Periodontitis is an inflammatory disease that causes pathological alterations in the tooth-supporting tissues, potentially leading to tooth loss. National surveys have shown that the majority of adults in the population suffer from moderate periodontitis, with up to 15% of the population being affected by severe generalized periodontitis at some stage in their lives (2, 17). The significant burden of periodontal disease and its impact on general health and patient quality of life point to the need for more effective management of this condition (113, 143). Several procedures have been attempted to achieve periodontal regeneration, including root surface conditioning, bone graft placement, guided tissue regeneration and growth factor application. However, current regenerative procedures that are used either alone or in combination have limitations in attaining complete and predictable regeneration, especially in advanced periodontal defects (108, 109, 123, 139, 146). Recent advances in stem cell biology and regenerative medicine have presented opportunities for tissue engineering as well as gene-based approaches in periodontal therapy (60, 63, 70, 73, 138). The following discussion reviews our current understanding of stem cells and their potential application in regenerative periodontal therapy. Major progress in stem cell biology in the dental context is highlighted and the challenges in translating stem cell research into clinical practice are identified.

Definition of stem cells and their types

Stem cells are the foundation cells for every organ and tissue in the body, including the periodontium (129, 130). A stem cell has two defining characteristics: (i) the ability for indefinite self-renewal to give rise to more stem cells; and (ii) the ability to differentiate into a number of specialized daughter cells to perform specific function(s) (95, 115). A stem cell can divide asymmetrically, in which case one of the two daughter cells retains the stem cell characteristics while the other is destined for specialization under specific conditions (83). A pluripotent stem cell can differentiate into all cell types of the body, whereas a multipotent stem cell can differentiate along multilineages into many different cell types (95). The potential for self-renewal vs. differentiation is governed by extracellular signals coupled to intracellular signaling cascades (140). Information that specifies the fate of stem cells is encoded by the presence or absence of signals, and also by the combinations, localization, level and timing of these signals.

There are two main types of stem cells – embryonic stem cells and adult stem cells – which are classified according to their origin and differentiation potential (Table 1). Human embryonic stem cells, derived from the inner cell mass of blastocysts, are pluripotent stem cells capable of differentiating into cells of all three germ layers of the adult body (131). Human embryonic stem cell lines are unique in that they can be maintained in an undifferentiated state in vitro for an indefinite period of time, while retaining their ability to differentiate into all types of specialized cells in the body (57, 107, 131). These cells have been demonstrated to produce approximately 200 different types of cell within the adult body but, because of ethical concerns, have not been tested for their ability to participate in human embryonic development or to contribute to germ lines in vivo. It is estimated that at least 225 human embryonic stem cell lines, including some with genetic disorders, have been generated in different laboratories worldwide (47, 51, 100). The use of human embryonic stem cells for clinical therapy is a relatively new endeavor.
In 2006, cells with properties similar to those of embryonic stem cells, termed induced pluripotent stem cells, were created from specialized somatic cells via the forced over-expression of four key factors (126, 127). The authors reported that when plasmids containing Oct3/4, Sox2, cMyc, and Klf4 genes were introduced into murine fetal fibroblasts, the cells were reprogrammed to an embryonic-like state. These murine-induced pluripotent stem cells exhibited the morphology and growth properties of murine embryonic stem cells although they had different gene-expression and DNA-methylation profiles (Table 1). Follow-up reports with improved reprogramming techniques have yielded more embryonic stem cell-like cells in mice, with the reprogrammed cells contributing to every cell type in the body (77, 97, 141). Human counterparts of murine-induced pluripotent stem cells have subsequently been generated using various combinations of Oct3/4, Sox2, cMyc, Klf4, Nanog, LIN28, hTERT, and SV40 large-T factors (75, 99, 126, 155). Although the mechanism by which each of these factors restores pluripotency is not clearly understood, human-induced pluripotent stem cells attract immense interest from stem cell researchers because of the lack of ethical issues involving the use of human oocytes or embryos. Earlier techniques to restore pluripotency to human somatic cells, involving somatic cell nuclear transfer into enucleated oocytes (144) or fusion of somatic cell nuclei with human embryonic stem cells (25, 125), have drawn intense debate regarding the source of human oocytes/embryos and the use of oocyte progenitors in the adult ovary (26). Furthermore, somatic cell nuclear transfer has yet to be successfully demonstrated in humans, and the pluripotent cells resulting from the fusion of somatic cells with embryonic stem cells are often tetraploid with limited practical application. By contrast, the technology used to generate induced pluripotent stem cells can create patient-specific and disease-specific cell lines for research purposes with fewer ethical concerns, but this method of reprogramming is still inefficient and many fundamental questions remain unanswered. Thus, research on human pluripotent cells derived using different methods should be continued to identify the best method for regenerative therapy (56).

