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Concise Review

Advances in Regenerative Dentistry Approaches: An Update

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ABSTRACT

Regenerative dentistry is a rapidly evolving field in dentistry, which has been driven by advancements in biomedical engineering research and the rising treatment expectations and demands that exceed the scope of conventional approaches. Tissue engineering, the foundation of regenerative dentistry, mainly focuses on 3 key components: stem cells, bioactive molecules, and scaffolds. Dental tissue–derived stem cells are especially significant in this regard due to their remarkable properties. Regenerative techniques have provided novel approaches to many conventional treatment strategies in various disciplines of dentistry. For instance, regenerative endodontic procedures such as pulp revascularisation have provided an alternative approach to conventional root canal treatment. In addition, conventional surgical and nonsurgical periodontal treatment is being taken over by modified approaches of guided tissue regeneration with the aid of 3-dimensional bioprinting and computer-aided design, which has revolutionised oral and maxillofacial tissue engineering. This review presents a concise overview of the latest treatment strategies that have emerged into clinical practice, potential future technologies, and the role of dental tissue–derived stem cells in regenerative dentistry.

Introduction

The regenerative medicine and tissue engineering field is expanding rapidly due to the recent advancements in biomedical engineering research. Many researchers worldwide are working on advancing regenerative research due to its promising nature of unraveling curative and restorative treatment approaches for disease conditions which, at its highest expectation, is synonymous with reversing a disease process. It is well known that oral and craniofacial tissues have limited capacity to regenerate spontaneously and restore to their original state once they are severely damaged, such as in the case of dental caries, severe maxillofacial pathology, or trauma. Hence, dental and craniofacial tissue engineering has been researched and developed over the decades.

The advancement of regeneration and tissue engineering has been projected along 3 key components: stem cells, bioactive molecules, and biomaterials, which act as scaffolds to promote cell growth and differentiation.[1] The collaborative action of these 3 components is known to enhance the reparative potential of the resident cells of the tissue whilst promoting the migration of more stem cells towards the site of injury and propagating the overall regenerative or reparative process.[2] Numerous interventional approaches have been developed to enhance the efficacy and applicability of these strategies, mainly cell-free and cell-based approaches. Cell-free approaches aim to recruit resident cells, including stem cells, via bioactive molecules embedded in biomaterials or scaffolds to enhance the regenerative process. This phenomenon is also referred to as cell homing.[3] Cell-based approaches, on the other hand, involve the administration of exogenously cultured autologous or allogeneic stem cells into the affected tissue to mediate regeneration.[4]

The optimal combination of the above 3 key components is expected to produce desirable outcomes in tissue regeneration. This review will provide an overview of the

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recent advancements in tissue engineering applications in clinical dentistry, focusing on the contribution of dental stem cells (DSCs) and their current trends to regenerative dentistry.

Clinical advancements

Regenerative endodontics (dentin-pulp complex regeneration)

The goal of regenerative endodontics is to recover normal pulp function in teeth with reversible pulpitis and regeneration of pulp-dentinal complex in irreversibly inflamed or necrotic teeth.[5] Pulp revascularisation, which refers to the revascularisation of an immature permanent tooth with an infected necrotic pulp and apical periodontitis/abscess that can promote root development, is currently considered the only regenerative endodontic treatment approach in clinical practice.[6] This procedure involves chemical disinfection of the root canal using intracanal medicaments and antibiotics followed by induction of bleeding to generate a favourable regenerative niche.[7] The resulting blood clot acts as a scaffold that facilitates homing of stem cells, macrophages, and fibroblasts, whilst hard tissue deposition reinforces the dentinal walls. However, this may not be considered pulp regeneration as it gives rise to bone, cementum, and periodontal ligament-like fibrous tissue.[8]

The above method of pulp revascularisation has been advanced into approaches where natural or synthetic scaffolds/biomaterials are used as adjuncts to aid in the revascularisation process. Some examples of these include collagen scaffolds that are placed over the blood clot and platelet-rich fibrin (PRF) placed in the root canal to promote cell homing, differentiation of stem cells, entrapment, and slow release of angiogenic cytokines, including fibroblast growth factor (FGF), vascular endothelial growth factor, and platelet-derived growth factor (PDGF).[9,10] PRF is known to overcome many limitations of the basic method of bleeding induction, such as possible damages to Hertwig's epithelial root sheath resulting in impaired or no continued root development in immature teeth.[11]

