

Review Article

Cell Transplantation Promotes Healing of Periodontal Tissues

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INTRODUCTION

Periodontal disease is a major global public health issue and the effective therapy has been a challenge [1]. The application of cell therapy seems to be a viable strategy to enhance periodontal tissue regeneration [2]. Bone marrow derived mesenchymal stem cells and periodontal ligament progenitor cells have been found useful for periodontal tissue regeneration [3,4]. Recently, three dimensional (3-D) scaffolds and supporting matrices with natural or synthetic materials have been used [5-8]. The synthetic materials although, show predictable and reproducible mechanical and physical properties, lack sites for tissue adhesion and may need chemical modifications [9]. Nonetheless, they appear to enhance cell colonization, proliferation and differentiation [7,10]. In this article we review the usefulness of PL progenitor cells in healing of the periodontal tissues.

PL Cell Labeling and Cell-Tracking

Periodontal tissue healing is limited by the fact that most periodontal ligament (PL) cells do not undergo renewal and have limited mitotic activity [11,12]. A number of treatment approaches have been developed to promote cell proliferation and differentiation [13,14]. Encouraging results have been obtained after transplantation of epithelial cells [15,16] however, these results have been difficult to interpret and to distinguish between the recruitment and differentiation of host and transplanted cells [17,18]. To overcome these difficulties, cell-tracking studies have been used to study the migratory behavior of lac-Z-positive cells transplanted into rat brain or adult rat liver [19,20]. These results have shown that this labeling method could be used in the periodontal tissues for assessing the fate and differentiation of transplanted cells. Wei et al. [4] have reported that labeled transplanted mesenchymal stromal cells into periodontal defects of beagle dogs migrated through periodontal tissues and differentiated into osteoblasts and fibroblasts at 6 weeks.

Cell transplantation and tissue regeneration

The ex-vivo expanded Lac Z positive mouse mesenchymal PL and green fluorescent protein (GFP) and positive mouse embryonic stem (ES) cells transplanted at the periodontal wound-site in rats undergoing orthodontic tooth movement show enhanced capacity to differentiate to osteogenic and PL specific fibroblastic cell types with an increased number of

BSP, OPN and α -SMA labeled cells in the PL of treated animals that received orthodontic tooth movement, 24 hrs followed with cell transplantation (Nayak et al., 2008). We have shown, Lekic et al. [22] that the transplanted cells migrate to alveolar marrow following a brief homing at the wound site; differentiate to osteopontin (OPN), bone sialoprotein (BSP) and alpha smooth muscle actin (α SMA) expressing cell types in the PL after undergoing proliferation and initial differentiation in the alveolar bone marrow spaces. These cells then migrate to the periodontal wound site to regenerate the wounded PL and alveolar bone [22]. PL cells differentiated to osteogenic and non-osteogenic cell types and also to other organ specific cell types such as kidney, lung, spleen, brain, heart and liver. However, the transplantation of PL cells had no significant effect on the heart and liver. Transplantation of PL and embryonic stem (ES) cells increased the density of cellular matrices in the PL significantly; the PL cells showed the maximum effect on the PL extracellular matrix proteins. There was a significant increase in the fibronectin expression in the PL in treated animals. Fibronectin is a multidomain dimeric glycoprotein with multiple biological functions including cell adhesion, cell migration, embryonic cell differentiation and maintenance of cellular cytoskeleton [23]. Notably, no sign of rejection was found due to xenografting [21]. We examined different organs in rat to see if there were tumors in major organs, but visual inspection did not detect any. The main finding was that PL cells transplanted in vivo are capable of differentiating into specific organ cell types, other than the periodontal tissues. The ES cells differentiated into a broader range of organ specific cell types including PL, alveolar bone (AB), central nervous system (CNS) and cardiomyocytes and had a pronounced effect on the intercellular matrices in many organs compared to PL cells. However, the PL cells had pronounced effect on the extracellular matrix proteins in PL. These findings correlate with previous studies in which the ES cells have shown to differentiate to lineage specific functional cell types including

cardiomyocytes [24-27], kidney cells [28] and air way epithelial tissues [29]. Poulson et al. [30] have discussed the plasticity of adult stem cells suggesting that these cells may also give rise to different type of tissues other than the tissue of their origin.

