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Advances in tissue engineering strategies for periodontal and endodontic regeneration: Current therapies and future trends for disease treatment and tissue repair in the oral cavity

Eamon J. Sheehy [a,b,c], Niamh Coffey [d], Ross M. Quigley [a,e], Henry F. Duncan [c,e], Oran D. Kennedy [a,b,c], Fergal J. O Brien [a,b,c,*]

[a] Tissue Engineering Research Group, Department of Anatomy and Regenerative Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Trinity Centre for Biomedical Engineering, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland
[c] Advanced Materials and Bioengineering Research (AMBER) Centre, Royal College of Surgeons in Ireland & Trinity College Dublin, Dublin, Ireland
[d] School of Dentistry, Royal College of Surgeons in Ireland, 111 St. Stephen's Green, Dublin, Ireland
[e] Division of Restorative Dentistry & Periodontology, Dublin Dental University Hospital, Trinity College Dublin (TCD), University of Dublin, Lincoln Place, Dublin, Ireland

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ABSTRACT

Tissue damage within the oral cavity caused by periodontal and endodontic diseases impart significant socio-economic and healthcare impacts on the global population. In addition to the negative aesthetic effects, such oral diseases cause increased pain and discomfort during everyday activities and advanced forms of these diseases can ultimately result in tooth loss. This motivates the need for novel therapies aimed at regenerating tissues inside and around the tooth or, in the case of tooth extraction, to promote development of sufficient tissue volume to allow for implant placement. Tissue engineering strategies typically combine three-dimensional biomaterial scaffolds, cells and biologics in order to regenerate or replace damaged or diseased tissues. This review will focus on advances in tissue engineering applications within the oral cavity, with a particular emphasis put on periodontal and endodontic tissue regeneration. To that end, we begin by describing the aetiology and progression of the disease states that cause damage to tissues inside and surrounding the tooth and, furthermore, will describe the procedures that are currently used clinically in the treatment of these conditions. Subsequently, biomaterial-based approaches that can be leveraged to promote regeneration of periodontal and endodontic tissues are explored and, thereafter, the advances made in enhancing the efficacy of these biomaterials through the use of cells and biologics outlined. Finally, we describe the state-of-the-art technologies that are envisaged to become disruptive in the field as it moves towards the goal of functional periodontal and endodontic tissue engineering.

Abbreviations

3D	Three-dimensional
ADM	Acellular dermal matrix
BMP	Bone morphogenetic protein
CAp	Carbonate apatite
CM	Conditioned media
CTG	Connective tissue graft
DBBM	Deproteinized bovine bone matrix
DFDBA	Demineralized freeze-dried bone allograft
DPSC	Dental pulp stem cell
ECM	Extracellular matrix
EMD	Enamel matrix derivative
ESE S3 CPG	European Society of Endodontology S3-level clinical practice guideline
FDBA	Freeze-dried bone allograft
FGF	Fibroblast growth factor
GAG	Glycosaminoglycan
GBR	Guided bone regeneration
GTR	Guided tissue regeneration
HUVEC	Human umbilical vein endothelial cell
HyA	Hyaluronic acid
IL	Interleukin
MSC	Mesenchymal stem/stromal cell
MTA	Mineral trioxide aggregate
PCL	Polycaprolactone

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* Corresponding author. Department of Anatomy and Regenerative Medicine, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland.
E-mail address: fjobrien@rcsi.ie (F.J. O Brien).

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PDGF	Platelet derived growth factor
PDL	Periodontal ligament
PDLSC	Periodontal ligament stem cell
PDM	Porcine dermal matrix
PGA	Polyglycolic acid
PLA	Polylactic acid
PLGA	Polylactic-co-glycolic acid
PPP	Platelet poor plasma
PRF	Platelet rich fibrin
PRP	Platelet rich plasma
PTFE	Polytetrafluoroethylene
REP	Regenerative endodontic procedure
SCAP	Stem cells of the apical papilla
SHED	Stem cells of human exfoliated deciduous teeth
TCP	Tricalcium phosphate
TGF	Transforming growth factor
TNF-α	Tumour necrosis factor-alpha
VEGF	Vascular endothelial growth factor

1. Introduction

Oral diseases, including periodontal diseases and dental caries (cavities), in addition to other conditions such as edentulism, have significant socioeconomic and healthcare impacts globally. Oral diseases impose substantial financial burdens on economies due to the costs of treatments, procedures, and hospitalizations. Periodontitis and dental caries also have a significant impact on quality of life, resulting in increased pain and discomfort during activities such as eating and sleeping, while also imparting negative aesthetic effects, which are often detrimental to mental health wellbeing and self-esteem. Indeed, a recent study has estimated the overall annual global financial burden of oral disease, due to both the aforementioned direct costs as well as indirect costs owing to a reduction in productivity due to absenteeism and reduced efficiency, to be $710 billion [1].

Although mild forms of oral disease may be treated using routine dental procedures such as, for example, professional mechanical plaque removal in the case of mild periodontitis or dental fillings in the case of dental caries, advanced forms of these diseases typically require more invasive treatment procedures aimed at regenerating damaged tissues around and/or inside the tooth. The oral cavity, however, is a particularly challenging part of the human anatomy to treat due to the several distinct tissues present within the mouth as well as the highly diverse and complex oral microbiome, the second largest microbiome in the body, comprising bacteria, microeukaryotes, archaea and viruses [2]. Tissue engineering applications typically combine three-dimensional (3D) biomaterial scaffolds, cells and signalling factors such as biologics in order to regenerate or replace damaged or diseased tissues [3] (Fig. 1). Scaffolds for tissue engineering applications are generally fabricated from three types of materials; natural polymers, synthetic polymers and ceramics [4]. The composition and architecture of these scaffolds are elements that can be leveraged to direct tissue deposition and regulate cell fate. The cells used in tissue engineering applications may be deployed in an in vitro setting, where cell-seeded scaffolds are typically subjected to various environmental and biochemical culture conditions, or alternatively may be recruited to infiltrate and populate a scaffold upon implantation *in vivo*. Biologics such as proteins, growth factors and genetic materials are powerful mediators of cell growth and cell differentiation and can be harnessed to promote key regenerative processes such as vascularisation.

