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ROLE OF STEM CELLS IN ORTHODONTICS - A REVIEW

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Abstract

The purpose of this article was to review and update current data of the use of stem cells for dental but specifically orthodontic purpose. Interest regarding stem cell based therapies for the treatment of congenital or acquired craniofacial deformities is rapidly growing. Craniofacial problems such as periodontal disease, cleft lip and palate, ear microtia, craniofacial microsomia, and head and neck cancers are not only common but also some of the most burdensome surgical problems worldwide. Treatments often require a multi-staged multidisciplinary team approach. Current surgical therapies attempt to reduce the morbidity and social/emotional impact, yet outcomes can still be unpredictable and unsatisfactory. The concept of harvesting stem cells followed by expansion, differentiation, seeding onto a scaffold and re-transplanting them is likely to become a clinical reality. In this review, we will summarize the translational applications of stem cell therapy in tissue regeneration for craniofacial defects.

Introduction

Stem cells are those with the ability to divide for indefinite periods of time and with the ability to differentiate into a variety of cell types. Stem cells can be divided into three categories: totipotent, pluripotent, and multipotent cells.[1, 2, 3] Totipotent cells are the most primitive cells, followed by pluripotent cells. The multipotent cell type is the most differentiated type of stem cell[3]. Totipotent cells have the potential to differentiate into any type of cell in the body and are capable of developing into a complete organism. After several cell division cycles, totipotent cells will develop into pluripotent cells. Pluripotent cells are capable of dividing and differentiating into any type of cell, tissue, or organ. However, these cells are not capable of developing into a complete organism. Multipotent cells have more limited capacities than do pluripotent cells. Other types of primitive cells include progenitor cells, which are able to differentiate into only one type of mature cell.[4,5] Adult stem cells are defined as the undifferentiated cells that are found in a differentiated adult tissue,[6] residing in a specific area of each tissue where they remain quiescent in the body until they are activated by epigenetic and/or environmental factors, such as mechanical forces, disease, or trauma. Adult stem cell populations serve to regenerate multiple tissues that are damaged or are in need of repair or regeneration.[7] Stem cells have been defined in many different ways.

Moreover, the classical definition of a stem cell is changing in the face of increasing evidence suggesting that stem cells exist within adult tissues and retain significant phenotypic plasticity (ie, potency). The main principles in the definition of stem cell include the following: (1) Self-renewal, or the ability to generate at least one daughter cell with characteristics similar to the initiating cell; (2) Multilineage differentiation of a single cell; and (3) In vivo functional reconstitution of a given tissue or cell type.[8, 9] Regeneration involves slow replacement of tissues via identical cells derived from progenitor and/or adult stem cells. Previous studies have identified and isolated adult stem cells from bone, brain,

Muscle, and skin that have the potential for differentiation into various tissues and particularly the cell types present within the tissues from which the cells were isolated.[10-15] Although these cells are quite similar in terms of their differentiation potential, they are different in terms of their growth properties and perhaps their differentiation lineage prefer-ence.[16] In addition marrow- derived stem cells were found to differentiate at the single- cell level not only into mesenchymal cell types such as osteoblasts, chondroblasts, and adipocytes, but also into cells of visceral mesodermal origin.[17] Recent studies suggest that the postnatal craniofacial muscle compartment can be considered an alternative to bone marrow and a source of multipotent cells or muscle-derived stem cells.[15]This review focuses

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specifically on craniofacial bone, teeth, periodontium, and the temporomandibular joint (TMJ) within the craniofacial complex, interpreting the critical roles of adult stem cells in postnatal growth/development as well as remodelling and regeneration of the craniofacial tissues or organs.

Scaffolds And Biomaterials

Craniofacial reconstructive surgery manipulates available tissues in a three dimensional field, either by transferring tissue from a donor site or supporting and shaping the repair with artificial scaffolds and biomaterials. Biomaterials in stem cell tissue engineering and regeneration not only provide a supportive scaffold but also create an artificial niche that allows natural processes of stem cell renewal, proliferation, and differentiation while promoting vascularization, integration, adhesion, and survival of the newly generated.[18] Incorporating small molecules and growth or differentiation promoting factors within the biomaterials can further potentiate these natural repair processes resulting in efficient biological repair. The basic requirement for all biomaterial used for tissue engineering purposes is that it be inert and does not provoke a significant inflammatory response. However the tensile strength, biostability or biodegradability are features that will be favoured in a context dependent manner. Inert stable scaffolds provide rigidity but lack the ability to remodel with age. While biodegradable scaffolds that provide transient three- dimensional contour for the regenerating tissue are especially appealing for soft tissue repair but raise the concern of inadequate regeneration, inadequate mechanical properties of the newly formed tissue and sustained function over long periods of time.

