Review Article

Stem cells in orthodontics and dentofacial orthopedics: Current trends and future perspectives

ABSTRACT

A simple overview of daily orthodontic practice involves use of brackets, wires and elastomeric modules. However, investigating the underlying effect of orthodontic forces shows various molecular and cellular changes. Also, orthodontics is in close relation with dentofacial orthopedics which involves bone regeneration. In this review, current and future applications of stem cells (SCs) in orthodontics and dentofacial orthopedics have been discussed. For craniofacial anomalies, SCs have been applied to regenerate hard tissue (such as treatment of alveolar cleft) and soft tissue (such as treatment of hemifacial macrosomia). Several attempts have been done to reconstruct impaired temporomandibular joint. Also, SCs with or without bone scaffolds and growth factors have been used to regenerate bone following distraction osteogenesis of mandibular bone or maxillary expansion. Current evidence shows that SCs also have potential to be used to regenerate infrabony alveolar defects and move the teeth into regenerated areas. Future application of SCs in orthodontics could involve accelerating tooth movement, regenerating resorbed roots and expanding tooth movement limitations. However, evidence supporting these roles is weak and further studies are required to evaluate the possibility of these ideas.

Keywords: Cleft lip and cleft palate, dentofacial deformities, distraction osteogenesis, stem cells, tissue regeneration

INTRODUCTION

Orthodontics involves treatment of dental malocclusions and correction of dentofacial deformities. The aim of orthodontic treatment is to achieve facial esthetics and improve oral health related quality of life.[1] The prevalence of dental malocclusion varies in different communities and have been reported to be 22.5%–93%.[2] Orthodontic treatment of malocclusions has several shortcomings such as prolonged treatment time, apical root resorption, tooth movement limited to alveolar bone and difficulties to overcome periodontal defects. Although facial anomalies and jaw base deformities are less frequent compared to simple dental malocclusions, they are more burdensome.[3,4] As the embryo develops, embryonic stem cells (SCs) begin down a path of differentiation and maturity, at which time they lose this potential. The promise of regenerative medicine brings new energy and hope for improved outcomes by replacing damaged or absent tissues with healthy regenerated tissue [Figure 1]. SCs are present in many tissues throughout the body and at the different developmental stages of the organism. They are also frequently described as being located within close proximity to the vasculature, i.e., in a perivascular niche.[5,6] SCs have been characterised based on

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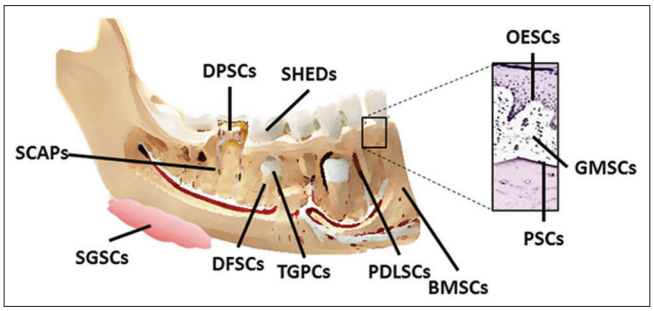

Figure 1: The locations of developmental and postnatal stem cell populations in the dental and craniofacial region indicating sources for isolation from the mandible and teeth

their abilities to self-renew, along with their multi-lineage differentiation capabilities which enable complex tissue regeneration.[7] They have varying degrees of potency ranging from totipotent, pluripotent, multipotent through to unipotent [Figure 2]. Totipotent SCs are derived from the zygote, and can form embryonic and extra-embryonic tissues, including the ability to generate the placenta.[8] Pluripotent SCs include embryonic SCs (ESCs) and are derived from the inner cell mass of the developing blastocyst. Notably, ESCs can differentiate into the three main germ layers of the organism including the endoderm, mesoderm and ectoderm. Postnatal/adult SCs are regarded as being multipotent and include populations of hematopoietic and mesenchymal SCs (MSCs). They are capable of differentiating toward several germ layer lineages giving rise to cell types which are necessary for natural organ and tissue turn-over and repair. SC populations which have been identified and characterised within these tissues include dental pulp SCs (DPSCs)[9] SCs from the apical papilla (SCAPs),[10] dental follicle.