In this review we will describe the advances in periodontal and endodontic tissue engineering applications that can be leveraged to promote regeneration within the oral cavity. To that end, we will begin by describing the composition and function of these tissue units and the disease states which ultimately require grafting procedures to regenerate or replace damaged tissues. Thereafter, the combinations of biomaterial scaffolds, cells and biologics that can be harnessed to promote regeneration of periodontal and endodontic tissues will be explored. Finally, we will outline the future trends that are accelerating

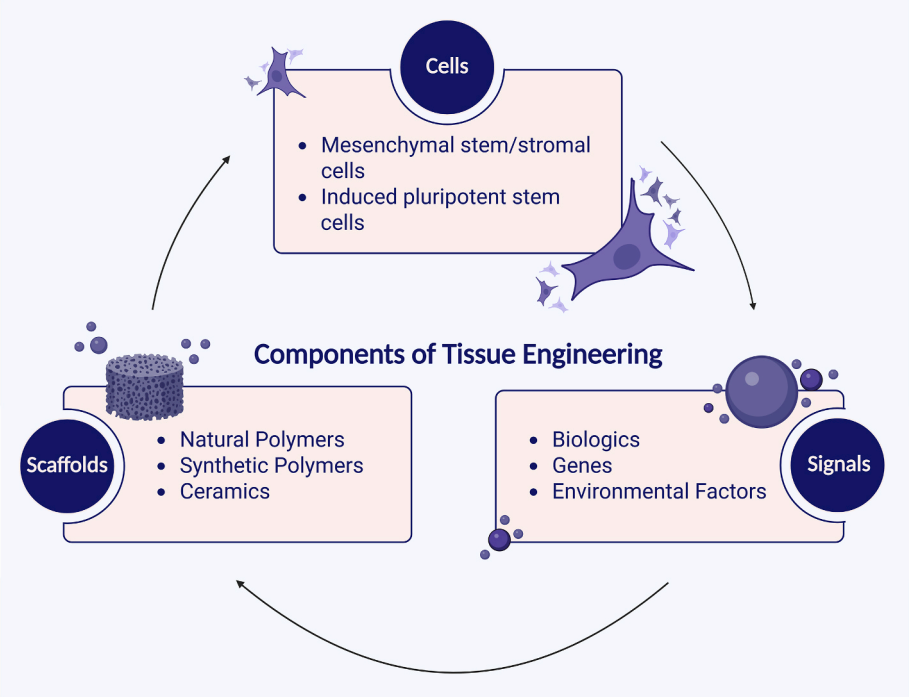

Fig. 1. The Tissue Engineering Triad in Dental Regeneration. Schematic representation of the three fundamental components of tissue engineering. Biomaterial scaffolds (natural polymers, synthetic polymers, or ceramics) provide a structural framework to support tissue development. Cells, including mesenchymal stem/stromal cells and dental-derived progenitors, contribute to regeneration through proliferation and differentiation. Biologics and signalling molecules (proteins, growth factors, and genetic materials) regulate cell behaviour and promote angiogenesis, osteogenesis, and neurogenesis. Together, these elements act synergistically to enable functional tissue repair in the oral cavity.

progress in these fields towards the aim of functional periodontal and endodontic tissue engineering.

2. Periodontitis

2.1. Composition and function of the periodontium

The periodontium is a highly specialized tissue unit that surrounds the teeth. It is composed of a number of different tissues which acting in concert work to support and maintain the teeth within the maxillary and mandibular bones. Specifically, the periodontium consists of the gingiva, the periodontal ligament (PDL), cementum and the alveolar bone (Fig. 2). The gingiva is the mucosal tissue located adjacent to the teeth which covers and protects the roots of the tooth. The gingiva comprises an epithelium on its outer surface, the keratinized nature of which provides a barrier to microbial invasion and offers protection against trauma. The connective tissue of the gingiva lies beneath the epithelium and consists of cells such as fibroblasts, endothelial cells and macrophages, and the extracellular matrix (ECM) which is made up of elastin, glycosaminoglycans (GAGs), proteoglycans, glycoproteins and collagen (types I and III), which anchor the gingiva to the cementum and alveolar bone. In addition to providing a barrier function and structural support, the epithelium and connective tissue of the gingiva act to generate the healthy-looking pink tissue which is key to an aesthetically pleasing smile.

The cementum is an avascular, calcified, connective tissue with no innervation that covers the root dentine of the tooth and connects the tooth to the alveolar bone through PDL fibre bundles [5]. The PDL is the fibrous connective tissue that plays a key role not only in the attachment of the tooth to the surrounding alveolar bone but also in resisting displacing forces and protecting the dental tissues from the effects of excessive occlusal loads via its oblique fibres. Furthermore, it is a source of adult stem cells which play a role in regenerating and maintaining homeostasis of the periodontium [6]. The alveolar bone forms the sockets for teeth and provides structural support for the teeth while playing a critical role in maintaining dental function. It is composed of a mineralized phase and an organic phase made up predominantly of collagen type I as well as non-collagenous proteins and proteoglycans as well as cells and water [7]. It is composed of outer (buccal and lingual) cortical plates, and an inner central trabecular (cancellous) bone filled with yellow fatty marrow [8]. In addition to providing structural support, the alveolar bone acts as a reservoir for blood vessels and nerves that supply nutrients and sensory feedback to the teeth and periodontal tissues [9,10].