Stem Cells In Craniofacial Tissue Engineering

Interest regarding stem cell based therapies for the treatment of congenital or acquired craniofacial deformities is rapidly growing. Craniofacial problems such as periodontal dis-ease, cleft lip and palate, ear microtia, craniofacial microsomia, and head and neck cancers are not only common but also some of the most burdensome surgical problems worldwide. Treatments often require a multi-staged multidisciplinary team approach. Current surgical therapies attempt to reduce the morbidity and social/emotional impact, yet outcomes can still be unpredictable and unsatisfactory. The concept of harvesting stem cells followed by expansion, differentiation, seeding onto a scaffold and re-transplanting them is likely to become a clinical reality. One potential stem cell based strategy for repairing craniofacial defects is the use of embryonic stem (ES) cells. ES cells are derived from the inner cell mass (ICM) of the blastocyst and possess the capacity to differentiate into all cell types.[19,20,21] However, the application of ES cells for clinical purposes has been limited by ethical issues, dysregulated ES cell differentiation, and immune rejection. In addition, the possibility of genomic instability and tumorigenesis still needs to be examined before any large-scale clinical experiments are planned. The ability to generate induced pluripotency stem (iPS) cells is one of the major breakthroughs in stem cell study in recent years.[22,23] Somatic cells from human fibroblast cells can be reprogrammed into a primordial, ES-like state and are able to differentiate into all three germ layers (ectoderm, endoderm, and mesoderm). This technology offers a revolutionary approach for the introduction of autologous multipotential stem cells into patient-specific, tissue-specific regeneration and repair.

To the craniofacial reconstructive surgeon, tissue engineering advancements over the last decade has provided a plethora of materials that may be suitable for the healing of craniofacial defects like the cleft palate. At a basic level, tissue engineering scaffolds can be broken down into three groups: autografts, allografts, and xenografts. Today the reconstructive surgeon makes best use of the autograft category, taking bone from another site (*e.g.*, iliac crest, rib) and transplanting it into the cleft defect.

Dental Stem Cells And Tooth Regeneration

Human teeth are comprised of enamel, dentin, tooth, pulp, and cementum covering the root surface. The periodontal ligament surrounds and supports the tooth. Unlike bone, most hard tissue in the tooth does not undergo renewal after its formation; only dentin can regenerate itself internally upon injury, suggesting the existence of stem cell populations within the tooth pulp. One of the first dental related stem cell populations identified are the DPSCs.[24] DPSCs are capable of differentiating into multiple types of tissue including odontoblast, bone, adipocyte, and neuron.[25] In addition, SHED teeth pulp opossess multipotential differentiation ability.[26,27] Both SHED and DPSCs are able to generate tissue resembling human tooth pulp under appropriate conditions.[28,29] Several studies have

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attempted to rebuild teeth in vitro by combining tooth pulp derived stem cells with proper scaffold materials . Other studies have used DPSCs or SHED for treatment of disease of non-dental tissue such as muscle dystrophies, critical size bony defect, spinal cord damage, corneal injury, and even systemic lupus erythematosus. Scaffolds provide a 3-D framework for cells and serve as an extracellular matrix for a finite period of time. Scaffolds provide an environment that allows both cell migration and proliferation, and may be fabricated in pre-determined shapes and composition. The first scaffold material used successfully for tooth tissue engineering was a copolymer of PGA/PLLA and PLGA, which are the most commonly used scaffold materials for tissue engineering studies. These scaffolds are biodegradable and biocompatible. Changing the component ratio can control the degradation rate of the PLLA/PGA scaffold. PLLA has also been used in many tooth tissue engineering studies, and tissue with morphology and structure resembling that of human tooth pulp has been generated after seeding dental pulp stem cells onto the PLLA scaffolds. Odontoblast specific marker DMP-1 is detectable within scaffolds generated with gelatin or salt porogens. In the future, the ability to control the shape of the tissue engineered tooth generated with appropriate scaffold mate- trials will be a crucial step towards bringing the technique to the clinic.

Engineering The TMJ Cartilage Using Adult Stem Cells

The TMJ is enclosed in a capsule that is lubricated with synovial fluid and serves as an important growth site during postnatal development with two articular surfaces that can adapt to changing environment conditions.[30,31,32] With regard to the glenoid (temporal) fossa, the sub articular osteogenic layer of the periosteum provides cartilage and bone cells for the superior surface of the TMJ.[32,33] Mandibular protrusion conducted in a stepwise fashion increased the number of mesenchymal cells (stem/progenitor cells) in the glenoid (temporal) fossa, which in turn shows new cortical bone formation.[34] However, the mandibular condyle is special because of its ossification of secondary cartilage, and changes its shape and length by sub articular proliferation of the progenitor/ stem cells that differentiate into chondrocytes,[30,31,35] leading to an earlier formation and increase in the amount of cartilage matrix, which eventually will be replaced with lamellar trabecular bone.[36] The temporo-mandibular joint (TMJ) is comprised of both osseous and cartilaginous structures. It can deteriorate due to injuries, osteoarthritis, or rheumatoid arthritis. The cartilage tissue has a limited capacity of intrinsic repair, so even minor lesions of injury may lead to progressive damage.[37-41] Severe TMJ lesions need surgical replacement of the mandibular condyl.[42] Currently, a few studies on TMJ tissue engineering have been conducted in animal models. In one study, bone marrow MSCs were isolated from the long bone marrow and expanded in vitro under either osteogenic or chondrogenic culture conditions.[43,44]