Adult, or tissue-specific, stem cells are found in the majority of fetal and adult tissues. They have been derived from tissues that continually replenish themselves [e.g. peripheral blood (3, 116), dermis (134, 153) and gastrointestinal epithelium (12)] as well as from tissues with lower regenerative capacity [e.g. brain (117)]. Adult stem cells are thought to function in long-term tissue maintenance and/or repair by replacing cells that are either injured or lost (71). They are generally multipotent stem cells that can form a limited number of cell types corresponding with their tissues of origin, although some studies have suggested that they are more versatile and can develop into many other cell types than previously expected (15, 68, 80). The most common

<table>
<thead>
<tr>
<th>Development stage</th>
<th>Type of stem cell</th>
<th>Differentiation potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blastocyst</td>
<td>Embryonic stem cells Derived from the inner cell mass of the pre-implantation embryo</td>
<td>Pluripotent</td>
</tr>
<tr>
<td>Fetus</td>
<td>Embryonic germ cells Derived from primordial germ cells isolated from the embryonal gonad</td>
<td>Pluripotent</td>
</tr>
<tr>
<td>Adult</td>
<td>Embryonal carcinoma cells Derived from primordial germ cells in embryonic gonad and usually found as components of testicular tumors in adults</td>
<td>Pluripotent</td>
</tr>
<tr>
<td></td>
<td>Adult stem cells Derived from ectodermal and mesodermal organs of adults</td>
<td>Multipotent</td>
</tr>
<tr>
<td></td>
<td>Adult cells that have undergone nuclear transformation</td>
<td>Totipotent</td>
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<td></td>
<td>Adult cells that can be induced to an embryonic stem cell phenotype</td>
<td>Inducible pluripotent</td>
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Table 1. Different stem cell populations and their differentiation potential
source of adult stem cells is the bone marrow, which contains hematopoietic stem cells (132) and bone marrow stromal cells or mesenchymal stromal/stem cells (29, 52). Hematopoietic stem cells were the first stem cells to be successfully used in therapies, particularly in the treatment of blood malignancies and immunodeficiency syndromes, but they are not capable of giving rise to supporting connective tissues (65). Mesenchymal stem cells, by contrast, are a cell type of interest with the therapeutic potential to treat a range of musculoskeletal abnormalities, cardiac diseases and immune abnormalities (65). This review will focus on the properties and function of mesenchymal stem cells as potential candidates for periodontal regeneration (50, 63).

**Human mesenchymal stem cells**

Mesenchymal stem cells were initially identified in rodent marrow as colony-forming unit fibroblasts capable of forming bone, cartilage and fat, as well as reconstituting the hematopoietic microenvironment (37, 38). Colony-forming unit fibroblasts have subsequently been detected in many species, including humans (19, 20, 46, 101), and the formation of colony-forming unit fibroblasts is considered to be a distinguishing feature of mesenchymal stem cells. Mesenchymal stem cells have also been characterized both morphologically and immunophenotypically using different cell-surface markers. Mesenchymal stem cells occur as either large and flat cells or as elongated and fibroblastic cells, but the functional significance of this diverse morphology is unclear (9). Phenotypically, mesenchymal stem cells can express the characteristics of endothelial, perivascular, neural, bone or muscle cells, and also express a range of surface markers (including CD49a/CD29, CD44, STRO-1, CD90, CD105, CD106, CD146, CD140b, CD166 and CD271). This suggests a common link between different cell types because most of these markers are expressed by all mesenchymal stem cells (45, 46, 101, 104). However, clonal studies have highlighted the heterogeneous nature of these cells, given that different mesenchymal stem cell colonies demonstrate different proliferative and developmental capacities both in vitro and in vivo (46, 67, 85, 101). Hence, characterization of candidate cells has involved the combined evaluation of their surface maker expression as well as of their proliferative ability (to form colonies) and developmental potentials (to differentiate into osteoblasts, adipocytes and chondrocytes) (11, 101, 103).