In the recent past, dentine has been identified as a rich source of growth factors favourable for pulp regeneration, many of which are determined to be signalling molecules. The effect of these proteins on dental pulp cells has been observed in terms of chemotaxis, increased gene expression of odontoblast phenotype, improved mineralisation, and enhanced neurogenesis and angiogenesis.[12] Researchers have experimented with preparations such as freeze-dried dentine matrix and dentine protein disks.[13] Based on in vivo studies, Galler et al have suggested a regenerative endodontic approach that can be attempted in the clinical setting, which involves root canal preparation and disinfection, irrigation with ethylenediaminetetraacetic acid (EDTA), and collection of EDTA with dentine matrix proteins followed by mixing of collected EDTA with a scaffold material and injection into the root canal (Figure 1A) The purpose of EDTA conditioning here is not only the removal of the smear layer but also the release of the bioactive molecules embedded in dentin and exposure of dentin's collagenous structures to facilitate cell adhesion.[14]

Whilst all the above treatment approaches are cell-free methods targeting endogenous cell homing, a few cell-based regenerative endodontic approaches are emerging into clinical practice, with clinical trials underway based on the promising results observed in robust animal studies. In a clinical trial, autologous dental pulp stem cells (DPSCs) isolated from extracted third molars and expanded in vitro were transplanted into pulpectomised teeth with granulocyte colony-stimulating factor in atelocollagen. In these patients, a massive positive response for electric pulp testing and dentine formation in cone beam computed tomography has been observed in 3 out of 5 cases.[15] In addition, transplant of autologous DPSCs of human exfoliated deciduous teeth (SHED) in teeth with pulp necrosis due to traumatic dental injuries has shown regeneration of 3D pulp tissue along with blood vessels and sensory nerves at 12 months post-treatment.[16] Further, regenerative endodontic procedures using allogeneic human umbilical cord mesenchymal stem cells in a plasma-derived biomaterial in mature permanent teeth with apical lesions have shown increased sensitivity and blood flow in 12 months follow-up, highlighting the clinical safety and efficacy of allogeneic endodontic regenerative cell therapy.[17]

Periodontal tissue regeneration

Periodontal therapy aims to restore the affected soft and hard tissue components of the periodontium to their original architecture and function.[18] Due to many limitations of the conventional treatment approaches including nonsurgical and surgical periodontal debridement and autologous and connective tissue grafts, the current trend of periodontal therapy has shifted towards "true" regenerative rather than reparative approaches.[19] One such approach is bone grafts introduced as alloplastic material (synthetic fillers), autografts, allografts, and xenografts that can induce bone formation.[20]

Guided tissue regeneration is a widely practiced therapeutic approach currently considered the gold standard of periodontal tissue regeneration.[21] This method, though superior to conventional periodontal treatment, is reported to have varying success rates depending on the technique and properties of the barrier membrane where microbial colonisation and rupture of the membranes have been identified as potential causes for poor treatment outcomes.[22] To overcome these limitations, composite membranes of polycaprolactone and gelatin loaded with zinc oxide nanoparticles have been fabricated, which have been found to significantly reduce the growth of *Staphylococcus aureus* over time whilst leaving the ability of periodontal cells to repopulate unaffected.[23]

Moreover, the use of PRF with open flap debridement/bone graft was reported to lead to significant improvements in clinical attachment levels and radiographic bone fill.[24] In contrast, growth factors such as FGF-2, PDGF, and bone morphogenetic protein-2, in conjunction with various biomaterials, have also demonstrated improved clinical outcomes.[25-28]

Based on the highly positive outcomes of many animal studies, several clinical trials have been conducted on treating periodontal defects with cell-based regenerative approaches. These include transplantation of autologous

