EDITORIAL

Stem Cell Role in Regenerative Dental Medicine

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Regeneration therapies have widely permeated advanced research that aims to reproduce and repair a lost or damaged organ or tissue in order to restore the function and architecture as close to its original state as possible[1,2]. Tissue engineering refers to the process of regeneration using techniques such as scaffold based cell cultures, stem cell therapy, and biomolecular signaling.

Advances in gene-based knowledge on the stem cells within the stomatognathic tissues has contributed to the variety of pioneering treatment modalities[3]. Mesenchymal stem/stromal cells (MSCs) are currently thought to be ideal prospects for tissue replacement therapy and tissue engineering[4]. The clinical success of MSCs treatment is greatly influenced by the donor cells and immune cells[5]. Recent literature highlights the evidence for the regenerative potential of dental stem cells, which has further heightened the curiosity of scientist, researchers, and dental practitioners[6].

In advanced molecular dentistry, focus has been towards multidisciplinary approaches exploiting combination of advanced tissue engineering, stem cells, scaffolds, biomaterials, and digital technology that exhibit significant potentials for extra-oral and intra-oral regeneration[1]. Stem cells play a vital role in treatment modalities including tissue engineering of hard and soft tissue defects. Currently, substituting lost stomatognathic tissues such as dental pulp, salivary glands, temporomandibular joint and alveolar bone are set to be employed as regenerative medicine[2]. The process of collecting stem cells of dental origin is easy, convenient, and relatively noninvasive, with these cells having a plethora of potential therapeutic and regenerative roles in medicine and dentistry[7].

Mesenchymal stem cells (MSCs) are undifferentiated cells having potential to regenerate and differentiate into many different cell types[5]. Broadly, these can be classified as Adult Stem Cells (ASCs) and Embryonic Stem Cells (ESCs)[8]. The ASCs are limited in number and have 'multipotent' potential, which allows them to regenerate and convert into certain particular cell varieties, thereby contributing to the healing and maintenance of tissues. On the contrary, ESCs are considered 'pluripotent' and can differentiate into almost all cell lines, depending on the stimulus. However, ESCs are found in the blastocyst stage embryo, whereas ASCs have been isolated from skin, muscle, nerve, bone, and dental tissues.[8] As a result of the ease of accessibility of ASCs, recent advancements have led to the development of 'cell plasticity', which involves the reprogramming of ASCs to produce pluripotent stem cells, allowing them to develop into any cell lineage, depending on the stimulus[5]. In addition to bone marrow, where unspecialized cells known as 'stem cells' were originally exploited in regenerative medicine applications, it has been shown that they are found in many other sites of the body including dental pulp cells. The bone marrow and non-marrow tissues from extra- or intra-oral niches are two possible origins of the mesenchymal dental stem cells. The bone marrow-derived stem cells (BMSCs) that are employed to regenerate dental tissues are often extracted from extra-oral sources (such as the iliac crest and femur) or those from the oro-facial region including the maxilla and mandible, acquired during dental procedures[9].

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The Bone Marrow Derived Stem Cells (BMSCs) can be acquired from intra-oral sites such as the maxilla or mandible; as well as extra-oral sites including the iliac crest or femur[10]. Although BMSCs have had uneventful outcomes with regeneration, the process of obtaining and isolating these stem cells is invasive.There are various challenges and limitations, such as the invasive process of isolating extra-oral BMSCs and the paucity of other sources of dental stem cells[2,11].

On the other hand, dental origin stem cells are easier to access, and these include Dental Pulp Stem Cells (DPSC), human exfoliated deciduous teeth (SHED), gingival mesenchymal stem/progenitor cells (GMSCs), stem/progenitor cells from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), and dental follicle stem/progenitor cells (DFSCs)[7]. Dental tissues are demonstrated to have high numbers of MSCs among the progressively identified niches and tissues holding increased SCs[6,7]. Dental SCs are typically found in the dental pulp, periodontal ligament, and dental follicle tissues[10]. Despite the variety of available sources, it is important to consider that successful tissue regeneration is a result of a complex interplay between three main factors: Stem cells, scaffolds, and growth factors, also described as the ‘Tissue Engineering Triad’[6].

Due to the insurmountable hurdles involved with the translation of cell delivery-based tooth regeneration techniques into medicines, cell homing has been suggested as an alternate to cell transplantation for tooth regeneration[12]. Translational challenges are present in all cell-based treatments, including those used for tooth tissue regeneration. Another barrier to considerable clinical translation of tooth regeneration currently is the enormous expense of commercialization and constraints surrounding regulatory approval[8]. As a result, cell homing is becoming increasingly popular among the already accepted techniques for tissue regeneration. Cell homing is more adaptable and has a greater chance of being commercialized for therapeutic applications when the ex-vivo cell manipulation and cell isolation steps are omitted. Therefore, although further investigation is required, cell homing is still a promising substitute to cell delivery-based tooth regeneration. Cell homing has emerged as a promising strategy for tooth regeneration, demonstrating effective recruitment of adequate cells from various lineages into the micro-channels of the scaffold, regeneration of a hypothetical PDL, and formation of new alveolar bone.

Currently, literatures regarding stem cell approaches in dentistry does not present clear guidelines. This needs to be addressed in order to help forge basic understanding of principles, techniques, and application areas. Moreover, the limitations and challenges of stem cell therapy need to be explored further to develop a better understanding of this treatment modality. Modern science utilizes stem cells to cure the diseases labelled as incurable, aiming to increase the health span. This is far from forming a synthetic organ in-vitro. The blooming industry of stem cells have been a topic of public discussion over a wide range of ethical implications. The initial studies surrounding stem cells have many pressing ethical issues. However, all translational studies begin with an ethical question of whether the study answers the scientific question within the social values. It is important to consider the merits and demerits of stem cell therapy.

The mechanisms that govern the outcomes and activities of transplanted stem cells must be investigated. Literature is abundant with stem cell based preclinical studies on dental pulp and periodontal regeneration. However, clinical studies with long term follow-ups are still scarce, which makes it challenging to translate these preclinical studies in terms of host response, ethical concerns, regulation, technology, and ethical considerations. These underlying challenges must be addressed in order for regenerative therapies to be practicable and effective for patients with dental pulp and/or PDL that is diseased or injured.

For the purpose of regenerating these essential components of dental tissues, autologous stem cells have already begun to be utilized in several clinical studies. It is crucial to note that this modality has not received approval yet, nor have the associated results been disseminated or included in pertinent guidelines. Many individuals suffering from dental disorders across the world may benefit from stem cell-based regenerative techniques, which demand further investigation. Fortunately, advances in nanotechnology, mathematical modelling, and contemporary imaging techniques are paving the way for stem cell-based regeneration trials to produce higher-quality results more efficiently and with more reliability.

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