair of damaged periodontium rather than regeneration i.e., they do not regenerate cementum or form attachment of new connective tissue fibers. The fact that ERM are involved in cementogenesis and cementum repair suggests that these cells can play a role in bringing true periodontal regeneration.

It is also shown that ERM express enamel matrix proteins amelogenin and enamelin. Such proteins are known to induce the formation of the periodontal attachment during tooth formation. Enamel matrix derivatives enhance the expression of tissue-specific maturation markers like alkaline phosphatase, collagen, osteocalcin, etc. Now, emdogain (Enamel Matrix Derivative), the commercially available form of enamel matrix proteins, is largely used in periodontal therapy as an alternative for achieving periodontal regeneration. It acts as a tissue-healing modulator taking off the events that come about during root development and helps to kindle periodontal regeneration. Thus ERM can be used as a source of enamel matrix proteins and thus in periodontal regeneration.^{23,24}

Stem cell characters of ERM

Cells of ERM are also found to have primitive stem cell characters i.e., those of embryonic stem cells and epithelial stem cells. Expression of epithelial stem cell-related genes such as ABCG2, ANP63, p75, EpCAM, Bmi-1 and embryonic stem cell markers like Oct-4, Nanog, and SSEA-4 have been detected by the studies done by Nam H et al., 2011. They also demonstrated that the expression of these stem cell markers was also found to be maintained during further sub-cultures and showed various expression levels of these genes at each passage, maintaining their expression right through the passages.²⁵

Xiong J et al in 2012 stated that cells of ERM have unique stem cell characters. They by their in vitro studies showed that these cells can undergo epithelial-mesenchymal transition i.e., these cells can differentiate into osteocytes/cementocytes, adipocytes, or chondrocytes, which are the cells of mesodermal origin. They also demonstrated that these cells can differentiate into neural cells under suitable conditions.²⁶

The findings that ERM express stem cell related genes and their pluripotent nature suggest that epithelial cell rests of Malassez can be used as a source of stem cells in accomplishing tissue engineering.

CONCLUSION

A true periodontal regeneration requires the formation of bone, cementum and periodontal ligament fibres. Among the current regenerative techniques, none proved to be 100% effective as they lack in mimicking embryological formation of cementum or attachment apparatus. With the knowledge that ERM is involved in maintaining periodontal ligament homeostasis, aiding in cementum repair and regeneration and expressing proteins like OPN, BSP and enamel matrix derivatives and with stem cell markers, it is considered that these cells can serve as a source for complete periodontal regeneration. Further studies are needed to elaborate their role in

cementogenesis, and the nature of their stem cell characteristics so that with these epithelial cell rests of Malassez a true and complete periodontal regeneration will be possible in the future.

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