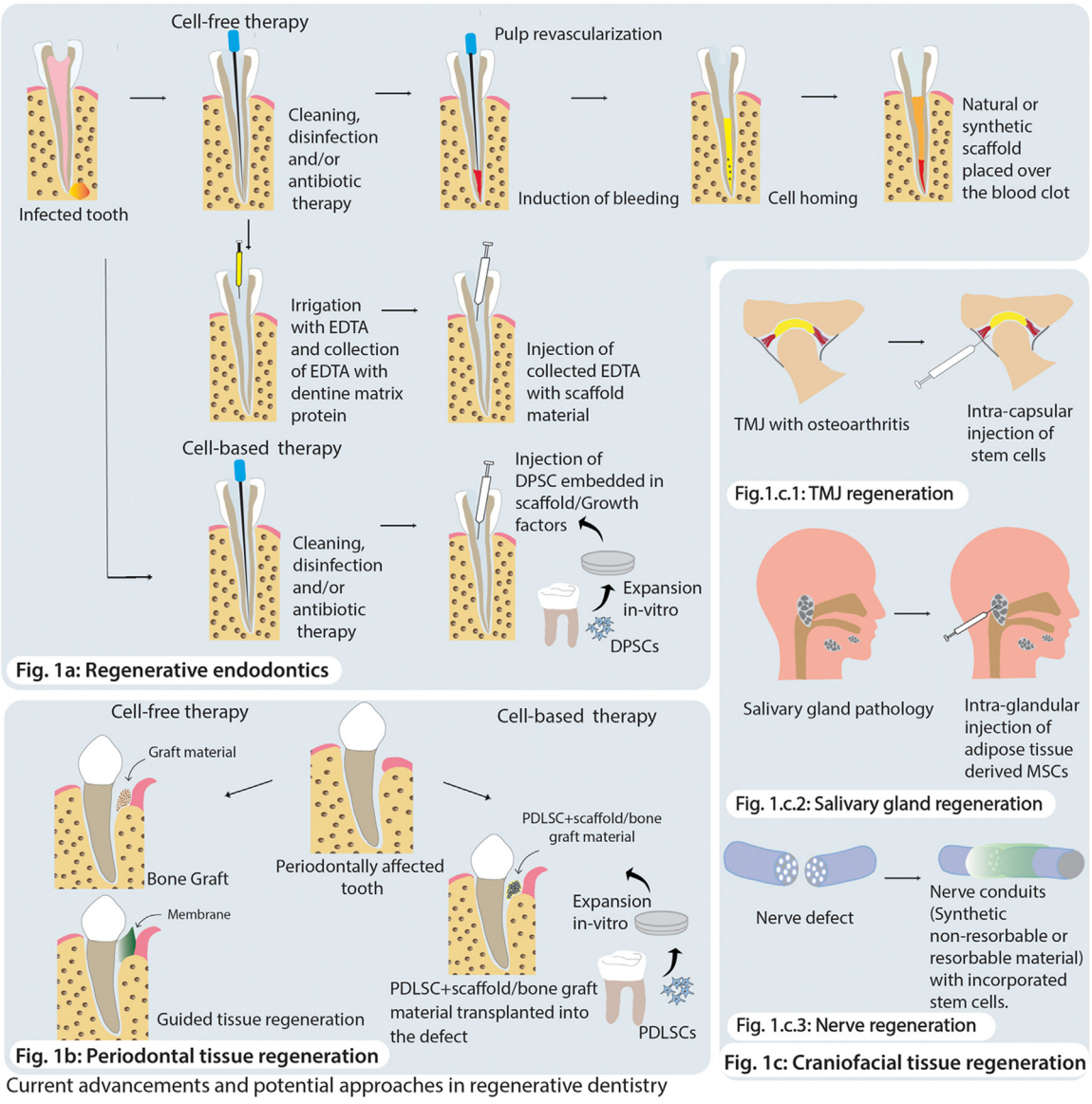

Fig. 1 – Current advancements and potential approaches in regenerative dentistry.

human periodontal ligament stem cells isolated from extracted third molars mixed with bone grafting material or gelatin scaffolds into periodontal defects following open flap debridement. This has shown favourable outcomes in terms of tooth mobility, clinical attachment loss, and bone density on postsurgical follow-up over extended periods[29] (Figure 1B).