MATERIALS AND METHODS

The electronic databases PubMed, Google Scholar, Science Direct, Cochrane Library along with a complimentary manual search of all journal till the year 2016. No limits and language restriction were applied during the electronic search in order to include all the relevant articles pertaining to the topic of interest. The search in PubMed yielded 149 articles which were screened based on the relevance of the title and abstract to the topic of interest. 125 articles were excluded based on this criterion. The full texts of the 24 articles were analyzed, of which 12 were excluded based on the exclusion criteria of this systematic review. Only one relevant article could be extracted through hand search and no articles were retrieved from other databases. The inclusion criteria include *in vitro* and *ex vivo* studies where the tissue was obtained purely from oral cavity of human samples, those in which both the isolation and differentiation of SCs were analyzed and all there was no restriction in the usage of the markers. Studies where the source was from animals and where only isolation of SCs was done were excluded from the study.

Precursor cells (DFSCs)[11] periodontal ligament SCs (PDLSCs),[12-14] gingiva-derived MSCs,[15] periosteum-derived SCs and salivary gland-derived SCs. In addition, well-characterized MSCs, which are not exclusive to the oral and craniofacial tissues, include bone marrow-derived MSCs (BMMSCs),[16] which can be harvested from maxilla and mandibular bone, as well as adipose tissue-derived SCs (ADSCs).[17] Figure 1 pictorially shows the dental and craniofacial locations of these SC groups. The oral and dental SC populations are defined as MSCs according to the minimal criteria proposed by the International Society for Cellular Therapy in 2006.[18] The criteria defining them, which are tissue independent, include their ability to adhere to standard tissue cultureware along with their expression profile of cluster of differentiation and other markers.[19]

Scaffolds and bio-materials for stem cell tissue engineering

For dental and oral tissue engineering strategies, along with SCs, suitable biomimetic scaffolds and appropriate morphogens/growth factors are required.[20] Clinically, for periodontal tissue repair, material-based guided tissue regeneration (GTR) approaches have been developed. Subsequently, biocompatible or bioinert scaffolds are used to enable connective tissue and bone regeneration from local tissue MSC populations.[21] Alveolar bone augmentation approaches, such as guided bone regeneration, utilize bioactive materials, such as calcium phosphate-based biomaterials and collagen-based grafts. While these materials are bioactive and osteoconductive, they are not osteoinductive; hence, scaffolds are being developed, which incorporate bone formation promoting growth factors.[22] Fibrous silk protein (fibroin) biomaterial scaffolds are also being developed for their use in tooth and bone repair. Recent studies have demonstrated the utility of hydrogel scaffolds for tooth tissue engineering applications.

The seeding of pulp derived cells on collagen scaffolds with subsequent animal implantation has demonstrated the formation of dental tissue structures.[23] A peptide-amphiphile hydrogel scaffold containing bioactive osteogenic supplements has also been shown to promote differentiation of encapsulated SHED Stem cells from Human Exfoliated Deciduous teeth and DPSCs, While challenges still remain, the development of the most appropriate scaffolds which optimize SC responses for clinical application is progressing at a rapid rate.

Growth factors and morphogens for tissue regeneration

Current knowledge of this molecular signaling is advancing with the tooth's hard and soft tissue ECM [extracellular matrix] being shown to provide both biochemical and

