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REGENERATIVE ENDODONTICS-CHALLENGES AND FUTURE DIRECTION

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INTRODUCTION

Thus, there is a considerable interest in research and clinical studies aimed towards regeneration of a functional and healthy pulp- dentin complex.1, 2 The goal of Regenerative Dentistry is to induce biologic replacement of dental tissues and their supporting structures. The potential for regenerative dentistry is in large part due to advancements in biologic therapies that apply growth and differentiation factors which hasten or induce natural biologic regeneration. Most of the concepts have emerged from the growing fields of tissue engineering, which emphasizes the spatial assembly of distinct stem cells, growth factors and scaffolds to form a functional tissue or organ.3. Utilization of stem cells to regenerate the lost pulpal tissue may thereby reverse the tissue to its normal state. Regenerative endodontics deals with the healing of impaired dental tissues, including dentin, pulp, cementum and periodontal tissues. Thus, Regenerative endodontics has been defined as biologically based procedures designed to replace damaged structures such as dentin root structures and cells of pulp- dentin complex1. Presently, two concepts exist in regenerative endodontics to treat a non-vital infected teeth- One is the active pursuit of pulp- dentin regeneration to implant or regrow pulp (tissue engineering technology), and the other in which new living tissue is expected to form from the tissue present in the teeth itself, allowing continued root development (revascularization).4 12 Applying the tissue engineering technology to regenerate a functional pulp dentin complex would restore natural functions such as, formation of replacement dentin, maintenance of tissue immunity and neural sensation. From a tissue engineering perspective, the dental pulp may be relatively easier tissue to regenerate as the pulp occupies a relatively small volume and relatively simple cytoarchitecture as compared to complex organs such as heart and liver.5 Tissue engineering approaches include postnatal (adult) stem cell therapy, pulp implantation, scaffold implantation, three-dimensional cell printing, injectable scaffolds and gene therapy.

The pulp tissue repair/regeneration recapitulates tooth development. Despite the impressive progress in tissue engineering approaches to regenerative pulp therapy, numerous challenges remain. The associated broad spectrum of responses in pulp includes neural and vascular regeneration.

NERVE REGENERATION

Dental pulp is richly innervated. The main nerve supply enters the pulp through the apical foramen along with the vascular elements. Nerves proceed to the coronal area and form a plexus in proximity to the odontoblasts and finally enter the dentinal tubules. They include both sensory and sympathetic nerves. Their functions, locations and interactions with pulp, dentin, vasculature and immune cells are different. In general, the A type fibres are myelinated and C fibres are non-myelinated. (6) The cytochemical localization of neuropeptides, calcitonin-generelated peptide (CGRP), nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and neurofilaments vary with the type of nerve fibre. The temporal sequence of dental pulp innervation is dependent on gradients of neurotrophic growth factors emanating from the pulp cells, NGF, brain-derived neurotrophic factor (BDNF) and GDNF are expressed in dental pulp. Pulpal nerves play a key role in regulation of blood flow, dentinal fluid flow, and pressure. In addition, there is evidence for neural regulation of pulpal fibroblasts, inflammation and immunity. The innervation of the pulp has a critical role in the homeostasis of the dental pulp. Invasion of immune and inflammatory cells into sites of injury in the pulp is stimulated by sensory nerves. Sensory denervation results in rapid necrosis of the exposed pulp because of impaired blood flow and extravasation of immune cells. Reinnervation leads to recovery in the coronal dentin. Schwann cells appear to release neurotrophic growth factors and play a role in recruitment of sensory and sympathetic nerves during reinnervation. (7) Thus, the pulpal nerve fibres contribute to angiogenesis, extravasation of immune cells and regulate inflammation to minimize initial damage, maintain pulp tissue, and strengthen pulpal defence mechanisms. Bone morphogenic proteins have a role in reparative/regenerative

dentin formation. It is noteworthy that members of the BMP family have pronounced effects on neurogenesis. Thus, it 66 is likely Bone Morphogenic Proteins can be used for regenerative pulpal therapy and dentinogenesis may have concurrent beneficial effects on nerve regeneration. The increasing interest in tissue engineering of tooth must take in to account neuro-pulpal interactions and nerve regeneration. The challenges include, but not limited to nociceptive mechanisms, altered thresholds to pain in inflamed teeth and dental pain. Thus, the life of teeth can be possibly prolonged by preservation of pulp and odontoblasts and promoting repair and regeneration by the study of neuropulpal interactions. The recent progress in dental stem/progenitor cells and mechanism of dental pulp cells, assure advances in regeneration of nerves based on neuropulpal interactions. (6,8)