2.2. Aetiology and progression of periodontitis

Periodontitis is a chronic, multifactorial, inflammatory disease associated with dysbiotic plaque biofilms and characterized by the progressive destruction of the tooth-supporting apparatus [11]. Prevalence of the disease is high with almost 50 % of adults over 30 years of age in the US determined to be affected [12], with an even higher prevalence recorded in parts of Europe [13]. The risk factors associated with periodontitis are multi-faceted and are influenced by both local factors such as plaque, occlusal trauma and calculus, and systemic factors including autoimmune conditions, genetic predispositions and systemic diseases. The interaction between the oral microbiome and immune response of the host in the development of periodontitis is complex. Typically, the onset of the disease begins with the build-up of dental plaque initially inducing gingivitis thereby altering the microenvironment within the periodontium (Fig. 3A). This dysbiosis of the microbiota appears to present not through the acquisition of new organisms, but by an up-regulation in the virulence of specific bacteria within the periodontium [14]. In response to microbial invasion, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumour necrosis factor-alpha (TNF-α) are released, activating the RANKL pathway. This leads to downstream activation of TRAF6 and NF-κB, ultimately promoting osteoclast-mediated bone resorption [15,16]. When combined with a dysfunctional immune system, this initiates a positive feedback loop whereby biological and inflammatory disorders reinforce each other resulting in the progression from gingivitis to periodontitis [17]. This destructive response causes the development of periodontal pockets which provide an ideal milieu for the proliferation of infectious microorganisms [18]. As the disease advances, inflammation spreads to the PDL and alveolar bone, causing degeneration of those tissues and increasing the depth of the periodontal pockets. If left untreated, the destruction of the supporting structures of the tooth may ultimately result in the loss of the tooth.

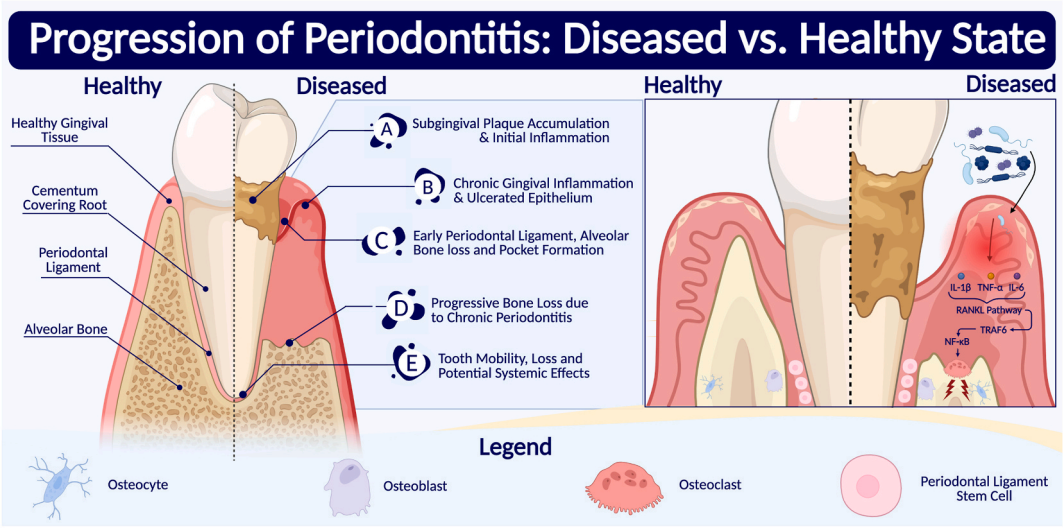

Fig. 2. Schematic of Healthy and Diseased Periodontal Tissues. The healthy periodontium comprises the gingiva, cementum, PDL and alveolar bone. (A) In the progression of periodontitis, a build-up of dental plaque initially induces gingivitis. (B) An up-regulation in microbial activity releases pro-inflammatory cytokines such as interleukin IL-1β, IL-6, and TNF-α. (C) The subsequent activation of the RANKL pathway leads to downstream activation of TRAF6 and NF-κB, promoting osteoclast-mediated bone resorption and resulting in PDL damage, alveolar bone loss and pocket formation. (D) Periodontal pockets provide an ideal milieu for the proliferation of infectious microorganisms, causing further degeneration of the PDL and alveolar bone. (E) Advanced periodontitis increases the potential for tooth mobility and, ultimately, tooth loss.