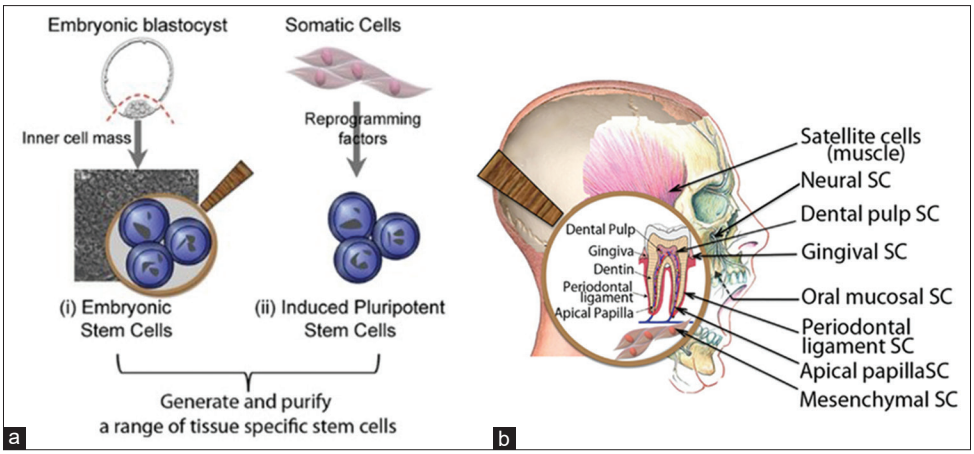

Figure 2: (a) Pluripotent AQ14 stem cells and (b) adult stem cells

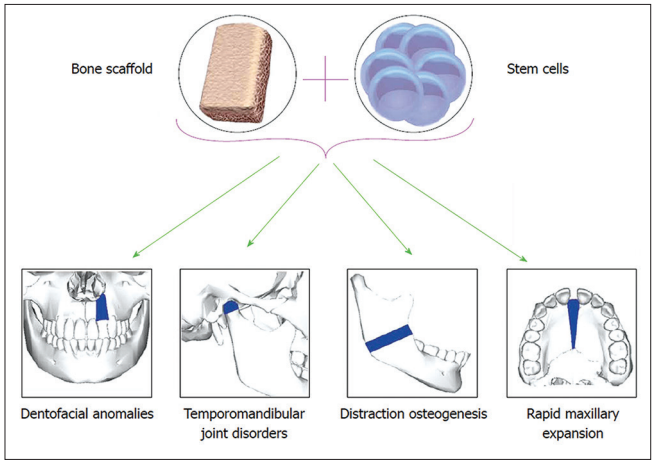

Figure 3: Applications of stem cells (alone or in conjugation with bone scaffolds) in dentofacial orthopedics (Google Scholar)

biomechanical regulatory cues. Indeed, comparable with repair processes in other tissues, the regulation of dental tissue regeneration involves signaling derived from its ECM with inherent growth factors known to coordinate recruitment, proliferation and differentiation of MSC populations. In the periodontal tissues, the application of platelet rich plasma (PRP) enables the delivery of a cocktail of potent growth factors and morphogens. Use of PRP in combination with bone grafts and/or SCs to enable more predictable periodontal regeneration. Enamel matrix derivatives (EMDs) obtained from porcine tooth buds, also contain a complex cocktail of growth factors and can also stimulate periodontal tissue regenerative events. Both PRP and EMD are morphogenically complex and have been shown to include Bone Morphogenic Protein (BMP)-2, platelet derived growth factor-BB and FGF-2, among others. These secretomes contain a multitude of bioactive molecules such as insulin-like growth factor-1 and vascular endothelial growth factor which promote many tissue repair mechanisms.[24]

Stem cell applications for dental and craniofacial tissue regeneration

The use of SCs for regenerative medicine/dentistry is progressing and currently, the use of adult/postnatal SCs exhibits the most realistic clinical opportunity. Regeneration of bone and periodontal tissues using MSCs has received considerable attention with several studies already reporting clinical application. Clearly, SCs used in dental tissue engineering should be; (i) relatively easily isolated, (ii) straightforward to deliver in a reproducible and clinically simple procedure, (iii) clear of any patient safety issues, and (iv) ultimately differentiate into and regenerate the target tissue or organ. BMMSCs and ADSCs, in particular those derived from the orofacial region, may provide an appropriate source for craniofacial tissue repair.[25] Other dental and craniofacial tissue-derived MSCs may be more appropriate for regenerating dental mesenchyme-derived hard and soft tissues, including those of the dentine, pulp, and supporting periodontal tissues. The application of MSCs for complete repair of complex oral organs, such as teeth and salivary glands, which also require cells to differentiate down epithelial lineages may however be challenging. Pluripotent ESCs may, therefore, have utility in these cases; however, medical and ethical issues associate with their application and the use of induced pluripotent SCs still require further technical and safety advancements before they can be applied. For all SC sources, their downstream processing following isolation still remains an issue for the clinician who would also require onsite specialist equipment and expertise to enable their purification and expansion.

Tooth and tooth component tissue regeneration

Ultimately, it is aimed that a lost tooth will be replaced by a fully functional bioengineering done; however, current studies indicate that tooth component tissue, such as root and crown dentine are more realistically clinically achievable. Recent