Bone marrow mesenchymal stem cells are the most widely studied mesenchymal stem cells because they are easily accessible in quantities appropriate for clinical applications (19, 20, 46). These cells are clonogenic and have demonstrated the ability to form bone and cartilage in vivo (101, 102). Because of their differentiation potential, bone marrow mesenchymal stem cells have been used in various phases of clinical application, particularly in orthopedics (21, 53). Mesenchymal stem cells have also been shown to form cementum, periodontal ligament and alveolar bone in vivo after implantation into periodontal defects in beagle dogs (50, 63), suggesting that bone marrow may be a useful source of mesenchymal stem cells for periodontal regeneration. Apart from the bone marrow, mesenchymal stem cell-like cells have also been identified in many other tissues, including adipose tissue, muscle, peripheral blood, fetal pancreas and liver (6, 18, 54, 67, 157). Adipose tissue-derived mesenchymal stem cells exhibit stable growth kinetics in vitro and display a multilineage differentiation capacity (including osteogenesis, chondrogenesis and adipogenesis) which is similar to that of bone marrow mesenchymal stem cells (42, 59, 74, 159). As adipose tissue can be obtained by using less-invasive methods and in larger quantities than bone marrow cells, the use of adipose-derived mesenchymal stem cells as an alternative to bone marrow mesenchymal stem cells is very appealing. Indeed, at least one study has demonstrated that eight weeks after implantation of adipose-derived stem cells into rat periodontal defects, new periodontal ligament-like and alveolar bone-like structures were formed, implying that adipose-derived stem cells could promote periodontal regeneration in vivo (133). The abundance of human lipoaspirates, coupled with low host morbidity in their procurement, makes them a unique stem cell reservoir for regenerative periodontal therapy.

**Stem cells in dental and periodontal tissues**

In addition to nondental stem cells, the potential of dental mesenchymal stem cell-like cells for periodontal regeneration and repair has been extensively studied in recent years. The ability of mesenchymal stem cells to differentiate into multiple specialized cell types in many adult tissues (including dental tissues) has made them a promising cell source for use in periodontal regeneration.

The first human dental stem cells were isolated from dental pulp tissue of extracted third-molar teeth.
and were characterized relative to bone marrow mesenchymal stem cells (43). These dental pulp stem cells were found to be highly proliferative, clonogenic cells capable of differentiating into odontoblast-like cells and forming dentin/pulp-like complex when implanted into immunocompromised mice (41, 43). Subsequently, human mesenchymal stem cells were isolated from exfoliated deciduous teeth and were noted to induce bone and dentin formation in vivo (82). Periodontal ligament stem cells were first isolated in 2004 and have been shown to give rise to adherent clonogenic clusters resembling fibroblasts (110). They are capable of developing into adipocytes, osteoblast-like cells and cementoblast-like cells in vitro as well as producing cementum-like and periodontal ligament-like tissues in vivo (39, 110, 112). Recent studies have also shown their ability to differentiate into neuronal precursors (24, 128). Periodontal ligament stem cells also express an array of cementoblast and osteoblast markers as well as the STRO-1 and CD146 antigens, which are found on dental pulp stem cells and bone marrow mesenchymal stem cells (43, 135). These findings indicate that periodontal ligament stem cells have properties similar to those of dental pulp stem cells and bone marrow mesenchymal stem cells, and this may represent another mesenchymal stem cell-like population (Fig. 1).