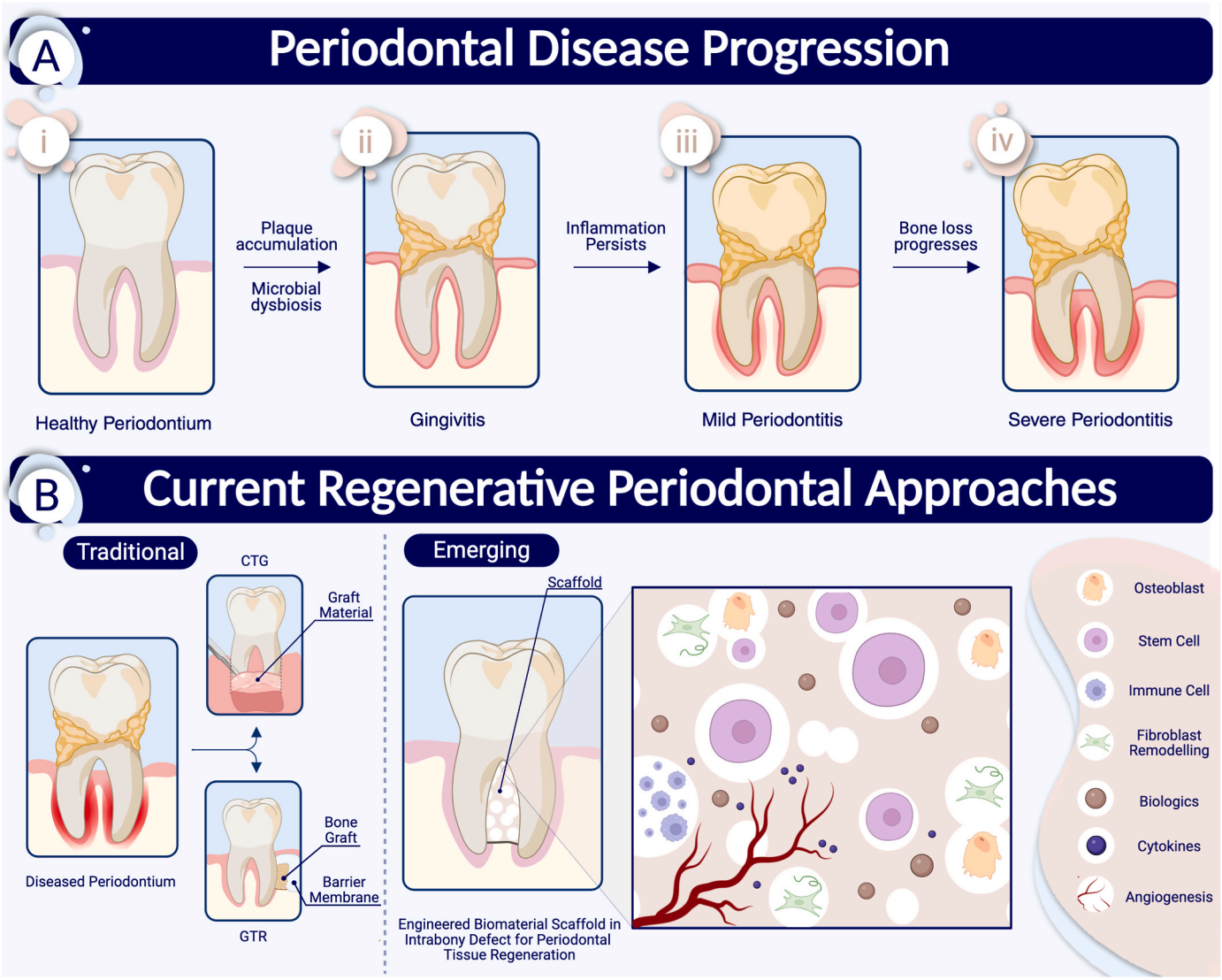

Fig. 3. Disease Progression and Regenerative Strategies in Periodontal Disease (A) Periodontal Disease Progression: A schematic representation of the stages of periodontal disease, beginning with a healthy periodontal state, progressing through gingivitis, mild periodontitis, and advancing to severe periodontitis. This progression is driven by microbial dysbiosis, prolonged inflammation, and the loss of connective tissue and alveolar bone. (B) Regenerative Approaches in Periodontal Disease Treatment: A comparison of traditional and experimental regenerative therapies for managing periodontal tissue damage. Traditional methods, such as CTG implantation and GTR, are shown alongside innovative regenerative techniques that employ scaffolds for periodontal regeneration in applications such as intrabony defect repair. The regenerative microenvironment is depicted, showcasing stem cells, biologics, immune modulation, and cytokines, with a focus on bone formation and angiogenesis.

2.3. Surgical treatment options for mucogingival and periodontal conditions

2.3.1. Gingival graft surgery

Chronic conditions such as gingivitis and periodontitis, in addition to other damage mechanisms including injuries due to trauma and overly aggressive brushing, can result in gingival recessions which exposes the root of the tooth, causing dentine hypersensitivity and imparting a significant negative aesthetic impact. In order to treat gingival recession defects and achieve root coverage, two different surgical techniques are most frequently employed. In the coronally advanced flap procedure, horizontal and vertical incisions are made to create a flap elevation whereby the epithelium of the gingiva is separated from the underlying connective tissue resulting in a partial-thickness flap under which a graft can be placed [19]. The flap is then mobilised and advanced coronally towards the crown of the tooth prior to wound closure via suturing. Alternatively, a less invasive procedure known as the tunnel technique can be used which involves the creation of a sub-epithelial tunnel at the gingival margins allowing for the placement of a graft prior to coronal advancement and suturing.

Traditionally, the graft used in either the coronally advanced flap procedure or the tunnel technique has been the connective tissue graft (CTG), which is harvested from the palate of the patient (Fig. 3B). Harvesting of the CTG involves the creation of a flap in the palate and the removal of the underlying sub-epithelial connective tissue. The use of the CTG is associated with a number of desirable outcomes including root coverage, increased soft tissue volume, increased keratinized tissue width and improved aesthetics, making it the gold standard graft for the treatment of gingival recessions [20]. Despite its high success rate, however, the CTG suffers from a number of drawbacks; for example, it requires an additional procedure with a limitation on the quantity of tissue that can be removed. Furthermore, harvesting of the CTG can cause donor site morbidity and is associated with increased pain and discomfort for the patient. Moreover, the quality of CTG can vary

significantly due to factors dependent on the skill of the clinician and the variability of the donor tissue, issues which may impair the reproducibility of the gum graft procedure.

2.3.2. Bone graft surgery

Tooth extraction initiates physiological remodelling of the alveolar ridge, characterized by significant horizontal and vertical bone loss, predominantly on the buccal aspect. These dimensional changes, most pronounced within the first 6 months post-extraction, result in a narrower, shorter ridge positioned more palatally/lingually, especially in sites with prior pathology [21]. Bone augmentation procedures are often a prerequisite for dental implant surgery so as to ensure sufficient bone volume is present prior to the insertion of the implant for long-term function and predictable aesthetic outcomes [22]. The bone grafting procedure involves debridement of the affected area to physically remove any bacteria that may be present and to stimulate the migration of osteogenic cells from the surrounding bone into the defect site. Thereafter, the graft is inserted into the defect and the site is sutured closed.

The gold standard graft for bone regeneration applications is an extra-oral autologous bone graft harvested from the iliac crest or the tibia. Advantages associated with use of the extra-oral autologous graft include shortened healing times, increased bone formation and a capacity to treat larger defects and achieve vertical augmentation [23]. Nonetheless, these grafts do suffer from limitations including donor site morbidity and limited supply. Furthermore, the harvesting procedure requires additional surgical training in addition to the increased costs due to longer surgeries and hospitalisations. Some of these drawbacks can be addressed through the use of intra-oral bone grafts, which circumvents the requirement for an additional surgery outside the oral cavity. However, a variable cellular content has been reported with use of these grafts and there is an even greater limitation on the quantity of bone that can be harvested from the mandible and maxilla [24]. Due to these limitations, bone scaffolds, implanted alone or in combination with a particulate autogenous bone graft [25], and discussed in further detail below are increasingly used to simplify the surgical procedure and minimize donor site morbidity (Fig. 3B).