Table 1: Abbreviations of all the stem cell populations

BMMSCs	Bone marrow-derived mesenchymal stem cells
MSCs	Mandible (also maxilla) stem cells
DPSCs	Dental pulp stem cells
SHEDs	Stem cells from human exfoliated deciduous teeth
PDLSC	Periodontal ligament stem cells
DFSCs	Dental follicle stem cells
TGPCs	Tooth germ progenitor cells;
SCAPs	Stem cells from the apical papilla
OESCs	Oral epithelial progenitor/stem cells
GMSCs	Gingiva-derived MSCs
PSCs	Periosteum-derived stem cells;
SGSCs	Salivary gland-derived stem cells

work using animal models has shown that complex root/periodontal structures can be regenerated using PDLSCs and SCAPs Table 1in conjunction with hydroxyapatite scaffolds.[26] For tooth bioengineering, the generation of embryonic tooth primordia has been common lyused. Initial studies have transplanted pelleted dissociated porcine tooth buds in theomentum of athymic rats which resulted in the generation of complex tooth structures which comprised a pulp chamber, dentine, putative Hertwig's epithelial root sheath and an enamel organ[27] has demonstrated tooth tissue regeneration following transplantation of human adult gingival epithelial cells combined with mouse embryonic tooth mesenchyme cells in kidney capsules. The tooth structures generated at 6 weeks of transplantation contained vascularized pulp-like tissue and signs of root development including the presence of ameloblast-like cells and epithelial rests of malassez. Clearly, significant work is still required to bring this to fruition and to provide clinically relevant alternatives for patients who require dental implants.

Temporomandibular joint tissue engineering and stem cells

The temporomandibular joint (TMJ) comprised both osseous and cartilaginous structures. It 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 [Figure 3]. The mandibular condyle grows by proliferation of the progenitor/SCs that differentiate into chondrocytes leading to formation and increase of cartilage matrix, which will be replaced with lamellar trabecular bone.[28] As SCs possess the ability to differentiate into chondrogenic and osteogenic cells, they could be used for both maintenance of mandible in new position and repair of TMJ lesions. Forward positioning of mandible, for example in functional therapy, leads to increase in the number of mesenchymal cells (stem/progenitor cells) in the temporal fossa, which resulted in new cortical bone formation. TMJ is prone to injuries, tumors, osteoarthritis, rheumatoid arthritis and congenital anomalies. Temporomandibular disorder manifest as pain, myalgia, headaches, and structural destruction, collectively known as degenerative joint disease. The primary methods used to reconstruct the TMJ includes autogenous bone grafting such as harvesting from the rib, or the use of alloplastic materials, with neither being ideally suited for the task and sometimes leading to unwanted adverse effects. Recently, these cells have attracted much interest to joint reconstruction. Engineering a TMJ-like osteochondral graft has been studied in several studies. In one study, Combination of polylactide acid discs with adipose tissue SC demonstrated the potential to development a tissue-engineered TMJ disc. These data revealed possibility of application of SCs in combination with different scaffolds as a promising approach to regenerate osteochondral tissues of TMJ and ultimately the joint disk.

Periodontium tissue regeneration and stem cells

Periodontal complications are one of the most actual side effects linked to the orthodontics. It can be found in various forms, from gingivitis to periodontitis, dehiscence, fenestrations, interdental fold, gingival recession or overgrowth, black triangles. Periodontal regeneration has been defined as the formation of new cementum, alveolar bone, and a functional periodontal ligament (PDL) on a previously diseased root surface. The current treatment approaches include the use of surgery, GTR, bone fillers and growth factors and application of bioactive molecules to induce regeneration. On the one hand, because of the increasing number of adult patients seeking orthodontic treatment, encountering the periodontally involved patients may be a potential problem for every practitioner. It has been suggested that, by moving the teeth into infrabony defects, we can achieve the regeneration of the attachment apparatus. The periodontal defects such as fenestration, dehiscence and attachment loss are among common complications of orthodontic treatments. In a study, induced pluripotent SCs have been implanted into a mouse periodontal fenestration defect model with a silk fibroin scaffold in combination with EMD gel. Thus, the use of PDLSC transplantation in periodontal therapies can reduce treatment time and better outcomes followed by patient comfort; however, due to complex structure of periodontium, regeneration is a feasible and yet complicated procedure and may need pluripotent SCs and more investigations.

Oral mucosa stem cells and tissue engineering

The human oral mucosa is highly active in terms of cell turnover and regeneration, which suggests the existence of one or more types of SC populations. Recently, a SC population was identified from the lamina propria of adult human oral mucosa They are highly proliferative *in vitro* and are able to differentiate into tissue of mesodermal (osteoblast, chondrocyte, and

adipocyte), endodermal (endothelium), and ectodermal lineages (neuronal cells). Regenerative therapy aims to reduce wound healing time and minimize scar formation. Wound healing of the skin is comprised of three phases: Coagulation/early inflammation phase, late inflammation phase, and proliferative phase. Although oral mucosa healing goes through the same three phases, it proceeds with an accelerated rate and reduced scar formation. Fibroproliferative scars such as keloid and hypertrophic scars are rarely seen in the oral cavity. To date, no satisfactory Food and Drug Administration-approved therapy is available for the treatment of scar tissue.

