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Stem Cells in Regenerative Endodontics: Review

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ABSTRACT:
Endodontics therapy is a useful and very effective treatment in the case of a tooth which has lost its vitality. Which ensures to save the tooth from removing. But currently the field has grown beyond our imagination. Regenerative therapy which has taken part in the field and is still undergrowth. Regenerative therapy is light that can enlighten the patients' functional stabilities after actual loss of the tooth vitality in patients with pathological conditions or traumatic conditions. Stem cells have the potential of regeneration and revascularization of pulp(1). Numerous studies on stem cells and tissue engineering have been conducted in the last several years which have developed into a separate section as regenerative dentistry. Stem cell therapy can improve tissue regeneration and boost the body's natural reaction to these tissue damage. There is lots of study research undergoing for further understanding of this stem cell mechanism and to work in clinical practices in a better way with good results.

I. INTRODUCTION:

Tooth is mainly composed of hard tissue and soft tissue. Hard tissue is the outer structure which covers the soft tissue portion, commonly known as pulpal soft tissue. This pulp has a role to maintain the vitality of the tooth(2).When any injury or infection like dental caries affects the tooth, the infection travels down from the hard tissue – enamel and dentin, towards the pulpal region, which generally causes slight discomfort and pain to patients that is considered as the signs and symptoms for beginning of pulpal infection; further leading to pulpal necrosis if not treated. Now the endodontic therapy which deals with necrosed pulp is the root canal treatment. One of the crucial and frequent procedures performed in dental offices is root canal therapy, which involves inserting dental materials inside the canal site to remove the diseased pulp and restore the tooth's vitality. The current objective of regenerative endodontics is to establish the necrosed pulp tissue's regeneration process. Root canal treatment has a 90% success rate where the 10% is either due to secondary caries or failure of restoration. The possibility of reinfection is still possible (3). The tooth is saved by RCT at the cost of losing its vitality and reduced strength. In case of reinfection of an RCT treated tooth the success rate of doing an RCT again will just decline the stability of the tooth by reduced strength and it's more prone to cracking or fracture easily(4). To overcome this problem, regenerative endodontics is capable of turning the table around. A little number of stem cells in the tooth pulp react to the advancement of caries and release substances that can cause pulp revascularization. (5) Based on their capacity for differentiation, stem cells can be categorized as totipotent, pluripotent, or multipotent. Let's try to see how different types of stem cells are utilized in regenerative endodontics and how effective they can possibly be.

1.Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent cells that can differentiate into all types of cells. Numerous tissues, including bone marrow, adipose tissue, and dental tissues, have been discovered to contain mesenchymal stem cells (MSCs) (6).The advantage of using MSC-like cells isolated from dental tissues for endodontic regeneration therapy is that they can be readily obtained from extracted teeth or from periodontal tissues that are part of the tooth extraction process. These characteristics are beneficial in endodontic regeneration(7). Here odontogenic mesenchymal stem cells were used and they play a crucial part in the formation of teeth and the healing of injuries.

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Most significantly, it was shown in functional dental pulp regenerated by exogenous odontogenic MSC transplantation, which responded to clinical testing in a manner comparable to that of normal dental pulp(8). So eventually, in clinical practice, odontogenic MSC-based dental pulp regeneration could turn out to be an effective technique for restoring important teeth. Choosing an appropriate scaffold and proper environment for regeneration of pulp will be the next aspect. Then the cells are transplanted into the treated canal to process the formation of pulp-dentin complex development. In addition to providing a scaffold for the formation of dentin tissues and the regulation of mineralization during dentin regeneration, cell aggregates have demonstrated endogenous preservation of normal cellular connections and extracellular matrix (ECM) that are comparable to their native atmosphere for MSCs(9). So eventually with creating a proper environment dentin-pulp complex can be a better approach for pulp regeneration in endodontics.

2.Dental pulp stem cells (DPSC):

When Dental pulp stem cells were integrated with scaffolds it resulted in the formation of a structure resembling pulp that exhibits an irregular shape(10). But with bio engineering using in vitro technique with the help of synthetic matrices made up of poly glycolic acid which has the capability to synthesize pulp-like tissue and dentine complexes(11). Dental pulp stem cells are frequently extracted from dental pulp, which typically contains a tiny quantity of them. At first they are isolated from extracted wisdom teeth. So this eventually proves that it has the capacity to repair the infected pulp by reversing the infection and creating a new pulpal tissue in the teeth.