2.3.3. Guided tissue regeneration/guided bone regeneration

Guided tissue regeneration (GTR) or guided bone regeneration (GBR) refers to the process of regenerating periodontal tissue (bone, PDL, cementum) through the use of an occlusive barrier membrane between gingival (epithelial) and alveolar bone/PDL tissue [26]. The purpose of the barrier membrane is to spatially regulate tissue formation either side of the material and, specifically, to prevent the infiltration of the underlying bone with cells from the surrounding epithelium and connective tissue, thereby allowing the proliferation of pro-osteogenic cells and deposition of bone matrix. In order to fulfil this purpose, barrier membranes for GTR/GBR typically need to meet a number of design criteria [27,28]. Firstly, the material must be biocompatible and neither impair the healing process nor negatively affect surrounding tissues. Secondly, the membrane should possess sufficient mechanical properties so as to prevent collapse thus maintaining space for bone regeneration. Relatedly, the membrane should be suitably handleable to facilitate shaping around the bone space without compromising soft tissue integrity. Finally, occlusivity is an extremely important feature of barrier membranes for GTR in preventing epithelial downgrowth. It follows, therefore, that the pore size of membranes for GTR is a key consideration, as too large a pore size may allow for the infiltration of the defect site with epithelial cells and connective tissue. However, this design feature should be balanced with the need to facilitate oxygen and nutrient exchange across the barrier. Traditionally, membranes for GTR/GBR have been designed to play a passive role in tissue formation, merely facilitating cell differentiation and tissue deposition either side of the barrier. However, recent advances, and shifts from bioinert materials to functionalised materials containing bioactive compounds, have led to increased interest in membranes that play an active role in the regeneration process [29].

3. Pulpal and apical disease

3.1. Composition and function of the endodontium

The endodontium comprises the tissues of the dentine-pulp complex [30] and the apical tissues surrounding the root tip (Fig. 4). In an adult tooth, the pulp is protected by an outer shell of both dentine and enamel, preserving the pulp's blood and nerve supply, which are critical for both tooth development and repair [31]. The pulp is a richly innervated connective tissue with fibroblasts the predominate cell; however, other populations including defence cells, blood vessels and stem cells as well as the odontoblast. The formation of the dentine occurs around the pulp by a process of primary dentinogenesis driven by the terminal secretory odontoblast cell, which sit at the interface between the pulp and dentine and form tubular dentine [32]. Odontoblastic processes extend from the odontoblast into the dentinal tubules, aiding dentine formation and also acting as sensory link to the odontoblast when threatened by caries [30,32,33]. Primary odontoblasts also remain active after tooth formation is complete, continuing to synthesise new dentine, albeit it at a slower pace, in a process known as secondary dentinogenesis [34,35]. If the pulp tissue is challenged, existing odontoblasts can produce an accelerated form of tertiary reactionary dentine or in a complex process new 'odontoblast-like' cells can differentiate from pulp progenitor cells to produce tertiary reparative dentine locally adjacent to the external stimuli [36]. If the stimuli are mild and the stimuli does not cause odontoblast death the primary odontoblasts survive and secrete reactionary tubular dentine; however, reparative dentine formed by odontoblast-like cells is generally atubular resembling reparative rather regenerated tissue [37].

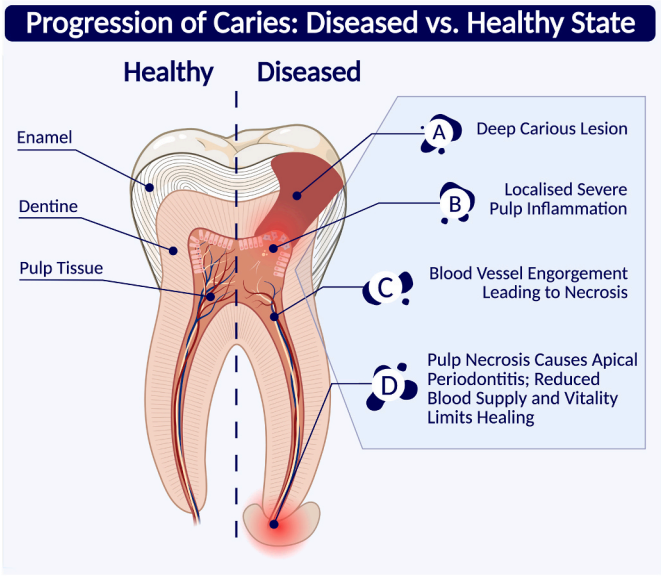

Fig. 4. Schematic of Healthy and Diseased Pulp Tissue. The healthy endodontium comprises the tissues of the dentine-pulp complex and the apical tissues surrounding the root tip. (A) At the onset of pulpitis, the microbial biofilm in the carious lesion advances through the dentine, stimulating the release of a range of inflammatory cytokines. (B) The pulpitic response intensifies as the lesion nears the pulp and the localised inflammation increases in severity. (C) Initial blood vessel engorgement leads to localised necrosis which spreads apically. (D) Apical periodontitis ensues when the canal is necrotic and the pulp space has become infected.

3.2. Aetiology and progression of pulpal and apical disease

Pulp and apical diseases come under the umbrella of endodontic diseases, which are essentially inflammatory dental conditions typically biofilm-induced by a polymicrobial flora [38]. Dental caries remains the predominant cause of endodontic disease and occurs due to the formation of a bacterial plaque initially on the tooth's surface [39]. The microbes in plaque are energised by recurrent exposure to fermentable dietary carbohydrates and, if not mechanically removed, lead to shifts in the microflora and invasion into the tooth structure [40]. The persistent synthesis of acid by bacteria leads to the demineralization of dental hard tissues, which, if allowed to progress without treatment, will lead to cavitation and progressive advancement of the lesion through dentine towards the pulp [41] (Fig. 5A). Without intervention, the carious lesion will steadily soften the dentine and move towards the pulp; however, it is not until the bacterial front enters the defensive tertiary dentine layer that the inflammation becomes severe, manifesting as an irreversible pulpitis, with areas of pulpal necrosis and eventually complete necrosis of the pulp and the development of apical periodontitis [42,43]. Although preventable, caries remains the world's most prevalent non-communicable disease [44], affecting socially disadvantaged groups and geriatric populations in particular [45].