In 2006, stem cells from the apical papilla of human teeth were isolated (1, 120). These cells form adherent clonogenic clusters and, similar to other mesenchymal stem cell populations, are capable of differentiating into adipocytes and odontoblasts/osteoblasts in vitro. Stem cells from the apical papilla have been shown to give rise to dentin tissue in immunocompromised mice, and to generate a root/periodontal complex capable of supporting a porcelain crown after transplantation with periodontal ligament stem cells in minipigs (119, 120). These findings provide support for the use of combined mesenchymal stem cell populations in root and periodontal regeneration.

Mesenchymal progenitor cells have also been isolated from the dental follicle of human third-molar teeth (84). These fibroblast-like, colony-forming and plastic-adherent cells express stem cell markers (STRO-1 and nestin) and can be maintained in culture for at least 15 passages. STRO-1-positive dental follicular progenitors have been shown to differentiate into cementoblasts in vitro (64, 148) and to form cementum in vivo (48). The finding that immortalized dental follicle cells can generate periodontal ligament-like tissue after in vivo implantation (151) implies that dental follicular progenitor cells may be a useful research tool for studying periodontal ligament formation and for regenerative periodontal therapies.

While the use of both dental and nondental mesenchymal stem cells for tooth formation and periodontal regeneration are promising, mesenchymal cell populations from different tissues display distinct biological properties (27). Even if they carry common genetic markers, they are likely to be conditioned by their specific microenvironment and to be committed towards a specific differentiation pathway (87, 88). This notion is supported by the observation that bone marrow mesenchymal stem cells display a lower odontogenic potential than dental mesenchymal stem cells (156). In this context, it remains to be determined which source of dental mesenchymal stem cells will be most suitable for regenerative periodontal therapy. The use of dental follicular cells is likely to be limited by the availability of tooth germs, and nondental stem cells may require the transfer of genes to enhance their odontogenic potential. Although the best stem cell source is yet to be identified, the prospect of using these cells for regeneration represents a step forward in the development of more predictable biologically based therapies for the periodontium.

Potential uses of stem cells in periodontal regeneration

Stem cells have been used extensively in many medical disciplines for the repair and/or regeneration of defective tissues and organs such as bone (53),

![Fig. 1. Schematic illustration of the isolation of mesenchymal stem cells from bone marrow, dental pulp and periodontal ligament.](image-url)
cartilage (86), heart (122) and spinal cord (81). In dentistry, the identification of mesenchymal stem cell-like populations from both dental and nondental tissues has presented exciting possibilities for the application of tissue engineering as well as gene-based therapies. These techniques have the potential to lead to the development of novel strategies for regenerative periodontal therapy.

**Periodontal tissue engineering**

Tissue engineering is a contemporary area of science based on the principles of cell biology, developmental biology and biomaterials science to develop new procedures and biomaterials to replace lost or damaged tissues (69, 93, 114). The main requirements for producing an engineered tissue are appropriate progenitor cells, signaling molecules, an extracellular matrix or carrier construct and an adequate blood supply (114, 121). Although tissue engineering encompasses many different strategies, including cell injection, tissue culturing, porous and injectable scaffolds, and three-dimensional printing (7, 114), this field is most frequently linked to the paradigm of cell delivery within biocompatible scaffolds (70, 138). In this context, a potential tissue-engineering approach to periodontal regeneration involves the incorporation of progenitor cells and instructive messages in a prefabricated three-dimensional construct and subsequent implantation of the construct into the defect site (7) (Fig. 2). This approach may overcome a major shortcoming associated with conventional regenerative procedures because the recruitment of progenitor cells and growth factors is negated and healing can be enhanced.