3.Apical Papilla Stem Cells (SCAP):

SCAP are cells which are very sustainable and have the ability to keep the pulp living even under the pathological condition. This ability to survive from necrotic pulp is commonly seen in immature teeth and allows them to undergo root formation or apexogenesis under these states (12). They also consist of various markers such as CD24, which functions as a pluripotency marker, has been found to be intimately linked to SCAP, as evidenced by the fact that it is expressed only in SCAP(13). CD24 serves as a marker of undifferentiation, signifying that its presence correlates with a heightened stemness in the cell. So the thing we got to understand is these cells still have the capability to differentiate and transform into a wanted cell and carry on its normal function. Stem cells required vascular supply for the regeneration process so the SCAP cells are introduced and revascularized inside the pulp rather than performing an RCT. The only disadvantage is the amount of blood supplied to the teeth. Since the teeth only have a single blood supply which is apical foramen it is required to be at least 1.1-1.5mm for the healing rate and revascularization(14). SCAP can retain their ability to proliferate and differentiate even when there is existing periapical pathosis. In addition, they possess significant angiogenic properties that may enhance the revascularization process. Additionally, SCAP influenced by the apical tissues, migrate with the bloodstream to reside in the clot formed within the sterilized canal, thereby aiding in the regeneration of the dentino-pulpal organ and fostering tooth maturation(15).

4.Induced Pluripotent Stem Cells (iPSCs):

iPSCs may represent a novel approach for addressing issues related to both dentin and pulp tissues. miPSCs (mouse Induced Pluripotent Stem Cells**)** which distinctly indicate the expression of odontogenic and osteogenic genes after their induction, were integrated with epithelial mesenchymal cells for the regeneration to occur or to provide the proper matrix. In an in vitro experiment, small interfering RNA targeting matrix metalloproteinase-3 (MMP-3) was introduced into odontoblast-like cells that were derived from induced pluripotent cells (iPSc). The application of polyphosphate stimulated the expression of MMP-3, which physiologically enhanced both the proliferation and differentiation of these odontoblast-like cells (16). In a different work, dental pulp stem cells (DPSCs) were transformed to become iPSCs. The cells were subsequently implanted subcutaneously in mice after being seeded on dentin discs using PLLA scaffolds. It shows positive results with the mice(17). Whereas iPSCs preserved their odontogenic and mineralization capacity in vitro, they produced a pulp-like tissue with tubular dentin. iPSCs and Whole Tooth Regeneration along with surrounding structures and pulp like structure is well seen, because these miPSCs can clearly express odontogenic and osteogenic genes followed by implanting combination of epithelial and mesenchymal cells in a tooth germ in the subrenal mouse capsule(18).

5.Dental Follicle Progenitor cells(DFPCs):

Bone formation, formation of the cementum-periodontal ligament, and the regeneration of dentin-pulp-like tissue are all

attributed to dental follicle progenitor cells. This capability enables the regeneration of a fully integrated tooth root. These cells were implanted with the biological scaffolds and implanted into mice(19). After a period of eight weeks, they identified the cementum-periodontal ligament complex, along with the fibers of the periodontal ligament and blood vessels.They also noticed the reconstruction of dentin-pulp-like tissue in the meantime. Additionally, polarized odontoblast-like structures, collagen fibers, predentin, and dentinal tubules are present beyond the scaffolds, which eventually bring light to the regenerative pulp and root formation and later crown restoration is done. So this shows it is capable of producing bio-root which mimics the original tooth nature and also provides good functional masticatory properties(20).

6.Neural crest cells:

Neural crest cells are said to be multipotent and self renewable(21). With these characteristics they are said to be stem cell like cells.These cells have the capacity to develop into various types of tissues, including dental stem cells. Dental pulp is a specific form of mesenchymal tissue that originates from the neural crest during the embryonic phase. So they are called ectomesenchyme(22). These ectomesenchymal cells are responsible for formation of bones, oral muscles, craniofacial nerves, and teeth, tongue and dental ectomesenchymal stem cells (EMSC)(23). After various experiments, EMSCs constitute a very good alternative for root canal treatment in case of dental caries with infected pulp. It has been observed that dental pulp stem cells (DPSCs), when transplanted alongside synthetic scaffolds into the empty pulp of mice, can regenerate the tissue of the pulp chamber and build new layers of dentin from scratch(24).