3.3. Treatment options for the management of pulpal and apical disease

Root canal treatment (RCT) is the traditional treatment of choice for irreversible pulpitis and pulp necrosis and, if well carried out, is very successful [46]. However, the bulk of RCT is carried out in primary care settings with reports suggesting that within Europe 50 % will fail within 5 years (https://cordis.europa.eu/article/id/413194). The latter figures are supported by reports of apical disease in 10–50 % of endodontically treated teeth in cross-sectional studies of the general population in various territories [47–49]. Recently there has been a shift towards biologically-based therapies, such as vital pulp treatment (VPT), which includes indirect and direct pulp capping as well as partial and full pulpotomy. VPT aims to preserve the health of all or part of the pulp by

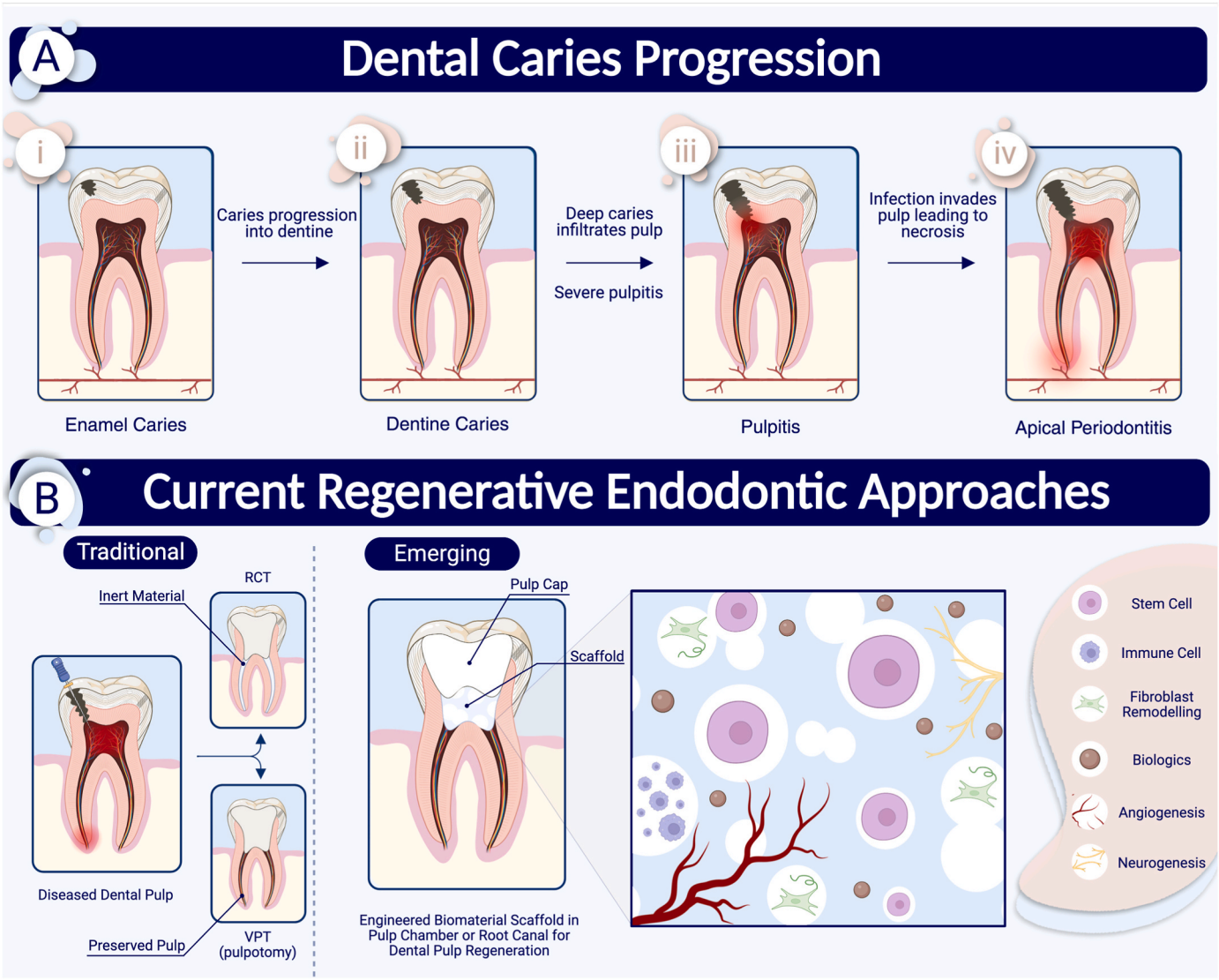

Fig. 5. Disease Progression and Regenerative Strategies in Dental Caries. (A) Dental Caries Progression: A visual timeline illustrating the stages of dental caries development, from initial enamel caries through to dentine caries, pulpitis, and apical periodontitis. This progression demonstrates how microbial infiltration exacerbates pulp damage and triggers periapical inflammation. (B) Regenerative Approaches in Dental Caries Treatment: Traditional and emerging endodontic therapies for regenerating the pulp-dentine complex. Traditional treatments, RCT and VPT, are shown alongside scaffold-based regenerative strategies that promote tissue regeneration through cell-based or cell-homing approaches. The regenerative microenvironment is depicted, highlighting stem cells, biologics, and other bioactive signals crucial for angiogenesis, neurogenesis, and pulp regeneration. Adapted with permission from Ref. [375].

harnessing its intrinsic reparative capacity [50] and recently even in cases with signs and symptoms indicative of irreversible pulpitis pulpotomy has been shown to have success rates at a similar level to well conducted RCT [51] (Fig. 5B). This recent systematic review was based on two clinical trials and reported that although the initial success was good for both pulpotomy and RCT, they both decreased over time, however, the authors concluded that based on available evidence pulpotomy was as effective as RCT for definitive treatment of symptomatic pulpitis [52]. These minimally invasive and biologically-based vital pulp techniques have also been advocated in global position statements written by the European Society of Endodontology [50] and American Association of Endodontists [53]. Furthermore, the inaugural European Society of Endodontology S3-level clinical practice guideline (ESE S3 CPG) recommended that in teeth with cariously-exposed pulp tissue root canal treatment or VPT (e.g., pulpotomy) could be carried out [54] in both the presence or absence of symptoms indicative of irreversible pulpitis.