Tissue-engineering strategies have been applied to reconstruct damaged periodontal apparatus, either by reiteration of tooth development based on epithelial–mesenchymal tissue recombination or by seeding of cells on biomaterial scaffolds (32, 63, 89–92, 98, 120, 133). The tissue-recombination technique aims to replicate key reciprocal interactions between the dental epithelium and the ectomesenchyme during odontogenesis to regenerate the periodontium. For example, following the combination of embryonic epithelial and mesenchymal cells derived from mouse fetuses, the re-associated tooth germs result in tooth-like structures including roots, periodontal ligament and alveolar bone in vivo (55, 91). Furthermore, the combination of oral epithelium with nondental-derived mesenchymal (e.g. embryonic stem cells, neural stem cells and adult bone-marrow-derived cells), results in the formation of both tooth crown and bone in vivo (96). Several studies have reported that engineered tooth primordia give rise to proper tooth development after being transferred into the adult mandible (32, 91, 96), indicating that cultured stem cells can replace lost or damaged dental structures following transplantation into the adult oral cavity. However, the periodontal structures regenerated using tissue-recombination techniques are not formed in isolation from other dental tissues and this may pose problems for implantation into periodontal defects. In addition, there is currently no suitable substitute for the embryonic epithelial compartment of the engineered tooth germ, and the use of human embryonic tissues for periodontal engineering may limit the practical application of this approach.

The technique of cell transplantation, within three-dimensional matrices, to regenerate the periodontium has been extensively studied. Nondental stem cells (such as bone marrow mesenchymal stem cells and adipose-derived stem cells) have been...
investigated as cell sources for periodontal regeneration. Autologous bone marrow mesenchymal stem cells and adipose-derived stem cells can regenerate alveolar bone and periodontal ligament-like structures after transplantation \textit{in vivo}, and this provides support for the use of these cells in regenerative periodontal therapy (63, 72, 133). Studies have also used dental stem cells to achieve periodontal regeneration both \textit{in vitro} (136, 137) and \textit{in vivo} (32, 44, 66, 120, 152). In these studies, progenitor cells were seeded directly onto biomaterial scaffolds (e.g. polyglycolic acid, calcium phosphate material, collagen sponges) followed by transplantation into periodontal defects in animal models (such as mice, rats, dogs, pigs and sheep). Seeding of tooth bud cells (which presumably include some progenitor cells) on biodegradable scaffolds resulted in the formation of new periodontal ligament and bone tissues after implantation into the omenta of adult rat hosts and at the site of previously lost teeth (32, 152). A novel study has reported the combination of swine stem cells from the apical papilla with periodontal ligament stem cells to regenerate root and periodontal structure in minipigs (117). The swine stem cells from the apical papilla were seeded into a root-shaped scaffold that was then wrapped with gelfoam containing porcine periodontal ligament stem cells. After a three-month healing period, periodontal ligament tissue was noted to form around this bio-root structure and appeared to have a natural relationship with the surrounding bone. Regenerated root structure containing new cementum and periodontal ligament has been reported to occur by culturing swine dental bud cells on a cylinder scaffold and then grafting it back into the alveolar socket (66). These promising results reported in animal models using dental stem cells are paving the way for human regenerative periodontal therapy.

Overall, these findings demonstrate the feasibility and potential of using dental and nondental stem cells for functional periodontal and tooth regeneration. An ideal source of stem cells for periodontal regeneration should be nonimmunogenic, highly proliferative, easy to harvest, resilient to prolonged processing and have the ability to differentiate into desired cell types (40). Recent findings confirming that human adult dental fibroblasts can be reprogrammed to pluripotency (75, 99, 126, 155) may enable researchers to overcome immune rejection and to produce large quantities of cells for regenerative periodontal therapy. Human-induced pluripotent stem cells can be derived from a dental source (e.g. gingival fibroblasts of the patient) and then differentiated into a variety of autologous cell types (including dental stem cells and dental epithelium) \textit{for in vivo} administration.