Tissue specific differentiation of transplanted cells

Transplanted PL cells upon implantation migrate to alveolar marrow to home, proliferate and migrate Lekic et al. [22]. Interestingly the ES cells compared to the transplanted PL cells differentiated to a broader range of tissues and organ specific cell types that included cardiomyocytes, neuronal cell type, kidney tubular cells and Type II cells in the lung. Courax et al. [29] have also reported the differentiating ability of ES cells to air way epithelial tissues. The PL cells showed a higher degree of differentiation in the PL tissue environment as determined by the expressions of the cell differentiation markers such as OPN, BSP and alpha smooth muscle actin. The possible explanation for this is that the PL cells are at a more advanced state of differentiation than the ES cells. The ES cells are found to be more primitive progenitor cells carrying lineage specific genetic blue print that result in larger number of organ specific cell types [29]. To replace periodontal ligament cells in case of periodontal diseases or injury, the PL mesenchymal cells are more suitable than the ES cells. For other type of transplantation, for example myocardial diseases, the ES cells may be better suited over the PL cells. Results of this study support the findings of Bussolati et al. [31] that the stromal mesenchymal cells isolated from the target tissue or organ may in fact be effective, transplantable cells for its own regeneration. Based on our very recent data this statement is generally true but there are exceptions. For example the transplantation of stem cells isolated from the kidney underwent less differentiation into kidney tubular cells than the transplanted spleen cells (data not published).

The transplantation of ES cells resulted in a localized distribution of OPN, BSP and STRO-1 labeled cells in the PL. STRO-1 is a marker for stromal cell in bone marrow and STRO-1 positive cells which are capable of differentiating to functional osteoblasts [32] and have potential to generate cementum/PL like structures [33]. It is of no surprise that a significant number of STRO-1 positive cells were found in the bone marrow of animals receiving PL cell transplantation and undergoing orthodontic tooth movement. This may suggest that the marrow may contain pre-mesenchymal cells, which are activated as a result of transplantation. Recently, Seo et al. [33] have also reported that the PL stem cells express mesenchymal stem cell marker STRO-1 and CD 146 (MUC 18/s-endo). The latter marker has been shown to be expressed in human endothelial cells but absent from haemopoietic cells [34]. McKay et al. [35] have reported that the mesenchymal cells differentiate to chondrogenic lineage when cultured without serum in the presence of a transforming growth factor. Pittenger et al. [36] have reported that the mesenchymal stromal cells when cultured in the presence of dexamethasone and ascorbic acid differentiated to alkaline phosphatase positive osteogenic cell types.

The ES cells were more readily differentiable to cardiomyocytes than the PL cells. Mummery et al. [25] have shown that mouse and human embryonic stem cells differentiate

into cardiomyocytes. Several pyramidal cells in the cerebrum of treated animals were strongly OPN positive. Iczkiewicz et al [37] has reported the presence of OPN in the basal ganglia, however, the exact function of OPN in the CNS is not known. Recently, Stier et al. [38] showed that OPN is a hematopoietic stem cell niche component that negatively regulates stem cell pool size Yoon et al. [39].

A group of PL fibroblasts, which were positive to anti-macrophage antibody (ED1) at one end and negative on the other end, may represent a subset of specialized fibroblast cell populations in the PL, that engage in collagen synthesis via Golgi-endoplasmic reticulum and collagen breakdown via a phagosome-lysosome pathway. ED 1 is a lysosomal membrane antibody that has high affinity for mononuclear and multinuclear inflammatory cells of macrophage-phagocytic lineage [40]. The dual functioning fibroblasts may be a specialized group of cells, which are responsible in maintaining the collagen content of the PL. Le Hir and Kaissling [40], have reported antibodies against macrophages that overlap in specificity with fibroblasts. Collectively, results from this study may suggest that the PL or ES cells are capable of differentiating into osteogenic cell types as well as other tissue and organs specific cell types. Findings that mesenchymal cells are capable of differentiating into tissue/organ specific cell types *in vivo* make these cells very valuable in biotherapy of wounded tissues and organs. Overall, transplantation of undifferentiated PL progenitor/stem cells may successfully be used to treat injured/damaged periodontal tissues and other organ specific diseases.

FUTURE STUDIES

Although there has been significant research done to understand the effects of various growth factors, cytokines, hormones and transcription factors including mechanical force on the differentiation of stromal stem/progenitor cells, the information on the fate and differentiation of lineage committed transplanted cells and their ability to regenerate periodontal wounding is limited. Whether differentiated adult cells have the necessary cues to differentiate to other cell types require further research. If these cells can be induced *in vitro* in culture conditions to a state of stable differentiation, using a variety of growth and differentiation-promoting factors including hydrogel and scaffolds and synthetic materials such as poly (epsilon-caprolactone) or fibrin scaffold and can lead to stable terminal differentiation *in vivo*, then they can be useful in cell therapy. Recent reports that the transcription factors play a significant role in controlling the differentiation of periodontal stromal progenitor cells as well as maintaining the balance between the proliferation, apoptosis and differentiation also require further research. Many work on transplanted mesenchymal stem cells show that extensive cell loss occurs after one week of transplantation. This problem may be overcome by using composite hydrogel [41].

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