Although VPT has developed into an evidenced-based alternative to RCT, it is not actually a tissue engineering technique as the biomaterial is placed directly onto the exposed pulp tissue and a mineralized barrier is formed against the material without the regeneration of any lost tissue [55]. This is in contrast to other tissue engineering techniques employed in the oral cavity which aim to regenerate periodontal tissue, bone or necrotic pulp tissue [56] using scaffolds, morphogens and cell-based or cell-homing techniques. Tissue engineering-based regenerative endodontic procedures (REPs) have been introduced clinically over the last 10 years for the management of teeth with necrotic pulps to encourage regeneration not replacement of lost tissue [57]. A cell homing REP called revitalization, uses a natural blood clot to form a scaffold for cells to migrate into the empty root canal restoring vitality [58]. As this is relatively simple to carry out and does not involve the insertion of a new cell population into the root canal, this technique has gained popularity with dentists and researchers with a recent systematic review highlighting high clinical success of the procedure, but noting that there was no robust evidence available to support its use over conventional apexification techniques [59]. Furthermore, although labelled a regenerative technique, histological analysis after revitalization suggests the new 'pulp-tissue' was more similar to cementum or bone rather than dental pulp [60]. Two studies investigated endodontic tissue engineering using a cell-based technique for the management of pulp necrosis and noted good survival of the tooth and evidence of vitality at 12 months [61,62], however both studies were considered to have a moderate risk of bias due to issues including lack of a proper control [63]. In response to this the ESE S3 CPG stated that they did not know whether endodontic tissue engineering represented a valid treatment option for pulp necrosis and apical disease and that more research was needed [54].

4. Biomaterials for periodontal and endodontic tissue engineering applications

As part of the tissue engineering triad, biomaterials are powerful tools that can guide biological processes towards regenerative outcomes. Biomaterials provide a 3D template for cells to populate and deposit matrix. Furthermore, the architecture, topography, composition and mechanical characteristics of the biomaterial are all properties that can leveraged to regulate cell fate. This section examines the various biomaterials that can be leveraged as alternatives to autologous grafts for periodontal and endodontic tissue engineering applications.

4.1. Allogeneic grafts

Allografts harvested from cadaveric or donor tissues can circumvent some of the limitations associated with the use of CTGs for the treatment of gingival recessions; namely, those issues that arise due to harvesting of the autograft and the limited supply of tissue that is available. Acellular dermal matrix (ADM) is a soft tissue graft derived from human skin which is decellularized in order to remove the graft of epithelial and cellular components. The decellularization process leaves in place the ECM which acts as a scaffold to facilitate cellular infiltration and vascularisation from the host upon implantation. The ADM has previously been investigated as an alternative to autologous grafts in applications aiming to increase keratinized tissue width, enhance soft tissue volume, and achieve root coverage [64]. However, studies have reported reduced thicknesses [65] and a relapse in the gingival margin [66] in patients treated with the ADM.

Bone allografts such as mineralized freeze-dried bone allografts (FDBA) and demineralized freeze-dried bone allografts (DFDBA) are commonly used by clinicians in alveolar ridge preservation procedures. The osteoinductivity of these grafts appear to depend on the degree to which native bone morphogenetic proteins (BMPs) can be maintained in the graft following processing and remain active, as BMPs have been demonstrated to be robust promoters of osteogenesis [67,68]. *In vivo*, BMPs are released when osteoclasts demineralize bone matrix during remodelling. It follows, therefore, that demineralization of bone allografts may be an important factor in ensuring sufficient levels of BMPs can be accessed by host cells upon implantation. On the contrary, calcified tissue is known to facilitate hydroxyapatite (HA) crystal formation, suggesting there may a balance to be struck when demineralizing bone allografts so that the graft contains appropriate levels of demineralized matrix for BMP release and mineralized matrix to support HA formation [69]. Studies comparing alveolar ridge preservation conducted using DFDBA with FDBA in humans have reported significantly greater new bone formation with the use of DFDBA [70].

Maintenance of other biological factors beyond just BMPs can play a key role in allograft-mediated tissue regeneration. Human amnion-chorion membranes represent the inner and outermost layers of the amniotic membrane and is derived from healthy maternal donors during an elective caesarian section. Processing of these membranes without the use of detergents, cryoprotectant additives or freeze-drying maintains the reservoir of growth factors, cytokines and chemokines which have been shown to reduce inflammation and promote wound healing [71–73]. Furthermore, placental tissues are inherently antimicrobial, and amnion-chorion membranes have been demonstrated to be bactericidal against bacterial strains found in periodontitis such as *P. gingivalis* and *P. intermedia* [74,75]. Moreover, such membranes have been demonstrated to resorb over a period of 8–12 weeks *in vivo* [76],which offers advantages over traditional non-resorbable membranes in applications such as GTR as it avoids the need for a revision procedure to facilitate removal of the graft. The properties and indications of various allogeneic grafts in addition to examples of commercially available products are presented in Table 1.

4.2. Xenogeneic grafts

Despite the processing and sterilization of allografts prior to use, there remains some concerns regarding their potential for disease transmission and immune rejection [77]. Furthermore, whilst allografts are typically obtainable in larger quantities than autografts, they can still be subject to donor availability which can limit supply. Such drawbacks can be addressed in part through the use of xenogeneic grafts, generally harvested from porcine or bovine tissue. Porcine dermal matrix (PDM), for example, comprising collagen types I and III has been investigated as a graft for the augmentation of soft tissue and the treatment of gingival recessions. Treatment with PDM has been shown to increase soft tissue thickness and keratinized tissue width at 12 months compared to pre-operative levels in peri-implant soft tissue augmentation procedures [78,79]. However, when compared to the gold standard CTG in the treatment of gingival recessions, significant reductions in soft tissue thickness and root coverage have been reported with use of PDM [80,81]. Nevertheless, it should be noted that studies have also reported reduced postoperative pain intensity in the first week

Table 1
Commercial examples of allografts for periodontal and endodontic tissue engineering applications.