### Stem cell-mediated gene therapy

Gene therapy relies on genetic engineering involving molecular techniques to introduce, suppress or manipulate specific genes, thereby directing an individual’s own cells to produce a therapeutic agent (4). In the context of periodontal regeneration, gene therapy seeks to optimize the delivery of agents, such as growth factors, to periodontal defects so that the limitations associated with the efficacy of topical application of these factors (e.g. a short duration of action) can be overcome (106). Gene-delivery techniques have been used in periodontal ligament and alveolar bone regeneration in rats (60, 92), and embryonic stem cells have been shown to express tooth-initiation genes in mice (96, 149). Two potential strategies for delivering therapeutic transgenes into human recipients are: (i) the direct infusion of the gene of interest using viral or nonviral vectors \textit{in vivo}; and (ii) the introduction of the gene into delivery cells (often a stem cell) outside the body \textit{ex vivo} followed by transfer of the delivery cells back into the body (160). The inherent proliferative and pluripotent capabilities of stem cells may offer lifelong opportunities for treatment by repairing, replacing or regenerating the damaged tissues.

The use of adenoviral vectors to enable the overexpression of growth-promoting molecules, such as platelet-derived growth factor and bone morphogenetic protein-7, has been investigated for its potential in periodontal regeneration (5, 60, 61). Sustained release of bone morphogenetic protein-7 and platelet-derived growth factor by transformed cells implanted into experimental periodontal defects results in enhanced regeneration of bone and cementum (33, 60). The use of such technology with dental stem cells may offer an alternative to conventional methods as a result of their ability to provide a renewable source of growth factor release for regeneration. STRO-1-selected rat dental pulp stem cells transduced with bone morphogenetic protein-2 demonstrate enhanced odontogenic differentiation compared with nontransduced cells (147). However, much work is still needed to optimize the number of cells that are virally transduced and to maximize the duration and extent of gene expression. Further research is also needed to address the potential risks of viral recombination and immune responses towards viral antigens (36, 118), which may ultimately determine the
success of gene-transfer techniques in periodontal regeneration. Many challenges remain in bringing stem cell research to clinical practice in humans, and it is important to overcome these challenges to fulfill our goal of treating periodontal diseases with stem cell-based therapy.

Challenges in bringing stem cell-based research to practice

Biological challenges

Despite biological evidence showing that regeneration can occur in humans, complete and predictable regeneration still remains an elusive clinical goal (especially in advanced periodontal defects). The isolation and characterization of stem cells from periodontal tissues have provided a good starting point for understanding the role of progenitor cells in periodontal healing. However, we have incomplete understanding of the way that roots develop, and little is known about the signaling mechanisms that occur during this process (124, 130). The molecular pathways that underlie stem cell self-renewal and differentiation are also largely unknown (16). For periodontal regeneration to occur, we need to replicate the key cellular events that parallel periodontal development and to understand the specific cell types, the inductive factors and the cellular processes involved in formation of the periodontium (7). Given that the fate of stem cells is influenced by their interaction with the microenvironment (including soluble and immobilized factors, extracellular matrix and signals from neighboring cells), understanding the key components regulating the properties of stem cells may elucidate ways to expand stem cells properly and control their differentiation precisely (34). Numerous studies on stem cells to date have emerged from work on cell culture or animal models. While some species (e.g. primate) are more suited than others (e.g. mouse) for understanding stem cell behavior in humans, these findings may not always be directly extrapolated to humans.

Technical challenges

The technical challenges in stem cell therapy are associated with cell manipulations, scaffold materials and delivery systems. First, culture conditions are not sufficiently developed to mimic the cell microenvironment in vivo and to ensure that both cell proliferation and differentiation can be performed safely and consistently. Furthermore, as cell-culture medium often requires xenogenic products (such as fetal bovine serum or mouse feeder layers), cell cultures may not be completely free of pathogens and infectious risks are a concern (79). The establishment of an optimal culture condition free of potential cross-contaminations is relevant in producing clinical-grade human stem cell lines and for performing basic research involving the regulation of their self-renewal and lineage determination. Second, timing is an inherent constraint in cell therapy and tissue engineering. Some autologous construct-based approaches may involve weeks to months of ex vivo processing (35). Although the use of stem cells can often minimize the processing time compared with somatic cells, possible karyotypic instability and gene mutations of the cells after prolonged culture can also limit their usefulness (78). Third, the search for the ideal biocompatible scaffolding material(s) and delivery system is a significant technical pursuit. The ideal matrix scaffold should mimic native extracellular matrix, support cell attachment, allow controlled release of bioactive factors, be conducive to tissue ingrowth and facilitate laboratory handling (8, 10, 76, 142). There is evidence to suggest that cultured human periodontal ligament stem cells in a suitable scaffold implanted into surgically created periodontal defects can result in the formation of a periodontal ligament-like structure (111). However, further refinement of the methodology to propagate and incorporate these cells into a carrier scaffold is needed, and this should limit the ex vivo processing time and encourage the integration and function of the implanted cells with the host cells (62, 158).