Temporomandibular joint (TMJ) regeneration

The TMJ is a frequent site of pathology in the oral and maxillofacial (OMF) region. The most frequent TMJ pathologies include disc derangement disorders, autoimmune disorders, and osteoarthritis associated with TMJ (TMJ-OA).[30]

The treatment of TMJ-OA at present depends on its severity. It ranges from conservative treatment such as occlusal splints, intra-articular injections, arthrocentesis, or arthroscopy in mild or moderate cases to radical curative methods such as open joint surgery for severe cases.[31] These approaches often relieve symptoms successfully but do not facilitate permanent recovery, hence the need for novel regenerative curative treatment strategies for TMJ-OA.[32]

The use of bone marrow mesenchymal stem cells (BMMSCs) in TMJ-OA has been widely studied in animal models and proceeded to clinical trials where BMMSCs have been inoculated into the osteoarthritic TMJ resulting in improved pain relief, increased mouth opening and chewing efficiency[33,34] (Figure 1C).

The therapeutic action of DSCs in TMJ-OA is still being explored via in vivo experimentation. Intravenous administration of serum-free conditioned media of SHED can inhibit cartilage destruction and inflammation whilst promoting the regeneration of condylar cartilage and subchondral bone.[35] This evidence suggests that intra-articular stem cells may also be an effective treatment option for TMJ-OA.[31] TMJ-OA

has also been experimentally treated with mesenchymal stem cell (MSC)–derived exosomes and platelet-rich plasma in animal models, which have shown that exosome therapy controls the level of inflammation in TMJ followed by expression of the matrix and proliferation leading to healing of subcondylar cartilage and bone.[36-38]

Craniofacial tissue engineering

Regeneration of bone

Reconstruction of OMF structures is challenging due to the various tissues involved, functional complexity that requires fine neuromuscular coordination and aesthetic demands. OMF defects could result from trauma or surgical resection owing to benign or malignant tumours, infections, or developmental anomalies. Bony defects in the OMF region can be reconstructed using autologous bone grafts, allografts, demineralised bone matrices, hydroxyapatite calcium phosphate, bone morphogenetic proteins, collagen scaffolds, and bone marrow aspirate concentrate.[39,40]

Autologous grafts frequently delivered include iliac bone grafts and costochondral rib bone grafts.[41,42] However, the treatment of choice for reconstructing extensive bony defects, such as in segmental mandibular resection, consists of conventional autologous grafts that can be delivered as microvascular free fibula flaps.[43-45] A promising therapeutic approach to replace autologous bone grafts has not been discovered. However, many approaches have been introduced to optimise the bone graft, prolong its viability, and promote mineralisation. Improvement of graft vascularisation via growth factors and stimulation of bone marrow and adipose tissue-derived MSCs are a few such approaches.[46]

Bone augmentation before dental implant placement in resorbed alveolar ridges is a critical step that contributes to the longevity of the implant.[47] Whilst the gold standard of bone grafting materials is considered autogenous bone grafts,[48] customised 3D printed nanohydroxyapatite (3DHA) block grafts with incorporated growth factors have been introduced into clinical practice with promising outcomes.[49]

Nerve regeneration

Nerve injuries in the orofacial region are often the result of trauma, tumours, or iatrogenic causes and frequently involve the inferior alveolar nerve (IAN), lingual nerve, infraorbital nerve, and facial nerve.[50,51] In current surgical practice, autologous nerve grafts and nerve conduits are used to reconstruct nerve gaps, with many advancements and modifications involving the latter technique. Nerve conduits were initially made of synthetic non-resorbable material and then advanced to conduits composed of resorbable materials such as collagen. However, their treatment outcomes are not reported to be as successful as autologous nerve grafts due to the absence of cells.[52] The newest advancement is focused on incorporating Schwann cells, or stem cells, into the conduit to promote better regeneration (Figure 1C). Herein, nerve conduits constructed with cell spheroids and 3D bioprinted conduits have been used in animal studies with favourable outcomes as they enhance nerve regeneration via improved cell survival, differentiation, and extracellular matrix (ECM) formation.[53-55] Gingival MSCs have been identified as a potential cell source for 3D bioprinting of scaffold-free nerve constructs for the regeneration of peripheral nerves.[56]