Distraction osteogenesis

Distraction osteogenesis which is regarded as "endogenous bone tissue engineering" has been widely applied in orthopedic surgery for correction of limb length and also in the treatment of many craniofacial deformities.[29] DO is done by creating a corticotomy, placing a rigid distractor across the cut bone and gradually activating the device. Efforts have been made to accelerate osteogenesis in the distraction Gap, shorten the consolidation period and reduce complications such as the development of nonunion, infection, or fracture. Recently, because of the role of MSCs in osteogenesis, many researchers have successfully documented the ability of SCs on promoting bone formation and shortening the consolidation period during DO. The injection of MSCs 1 d before onset of distraction resulted in increase in new bone volume in the distracted callus and the bone mineral density (BMD), MSCs injection after distraction was complete showed higher radiodensity of the distraction zone and grater histologically callus, new bone volume and thickness of the new trabeculae and doing this intervention on the 1st day of consolidation resulted in greater biomechanical strength and increase in total and compact bone ratio in regenerate bone. The injection of SHED during osteotomy period showed higher percentage of newly formed bone after 2, 4, and 6 week. The injection of MSCs transfected with BMP showed greater bone formation and earlier mineralization in the distracted callus, more mature medullary cavity, better bone quality and higher trabecular parameters (trabecular thickness, trabecular number, volumetric BMD at tissue, and bone volume fraction) at the 2nd and 4th weeks of the consolidation period and acceleration of osteogenesis. These data show that SCs from various sources, alone or in combination of genes and factors, in different phases of treatment can lead to an increase in new bone volume and quality, BMD, trabecular thickness, and biomechanical strength.

Rapid maxillary expansion

Maxillary constriction can be associated with several problems that include occlusal disharmony and esthetics as well as such functional difficulties as narrowing of the pharyngeal airway, increased nasal resistance, and alterations in tongue posture, resulting in retroglossal airway narrowing and mouth breathing.[30] Maxillary constriction can be corrected with slow orthodontic expansion, rapid maxillary expansion (RME), surgically assisted rapid palatal expansion or a two-segmented Le Fort I-type osteotomy with expansion of RME is indicated in patients younger than 12 years, who have lateral discrepancies involving several teeth, whether the constriction is skeletal, dental or a combination of both.

It is an effective orthopedic procedure to open the midpalatal suture, providing appropriate and stable maxillary width increase and re-establish balance between the width of the jaws. RME is similar to DO histologically. During RME, a gap in the midpalatal suture is created which is filled with blood and granulated tissue and followed by active bone formation. The expanded arch width relapses unless followed by an appropriate retention period. Therefore, providing a strategy to accelerate bone formation in the midpalatal suture might shorten treatment and retention period, achieve stability and prevent relapse. Locally applied MCSs to the expanded maxilla might be a useful and practical treatment strategy to accelerate new bone formation in midpalatal suture and to shorten the treatment and retention period for patients undergoing orthopedic maxillary expansion.

Cleft lip and palate

Cleft lip and palate is a congenital malformation that requires a multidisciplinary treatment that evolves pediatrician, obstetrics, fetal medicine, genetics, plastic surgery, orthodontics, speech therapist, nursery, and psychology. The intrauterine diagnosis leads to preborn parental orientation and better parental collaboration to accept a precocious multidisciplinary treatment. New ideas to use SCs and blood from the umbilical cord and also blood from placenta are discussed to improve final surgical results.[31] Maternal SCs are easy to collect, there are no damage to the patient and mother, it is autologous and it could be very useful in the authors' protocol. A technique using umbilical cord blood SCs could be a promising new approach for repairing cleft palate in infants, Performed as part of reconstructive surgery when the infant is a few months old, the procedure provides good results in growing new bone to close the upper jaw cleft and may prevent the need for later bone graft surgery, the researchers report. Umbilical cord blood is a rich source of various types of SCs, which have the potential to develop into many different types of specialized cells, including bone and cartilage. Umbilical cord SCs also have greater regenerative potential, according to the researchers. For the first few months, the infant underwent a nonsurgical nasoalveolar shaping procedure to align the soft

tissues of the upper jaw. At the age of 5 months, the SCs were thawed for use as part of boneless bone grafting surgery, or gingivoperiostioplasty. The SCs were placed in a pocket of soft tissue bridging the gap in the upper jaw. It has potential complications and subjects the child to one or more additional surgeries. The study is the first to use SCs as part of primary surgery to repair cleft palate in an infant. The researchers say that their patient will need further monitoring to ensure adequate bone thickness in the upper jaw. Also, the researchers emphasize the need for further studies evaluating their SC technique in a large number of patients, including steps to confirm that bone formation results from the SCs and not from the initial boneless bone graft surgery.