VASCULAR REGENERATION

The vascular system in the dental pulp plays a role in nutrition and oxygen supply and as a conduit for removal of metabolite waste. The cellular elements of the blood vessels such as endothelial cells, pericytes and associated cells contribute to pulpal homeostasis along with the nerves. Thus, the vascular contribution to regeneration of dentin-pulp complex is immense. Arterioles enter the pulp chamber through the apical foramen along with the nerve supply. The branching arterioles form a capillary plexus under the odontoblast layer. During development and regeneration there is increased vascular activity and blood flow. There is a common pathway of vascular reaction to varied stimuli such as chemical, physical including mechanical and thermal. This reaction includes a local inflammation and attendant dilation of blood vessels and increased blood flow. Extravasation of leukocytes and increased vascular permeability is a hallmark of early vascular response. Pulp vasculature plays an important role in regulating inflammation and subsequent repair and regeneration of dentin. There is an intimate association of the neural elements with vascular supply of the dental pulp, suggesting the interplay of neural and vascular elements and involvement in pulp homeostasis. (9) The critical importance of vasculature in tissue repair and regeneration is well known. Vascular endothelial growth factor (VEGF) is an excellent regulator of angiogenesis and is known to increase vascular permeability. VGEF induced chemotaxis, proliferation and differentiation of human dental pulp cells. In addition, human dentin matrix contains VGEF. The presence of VGEF in dentin and response of dental pulp cells to VGEF raises the possibility of the presence of endothelial progenitor cells in dental pulp alongside progenitors for odontoblasts 67 and neuronal cells. In view of the role of endothelial progenitor cells in vascularization during tissue regeneration, it is likely VGEF and vascular endothelial cells are critical for dentin regeneration. The utility of gene therapy in stimulation of vascular growth permits local stimulation of vascularization during regeneration. In fact, gene therapy using members of BMP family including BMP7 and GDF11 successfully induced dentin-pulp regeneration. Thus, the recent advances in vascular biology and VEGF and techniques of gene therapy will be of potential clinical utility in dentistry especially in endodontics. (8,10-11)

OTHER CHALLENGES ARE

Although the replacement pulp has the potential to revitalize teeth, it may also become susceptible to further pulp disease and may require retreatment; the implantation of engineered tissue also requires enhanced microbiological control methods required for adequate tissue regeneration. The success of clinical applications of pulp stem cells is limited by the culture conditions and the nature of microenvironment in which the primitive multipotent pulp stem cells are maintained and expanded. To improve the ability of dental pulp constructs to adhere to root canal walls, it seems that the ideal scaffold design is in the same shape as gutta-percha cones. Researchers had used single canal teeth and cylindrical scaffolds in an attempt to simplify the transplantation process.(12-14) A more complex root canal anatomy will require more complex scaffolds or the use of more flexible scaffolds to perform regenerative endodontics. Dental pulp tissue constructs adhered more completely to the coronal aspects of the root canal and less completely to the middle and apical aspects. This likely was caused by the increasing complexity of root canal anatomy toward the apex and the physical constraints of the scaffold materials, as well as the placement method. Since most of the tissue-engineered parts have been developed using very potent signal molecules to induce the transformation and the growth of the stem cells, a way has to be found to ensure that these transformation and growth will not continue beyond control when implanted. Matching the aging of the implanted tissue-engineered parts with that of the

surrounding tissues and organs is a great obstacle too. The patient and parents should be informed about the potential of minocycline in triple antibiotic paste to stain teeth, especially the anterior teeth. (12,15-16)

CONCLUSION:

The proposed therapies involving stem cells, growth factors, and tissue engineering all require pulp revascularization, in itself an enormous challenge. One of the most challenging aspects of developing a regenerative endodontic therapy is to understand how the various component procedures can be optimized and integrated to produce the outcome of a regenerated pulp-dentin complex. The future development of regenerative endodontic procedures will require a comprehensive research program directed at each of these components and their application to our patients.

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