Salivary gland regeneration

Currently, individuals with impaired salivary gland function are symptomatically treated with artificial saliva and sialagogues.[57] Salivary gland regenerative treatment would be ideal for these patients. The use of DSCs in salivary gland regeneration has yet to be reported in the clinical setting. However, studies have shown that umbilical cord–derived MSC intravenous infusions result in increased salivary flow rate and alleviate other Sjogren syndrome–related symptoms[58] (Figure 1C) Further, intraglandular injection of adipose-derived MSCs (AMSCs) has shown improved salivary flow rate, increased acinar and ductal areas, and a decrease in fibrosis in irradiated individuals highlighting the potential of MSCs in salivary gland regeneration.[59,60]

Even though only a few regenerative therapeutic approaches in regenerative dentistry are currently in clinical practice, many studies are being conducted with promising results that pave the way for the discovery of more advanced treatment approaches. The Table summarises some of the recent preclinical studies on regenerative dentistry.

Current trends and future perspectives in regenerative dentistry

Cell sheets, spheroids, and organoids

Stem cell therapy has shown limited successful outcomes in clinical dentistry, as cells administered as monodispersed preparations are often poorly retained at the site or are subjected to rapid cell death.[72]

Cell sheets are a scaffold-free cell therapy that forms high-density sheet structures out of cells and their extracellular matrix. The ECM here preserves intercellular and cell-matrix connections and caters to the function of a scaffold by providing strength and support for cells and a 3D structure for cell proliferation and differentiation.[73]

Spheroids are dense, 3D cell aggregates that, in addition to having a well-formed network of cells in an ECM mimicking the microenvironment found in native tissues, are capable of creating a potent secretome that promotes angiogenesis, mitigates inflammation, and recruits host cells to enhance repair and regeneration.[72] The use of in vitro fabricated prevascularised microtissue spheroids of DPSCs has been reported to produce vascular dental pulp-like tissue in immunodeficient mice.[74]

Fabrication of organoids is another cell-based regenerative approach that involves in vitro generation of 3D tissue constructs that mimic the complex microanatomy and function of the corresponding tissue in vivo using induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), or adult stem cells[74,75] (Figure 2). Fabrication of tooth germ organoids that closely resemble the tissue interactions in human tooth development using DPSCs and dental pulp organoid models for toxicity screening of dental materials have been investigated.[76,77] However, the scarcity of readily obtainable DSCs may hinder their use in organoid fabrication due to the

Table – Recent preclinical studies that demonstrate novel approaches in regenerative dentistry.