Accelerated orthodontic tooth movement

Orthodontic tooth movement (OTM) is achieved by the remodeling of PDL and alveolar bone in response to mechanical loading.[32] The initiating inflammatory event at compression sites is caused by constriction of the PDL microvasculature, resulting in a focal necrosis, followed by recruiting of osteoclasts from the adjacent marrow spaces. These osteoclasts are mostly derived from hematopoietic SCs. Hence, SCs could be used to accelerate OTM by providing progenitor cells. The development of new methods to accelerate OTM has been sought by clinicians as a way to shorten treatment times, reduce adverse effects such as pain, discomfort, dental caries, and periodontal diseases, and minimize iatrogenic damages such as root resorption and the subsequent development of nonvital teeth. There are surgical methods like surgically-facilitated orthodontic therapy or corticotomy, periodontally accelerated osteogenic orthodontics and some nonsurgical procedures such as systemic/local administration of chemical substances such as epidermal growth factor, parathyroid hormone, 1,25-dihydroxyvitamin D3, osteocalcin and prostaglandins, resonance vibration, static or pulsed magnetic field, low-intensity laser irradiation therapy. This ability of SCs could be used to accelerate OTM in response to orthodontic forces. When orthodontic force is applied, tooth movement is hindered until the necrosis is removed, leading to the clinical manifestation of a delay period. Hypothetically, transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM. Hypothetically, transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM.

External root resorption

External root resorption (ERR) is a common and unfavorable side effect of orthodontic treatment which any specialist may encounter. Many factors seems to be involved in ERR such as genetics, individual biological variability, age, sex, and orthodontic forces and treatment duration. Orthodontic forces yet seem to be the main etiologic factors. ERR may lead to loss of tooth structure such as cementum and in more advanced stages, dentin; however, no specific treatment has been introduced so far. One possible treatment modality could be regeneration of resorbed roots by application SCs and tissue engineering.[33] In severe cases ERR may cause poor prognosis of tooth, resulting in tooth loss. Regeneration of these lesions increases the longevity of tooth and may play an important role in facilitating the treatment. In a study designed to induce *de novo* cementum formation by SC therapy, MSCs driven from PDL in *in vivo* transplantation were able to form cellular cementum-like hard tissue containing embedded osteocalcin-positive cells. Although it seems that there is a long way until regeneration of the teeth materials, cementogenesis and regeneration of dental structures through SC based therapies could be anticipated.

Limitations of the study

SCs are still controversial and of course their use is uneconomical. One requires high skill and knowledge to handle and use them. There are also no proper studies done on how many SCs are required to treat a defect. Variable results are seen, for example, implantation of osteo-induced rabbit adipose-derived SCs and gelfoam scaffolds into rabbit calvarian defects have not significantly improved bony healing when compared with the controls.[34] There are many records of using different kinds of SCs with different scaffolds, but to date no standard cell-scaffold system exists, which is accepted universally. This is a phase of transition and problems will exist, but they can only be solved by conducting more detailed researches and studies on them.

CONCLUSION

While promising data have already been generated *in vitro* and in preclinical studies using animals, research remains ongoing to ensure that there is a significant and sound knowledge base prior to clinical translation. In order for this translation to be realized, collaborative work and appropriate communication and dissemination between researchers, clinicians, industry, and health-care workers worldwide need to remain ongoing. Indeed, while considerable advancements have already been made over recent decades, it is imperative that attempts to translate basic science findings are not made too soon as this may generate risk for the patient. Therefore, appropriate restraint within the scientific and clinical communities is essential, and subsequent steps should be approached with caution as the patient's safety is of prime importance. Toward this goal, research governance and peer review processes need to be firmly in place. It is also important to determine which patient groups would best benefit from translation of SC science advances rather than incentives for application being driven due to any financial or industrial gain.

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Conflicts of interest

There are no conflicts of interest.

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