Clinical challenges

Clinical challenges in stem cell-based periodontal therapy relate to immune rejection after administration, oncogenic properties of stem cells and functional integration of transplanted tissues into the host (23). It is important to understand how the immune system will respond to stem cells or their derivatives upon transplantation. Generally, the immunogenicity of a human cell depends on its expression of class I and II major histocompatibility antigens, which allow the body to distinguish its own cells from foreign cells (14). Human embryonic stem cells express a low level of class I major histocompatibility antigens, but this expression is up-regulated with differentiation (30). A potential solution to this problem lies in the use of autologous stem cells (from cell/tissue banks) to
overcome immune rejection (14, 58). Furthermore, the production of patient-specific pluripotent stem cells (or induced pluripotent stem cells) from adult somatic cells is now feasible and the differentiation of autologous induced pluripotent stem cells into cell types desired for transplantation is being explored (49). Recent findings relating to the immunosuppressive effects of mesenchymal stem cells both in vitro and in vivo have also raised the possibility of using allogenic stem cells without the need for donor and recipient cross-matching (22, 94, 105).

The challenge relating to genomic stability and the risk of tumorigenesis following stem cell transplantation are major safety considerations because reliable methods to eliminate undifferentiated embryonic stem cells from culture are yet to be established (13), and current studies lack long-term follow-up to draw firm conclusions (154). It is likely that the more specific and extensive the therapeutic application, the longer the stem cells may have to remain in vitro. During this extended period in culture, there is a greater likelihood for genetic or epigenetic changes in stem cells (31, 78). Improvement in the understanding of such changes in vitro will better enable researchers to address the risk of tumorigenesis in stem cell therapy.

Finally, it is unclear whether human stem-cell derivatives can integrate into the recipient tissue and fulfill the specific functions of lost or injured tissues (28). It will be necessary to demonstrate that stem cells develop into stable cells and display the characteristics and functions of normal host cells following their transplantation. It is hoped that, as our knowledge on progenitor cells, growth factors and delivery systems improves, we will make stem cell-based therapy a safe and effective approach in periodontal regeneration.

Conclusion

Restoration of tissues destroyed by periodontitis to their original form and function has been a long-standing goal of periodontal therapy. However, our current available regenerative therapies are crude and of poor clinical predictability. There is need for novel regenerative technologies to be developed based on contemporary understanding. In order for this to become a reality it will be necessary for us to obtain a complete understanding of periodontal development and the progenitor cells involved in this process. Subsequent tissue-engineering approaches may then be developed using these progenitor cells within a matrix scaffold, together with the introduction of various signaling molecules in an orderly temporal and spatial sequence. To date, a number of studies have reported that stem cells, in conjunction with different physical matrices and growth factors, have the capacity to regenerate periodontal tissues in vivo. Notwithstanding these significant advances there are still numerous biological, technical and clinical hurdles to be overcome. In particular, a thorough understanding of the underlying processes in periodontal development, as well as the mechanisms behind stem cell self-renewal and differentiation, will be required. Refinement of current laboratory techniques to facilitate handling of stem cells and their translation to a clinical setting will be equally critical in advancing the field. Studies on both embryonic cells and adult stem cells should continue as part of a collective effort to expand our knowledge on how cells function and what fails in the disease process. It is this combined and solid knowledge base that will underpin future treatment modalities and ultimately make stem cell-based tissue engineering and gene therapy a realistic alternative in periodontal regeneration.

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