Study	Tissue	Approach	Experimental model	Findings/outcomes
Chen Ma et al[61]	Dental pulp	Exosomes of DPSCs as a cell homing approach.	A cell homing model using swine teeth. The cavity of the treated dental matrix of swine teeth was filled with dental pulp tissue–derived exosomes (DPT-exos), or dental pulp stem cell–derived exosomes (DPC-exos) laden scaffolds whilst SCAP-containing collagen gel was placed at the root tip. These teeth were implanted subcutaneously into immunodeficient nude mice. The exosomes were expected to recruit SCAPs from the root tip to the pulp cavity.	DPT-exos promoted recruitment and odontogenic and neurogenetic differentiation of SCAPs and enhanced revascularisation.
Li et al, 2022[62]	Dental pulp	Utilisation of apoptotic vesicles (apoVs), which are secreted in the ischemic-hypoxic environment to induce angiogenesis and dental pulp regeneration.	apoVs were derived from human deciduous pulp stem cells, incorporated into tooth scaffolds containing aggregated DPSCs, and implanted in the dorsum of mice.	apoVs recruited endogenous ECs and facilitated the formation of dental-pulp-like tissue, rich in blood vessels.
Han et al, 2022[63]	Dental pulp	Improving postimplantation cell survival and pulp regeneration of SHED with HIF-1α stabilisation.	HIF-1α–stabilised SHED were encapsulated in PuraMatrix hydrogel, injected into root canals of human tooth fragments, and implanted in the subcutaneous space of immunodeficient mice.	HIF-1α stabilisation enhanced cell survival of SHED by modulating various target genes and potential signalling pathways; it also promoted odontogenic tissue formation during dental pulp regeneration.
Liang et al, 2022[64]	Dental Pulp	Utilisation of cell-laden microfibers that offer a specialised structure and a biocompatible microenvironment for cell adhesion, growth, proliferation, and differentiation as a basic microscopic unit for the construction of macroscopic vascular architectures in pulp regeneration.	Ectopic pulp regeneration assay in nude mice to validate the regeneration of the aggregates of mixed DPSC-microfibers and human umbilical vein endothelial cell-microfibers in vivo.	The aggregates of cell-laden microfibers generated more pulp-like tissue, blood vessels, and odontoblast-like cells.
Siddiqui et al, 2021[65]	Dental Pulp	Hydrogels for dental pulp revascularisation. An acellular material with an optimised peptide sequence (SLan) that promotes tissue revascularisation in dental pulp without added growth factors.	Simulation of pulp revascularisation using self-assembling peptide hydrogel, SLan, in adult canine teeth after pulpectomy.	SLan-filled teeth showed organised soft tissue in the canal with collagen, blood vessels, and nerve bundles with an odontoblast-like layer representing tissue regeneration.
Yu et al, 2022[66]	Periodontal ligament	Hierarchical bilayer scaffolds for periodontal tissue regeneration.	Hierarchical bilayer architecture consisting of intrafibrillarly mineralised collagen and unmineralised parallel-aligned fibrils implanted in critical-sized periodontal tissue defects in rats.	The biomimetic bilayer architecture potently reconstructed native periodontium by inserting periodontal ligament fibers into newly formed cementum and alveolar bone by recruiting host mesenchymal stem cells and activating signalling molecules.
Ferreira et al, 2021[67]	Periodontal ligament	Personalised and defect-specific, electrospun, antibiotic-laden scaffolds that resemble the morphologic traits of the native ECM	Defect-specific, 3D, antibiotic-laden polymeric scaffolds containing 1:3 metronidazole/tetracycline (MET/TCH) formulation were used to treat periodontally	MET/TCH defect-specific scaffolds led to increased new bone formation, lower bone loss, and reduced inflammatory response

(*continued*)

Table (*Continued*)

Study	Tissue	Approach	Experimental model	Findings/outcomes
		and its 3D structure for periodontal infection ablation.	compromised 3-wall osseous defects in rats.	compared to antibiotic-free scaffolds.
Abramowicz et al, 2021[68]	Temporo-mandibular joint	3D-printed coated scaffolds implanted in a pedicled flap for TMJ regeneration.	3D-printed and bone morphogenic protein 2-coated scaffold implanted in a pedicled (temporal) flap for paediatric temporo-mandibular condyle reconstruction in pigs.	New bone formation and increased condylar height were observed post-treatment.
Adine et al, 2018[69]	Salivary gland	Innervated secretory epithelial organoids by magnetic 3D bioprinting.	The magnetic 3D bioprinting system generated innervated secretory epithelial organoids from DPSCs transplanted into an ex vivo model to assess their growth and innervation.	The spheroids exhibited high cell viability compared to controls. After differentiation, spheroids expressed salivary gland epithelial compartments, including secretory epithelial, ductal, myoepithelial, and neuronal. After transplant, the salivary gland-like organoids significantly stimulated epithelial and neuronal growth in damaged salivary glands.
Tanaka et al, 2022[70]	Salivary gland	Functional salivary gland organoid—hiSG generation using iPSCs.	Oral ectoderm cells were induced with multiple growth factors and cultured until the cells reached a branching stage with salivary gland buds expressing salivary gland markers, which at this stage were referred to as hiSG. hiSG were then cocultured with salivary gland MSC of mice and transplanted into parotid gland defective mice.	The organoids exhibited high success rates, with 80% of the transplanted organoids being engrafted at transplanted sites with organoid ducts linked to host excretory ducts.
Cho et al, 2022[71]		Neuroregeneration	Tissue-engineered nerve guides with MSCs.	Pre-induced MSC-coated cellulose/collagen nanofibrous nerve conduits were used to regenerate transected facial nerves. Nerve defects treated with the pre-induced MSC-coated cellulose/collagen nanofibrous nerve conduits showed a high degree of recovery based on functional and histologic evaluations.