7.Stem Cells from Human Exfoliated Deciduous Teeth (SHED):

The ability to develop into numerous cell types, include endothelial cells, adipocytes and neurons(25). SHED cells were initially extracted from human primary incisors. These cells display significant characteristics, including markers of mesenchymal stem cells (STRO-1 and CD146) and markers of embryonic stem cells (OCT4 and NANOG), indicating their stemness.The ability of SHED to stimulate in vivo dental pulp development was performed by SHED in biodegradable scaffolds prepared within human tooth slices of 1 mm thickness that were subsequently implanted in mice. One month later, the area where the scaffold had been was replaced by a pulp-like tissue with a circulatory network(26). Another study shows that after 28 days in vitro, SHEDs implanted into complete root canals with injectable scaffolds were able to proliferate in the root canal and express putative markers of odontoblast differentiation (DSPP, DMP-1, and MEPE). Moreover, when the roots with SHED were embedded within the subcutaneous space of mice, functional dental pulp was created in full-length root canals in vivo. After 28 days post-implantation, a tissue resembling human pulp primarily filled the root canal space where an injectable scaffold was utilized. This newly engineered pulp also deposits dental pulp and was able to produce the new dentin, as tetracycline injections were demonstrated, at an approximate rate of 10 µm per day(27).

8. Bone marrow and adipose tissue :

These bone marrow and adipose tissue derived cells are another source of pulp tissue regeneration. BMSCs and ADSCs were isolated with G-CSF-induced mobilization (MBMSCs and MADSCs are termed after the mobilization method). The experiment is done in a dog with completely closed apex at around 6-11 months of age (28). The entire pulp tissue is extracted, and the canals are expanded to access the apical foramen in incisors. Autologous transplantation of MBMSCs, MADSCs, and MDPSCs is performed within the pulp by incorporating a scaffold, and subsequently composite resin and zinc phosphate are used to fill the cavity. After a period of 14 days, this results in pulp-like connective tissue with vascularity. Further in-vitro odontoblastic differentiation occurred. According to recent research, transplanting MBMSCs or MADSCs with G-CSF can likewise create pulp and dentin, although on day 14, there was less volume of regenerated pulp tissue than with MDPSCs and G-CSF. However, G-CSF-mobilized MADSCs and MBMSCs for transplantation are alternatives to MDPSCs for regeneration of pulp, albeit with a slight drawback.(29).

9. Human Umbilical Cord mesenchymal stem cells :

The Human umbilical cord mesenchymal stem cells known as hUCMSCs, are collected from human umbilical cords obtained from patients who underwent Cesarean sections during full-term deliveries. These cells are protected by placental barriers so contamination is very low(30). hUCMSCs were allowed to grow in liquid extract of human treated dentin matrix (LE-TDM) in-vivo. For angiogenic potential the VEGF - Vascular

Endothelial Growth Factor is utilized to promote regeneration of dental pulp -like tissue that is vascular. Additionally, human umbilical cord mesenchymal stem cells (hUCMSCs) are co-transplanted alongside VEGF-induced hUCMSCs (V-hUCMSCs) to facilitate the regeneration of pulp-like structures.

Collagen-1 of 1 mg concentration used as Scaffold with the monoculture or co-culture of hUCMSCs and (V-hUCMSCs) induces and regenerates pulp-like structure in the root canal. Both cultures show pulp-like tissue formation. Collagen I lacks angiogenesis property but it is biocompatible for hUCMSCs and V-hUCMSC as scaffolds. Hence hUCMSCs are suitable for pulp complex regeneration, but with even more appropriate scaffolds provide better results for future advancement (31).

II. CONCLUSION:

Stem cells have a tendency to differentiate into unique cells that can produce a variety of tissues and can eventually bring changes using these stem cells for saving the vitality of the tooth. Pathology of dental caries can be severe and advanced in patients but only option is to treat the pathology and provide a better day to day life. With the current and future advancement of the tissue engineering and stem cells potential it is possible to revitalize the pulp after dental caries or other various pathologies. Definitely, regenerative endodontics will live up to its full potential. The field may sound complex, still it can create revolution and potential to change the world of dentistry in future.

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