The expanded osteogenic and chondrogenic cells were mixed with PEGDA hydrogel and seeded onto an adult human cadaver mandible condyle in two stratified yet integrated layers. These bilayer constructs were then placed under nude mice skin for culture. After 4weeks of implantation, de novo formation of human condyle like structures was detectable replicating the relevant shape and dimensions. Chondrocytes and osteocytes of donor origin were identified in separated layers, and the two cell types infiltrated into the territory of each other, resembling the native condition. However, both chondrogenic and osteogenic layers showed suboptimal maturation, possibly due to an insufficient amount of cells. The same group also constructed a mandibular condyle scaffold by using CAD/CAM techniques and combined it with autologous bone marrow MSC cells. The construct was then transplanted into mini pig TMJs. Evaluation and analysisafter1and 3months indicated bone regeneration of condyle shape and thus improvement of masticatory function.[45]

Mandibular Growth In Mandibular Hypoplasia Using Stem Cells

Viral vectors carrying vascular endothelial growth factor (rAAV-VEGF) have been shown to stimulate mandibular growth in vivo in rats.[46] Yet, more research is needed to optimize the technique and detailed toxicity evaluation of viral and non-viral vectors (both local and systemic), and testing optimized techniques in higher animals before clinical trials can be conducted. The hypothesis underlying local injection of vector-loaded VEGF into mandibular condyles is that this VEGF can modulate mandibular growth through added VEGF effect that has been shown to be correlated to mandibular growth stimulation.[47,48] VEGF may stimulate mandibular growth through two mechanisms: (1) through stimulation of endochondral bone growth and (2) through recruitment of new replicating mesenchymal stem cells, which is correlated to mandibular growth.[49,50] Gene therapy as well as LLL (Laser) or LED (Light emtting diode) seems to be promising approaches in stimulating mandibular growth. However, detailed toxicity investigations of these techniques are required before potential clinical trials can be performed.

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Periodontal Regeneration Using Stem Cells

Periodontal diseases affect 15% of the human adult population, with periodontal soft tissue loss and subsequent supporting bone resorption leading to loss of teeth.[51] Current treatment approaches include the use of guided tissue regeneration, bioactive grafting materials, and application of bioactive molecules to induce regeneration, but the overall effects of these approaches are relatively modest and limited in practical applications. Regenerating the periodontium is a challenge in the treatment of periodontal diseases due to its complex structure, consisting of cementum, periodontal ligament, gingiva, and supporting bone. Thus, regeneration of the periodontium will require either multiple cell populations or a multi potential stem cell population.

The Periodontal ligament is unique among the ligament and tendon tissues of the body, because it is the only soft tissue connecting two distinct hard tissues.[52] The periodontal ligament suspends the tooth like a cushion in order transduce the mechanical load from the teeth evenly onto the supporting bone. Early studies of different animal models demonstrated that the periodontal tissues possess some regeneration activity, suggesting the existence of stem cell population within the periodontium.[53,54] After depletion of various periodontal tissues, not only the periodontal ligaments, but also cementum and alveolar bone, can be regenerated, suggesting the presence of multi potential stem cell populations .[55,56,57]

Impact Of Craniofacial Tissue Engineering On Clinical Practice

Craniofacial tissue engineering is an opportunity that dentistry cannot afford to miss. This notion is based on both biological and strategic reasons. Biologically, mesenchymal cells are primarily responsible for the formation of virtually all dental, oral, and craniofacial structures. Mesenchymal stem cells, the reservoir of mesenchymal cells in the adult, have been demonstrated, in tissue engineering, to generate key dental, oral, and craniofacial structures. Many dental and craniofacial structures are readily accessible, thus presenting a convenient platform for biologists, bioengineers, and clinicians to test tissue-engineered prototypes.[58,59] The impact of craniofacial tissue engineering extends beyond dental practice. Several craniofacial structures engineered thus far serve as prototypes for the tissue engineering of non-craniofacial structures. Craniofacial-derived stem cells have potential implications in the tissue engineering of not only craniofacial structures, but also non-craniofacial tissues.[60,61] Tissue-engineered bone with customized shape and dimensions has the potential for the biological replacement of not only craniofacial bones, but also of segmental defects in the appendicular bones.[62,63,64]

Summary

It seems like every day we read about huge advances in the field of endothelial stem cells research detailing daring approaches in the application of these stem cells to the clinical world. The question is where is the adult stem cell researcher? True advances in the medical and scientific world using adult stem cells like the adult stem cells will not be achieved by playing it “safe.” In the modern marketing world, we hear phrases like “kick it up a notch” and “think outside the box.” The adult stem cell researcher needs to take these phrases to heart and look outside conventional fields for inspiration and knowledge. The combination of the stem cell researcher with the biomaterials engineer has been an example on how what appears to be an unconventional collaboration can advance the scientific community and benefit the general public. Who knows where these relationships will take us? But one thing is for sure—collaboration brings people together who look at the world in different ways. From these unions, we can propel the fields of adult stem cell biology and craniofacial tissue engineering into a whole new realm—where all things are possible.

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