DPT-exos, dental pulp tissue–derived exosomes; apoVs, apoptotic vesicles; DPSC, dental pulp stem cell; EC, Endothelial cells; ECM, extracellular matrix; HIF-1α, hypoxia-inducible factor-1 α; hiSG, human induced salivary gland; iPSC, induced pluripotent stem cells; MSC, Mesenchymal stem cells; SCAP, Stem cells from the apical papilla; SHED, Stem cells from human exfoliated deciduous teeth; TMJ, temporomandibular joint.

need for large cell numbers. Herein, iPSCs and ESCs are more befitting, considering their multipotent differentiation and self-renewal capacities.[78]

3D bioprinting

The limitations and challenges of organoid fabrication can be overcome in large part by 3D bioprinting, an advanced manufacturing technology capable of producing personalised 3D objects using standardised material based on computer-aided design (CAD) digital models.[79] This cutting-edge technique involves a complex process where the exact positioning of biomaterials/scaffolds is done with cells embedded in a desired pattern with spatial control of functional component placement.[80] One of the most important aspects of 3D bioprinting is its ability to manipulate the delivery of cells and materials in complex fabricated tissue-like constructs enabling it to maintain cell-to-cell growth interconnectivity for improved tissue regeneration.[81] It is expected that 3D-printed organs readily available for transplant may be fabricated in the near future.

Layered scaffolds

The applications of layered scaffolds in dentistry are especially beneficial in periodontal tissue regeneration. In this approach, 3D structures are generated layer-by-layer based on CAD, incorporating stem cells, biomaterials, and growth factors, facilitating the development of multiphasic scaffolds, with each layer designed to regenerate a specific section of

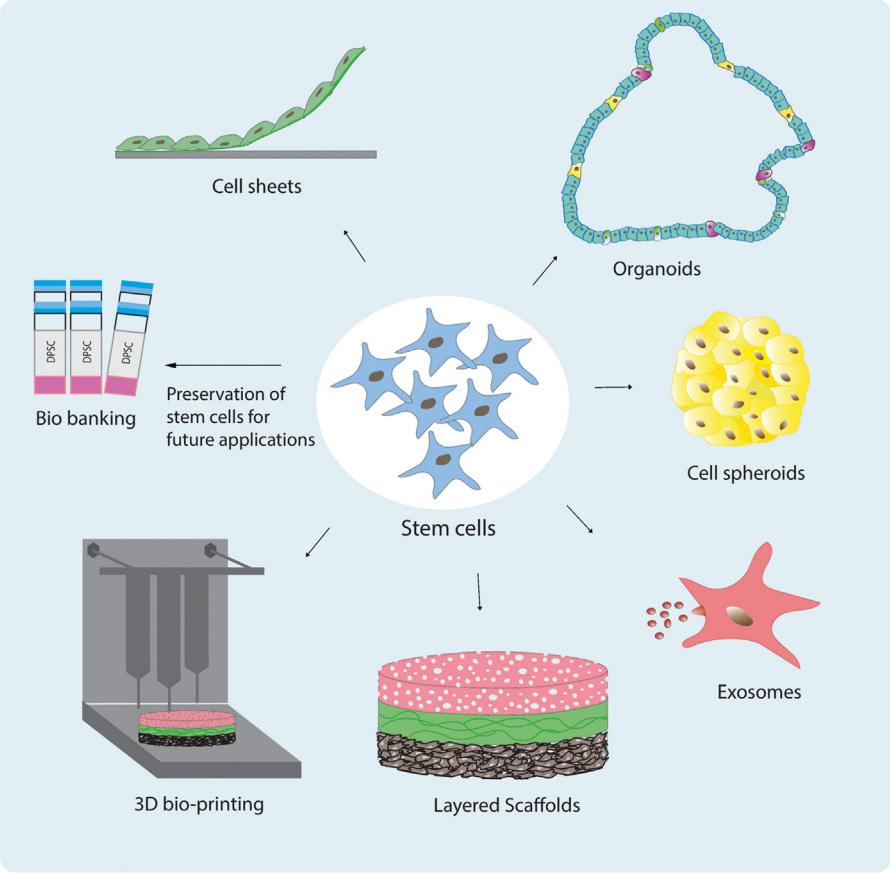

Fig. 2 – Current trends in stem cell–based regenerative dentistry.

the periodontium.[82] These scaffolds are designed according to a hierarchical architecture capable of guiding the tissue regeneration that takes place simultaneously. This is an ideal approach for tissues with sophisticated anatomy and is useful for establishing connections between soft and hard tissues.[82,83]

Exosomes

MSC-secreted exosomes are currently considered a viable, cell-free, therapeutic alternative for the use of cells.[84] The biological functions of exosomes depend on the cells' physiologic or pathologic status at the time of secretion and include immune response modulation, signal transduction, and epigenetic modification.[85] Their advantages over cell therapy include low immunogenicity, high drug loading capacity, biocompatibility, specificity and stability, and lack of cytotoxicity. DSC-derived exosomes have shown great potential for dentine-pulp and oral soft tissue regeneration in in vitro and in vivo models.[86-88]

Biobanking

DSCs hold great potential and promise for many clinical applications, but a large number of cells or their derivatives are required for therapeutic efficacy. Therefore, they need to be expanded in vitro and cryopreserved. However, long-term in vitro culture may pose potential hazards such as chromosomal abnormality, senescence, and microbial contamination.[89-91] Cell banking is used to avoid these risks and to preserve the cells at their most potent stage for future applications. The quality control and maintenance of this multistep process is carried out and kept following international guidelines to ensure its safety and effectiveness.[91]

Challenges in regenerative dentistry

There is no doubt that regenerative dentistry has progressed a long way, and many groundbreaking discoveries have been made throughout the years. However, most of the studies involving stem cells have halted at the stage of animal studies and have not proceeded to clinical trials due to numerous debatable safety and ethical concerns, particularly when it comes to the administration of stem cells. Even though the risk of infection and immune rejection is minimal with the use of heterogeneous cells, the potential risks of undesired tissue formation, tumourigenesis, and metastasis represent a controversial issue that has not yet been resolved.[92] Further, the experimental reproducibility of certain techniques, such as spheroid formation, is questionable as the exact mechanisms underlying these

processes are not yet clearly understood.[93] In addition to the above, the limited availability of certain MSCs and the required clinical grade and modern, sophisticated technologies that may be limited to advanced clinics and laboratories may also curb the opportunities for the progression of these approaches from bench to clinic.

Summary and conclusions

Regenerative dentistry is a burgeoning field where progress has been expedited using MSCs, including DSCs, BMMSCs, and AMSCs. DSCs have gained popularity over recent years as they surpass widely used BMMSCs in noninvasive accessibility. Hence, the current research trends are focused on using DSCs or their derivatives as adjuncts, along with other factors such as biomaterials and bioactive molecules that can optimise the performance of cells and mediate tissue regeneration. CAD and 3D bioprinting have further revolutionised tissue engineering and regenerative approaches where patient-specific customised constructs can be created with high accuracy and precision. Many of the recent achievements in regenerative dentistry are focused on restoring the structure of lost tissues. However, with the advancement of spheroid and organoid generation, significant levels of functional restoration could also be achieved in the near future.

Author contributions

DT conceived and designed the work, conducted the literature research, drafted the manuscript, and approved the final version. WD conceived and designed the work, revised the manuscript, approved the final version approval, and contributed to funding acquisition.

Conflict of interest

None disclosed.

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