Graft type	Commercial examples	Origin and description	Key benefits and properties	Indications	References
Soft tissue graft	Alloderm® from BioHorizons. Allopatch® from Musculoskeletal transplant foundation. Puros Dermis® from Zimmer Dental.	ADM from skin.	Good colour match. Long history of clinical results Minimal tissue reactivity.	Gingival augmentation. Peri-implant soft tissue augmentation Root coverage.	[183] [184]
Barrier membrane	BioXclude® from Snoasis Medical.	Amnion-chorion tissue from the placenta.	Antimicrobial. Growth factor retention. Short resorption time.	GTR/GBR. Intrabony defects. Pulp-dentin regeneration. Sinus augmentation. Socket preservation.	[71] [72] [73] [185]
Bone graft	DynaBlast® from Keystone Dental. OraGraft ® from LifeNet Health.	FDBA from cancellous/cortical bone.	Low risk of disease transmission. Osteoconductive.	Reconstruction of osseous defects including intrabony defects, furcation defects, bone voids from trauma, cysts, benign tumours, or endodontic lesions. Ridge augmentation. Sinus augmentation. Socket preservation.	[70]
	DBX® from Depuy Synthes. Accell Connexus® from Keystone Dental. Grafton® DBM from BioHorizons.	DFDBA from cancellous/cortical bone.	Low risk of disease transmission. Maintenance of BMPs Osteoinductive. Osteoconductive.	Ridge augmentation. Socket preservation. Reconstruction of osseous defects including intrabony defects, furcation defects, bone voids from trauma, cysts, benign tumours, or endodontic lesions	

after surgery in patients treated with PDM as compared to those who received the CTG [82].

Porcine tissue is also the typical source for xenograft barrier membranes with various sites including the peritoneum, pericardium and periderm having been identified for tissue extraction [83,84]. A study comparing the surface topography and osteogenic capacity of barrier membranes extracted from these different tissue sites identified rough surface topographies on pericardium-derived and periderm-derived constructs whereas peritoneum-derived constructs demonstrated two distinct sides with a smooth surface layered on top of a rougher, more porous surface [85]. Whereas greater cell viability and collagen deposition were reported in this study when cells were cultured on pericardium-derived and periderm-derived constructs, peritoneum-derived constructs demonstrated enhanced osteopontin expression indicating a greater osteogenic potential. Peritoneum grafts have also been combined with collagen matrices to generate bi-layered grafts, whereby the peritoneum acts as a barrier and provides stability, while the collagen matrix faces the host tissue and acts to support tissue integration and angiogenesis [86]. Indeed, clinical trials examining the use of bi-layered grafts to treat gingival recessions and augment soft tissue thickness have reported increased keratinized tissue width and excellent colour match [87,88]. However, such grafts were also recently demonstrated to not reach non-inferiority in the treatment of multiple gingival recessions when compared to the gold standard CTG [89].

Deproteinized bovine bone matrix (DBBM) is a xenogeneic bone grafting material in which all organic components of the bone are removed whilst the HA and natural architecture of the bone is retained. DBBM is commonly used in periodontal procedures such as alveolar ridge augmentation and in the filling of infrabony periodontal defects. In clinical trials, the use of DBBM has been shown to reduce the post-operative resorption of autologous iliac crest bone grafts during augmentation of the alveolar ridge [90]. *In vitro* studies investigating the mechanisms through which DBBM support osteogenesis have demonstrated that DBBM creates a favourable environment for osteogenesis by promoting macrophage fusion and polarization towards an M2 wound-healing phenotype [91]. There are concerns, however, about the extended resorption rates of DBBM grafts, with research in rat mandibles demonstrating that 12 months post-implantation, the majority of the implant site remained occupied with xenograft particles thereby arresting new bone formation when compared to empty controls [92]. Another xenogeneic source of grafts for dental applications is marine coral [93]. Composed of natural calcium carbonate [94], coral has been proposed as a graft for bone regeneration due its inherent porosity and high compressive stiffness [95–97]. Similar to DBBM however, difficulties attributed with controlling their degradation rate *in vivo* as well as the brittleness of block ceramic scaffolds and an insufficient capacity to promote vascularisation upon implantation are seen as limitations [98,99]. The properties and indications of various xenogeneic grafts in addition to examples of commercially available products are presented in Table 2.

4.3. Synthetic polymers

In addition to the concerns regarding viral and prion transmission with the use of mammalian derived grafts, there are also religious considerations which may limit their application in dentistry. For example, three of the world's major religions; Judaism, Islam and Hinduism prohibit the use of products derived from either bovine or porcine origin [100]. Such considerations do not arise with the use of synthetic polymers scaffolds, which have become widely used in the biomedical field as various fabrication techniques can be leveraged to alter and optimise their desired characteristics. Furthermore, unlike autogenous, allogeneic, or xenogeneic materials, synthetic polymers can be easily manufactured at scale and are therefore not subject to the same restrictions regarding availability.

One of the earliest barrier membranes developed for GTR was fabricated from polytetrafluoroethylene (PTFE) [101]. Since then, PTFE and its derivatives (expanded PTFE and high-density PTFE) have become widely used in GTR applications and have been demonstrated to facilitate bone regeneration in a number of clinical studies [27] due to its excellent barrier functionality. The low porosity of high-density PTFE, for example, has been shown to prevent cell and bacteria adhesion which may reduce the risk of bacterial infection [102]. However, the high stiffness of PTFE has also been shown to cause soft tissue dehiscence which can increase the possibility of infection by allowing bacteria from the oral cavity to enter the defect site [103]. More recently, flexible titanium has been incorporated into PTFE membranes in order to provide the membrane with superior stability and space maintenance [104].

Due to its non-resorbable nature, a second procedure is required to remove PTFE membranes, which increases hospital costs and the potential for complications. Synthetic resorbable polymer materials, such

Table 2
Commercial examples of xenografts for periodontal and endodontic tissue engineering applications.

Graft type	Commercial examples	Origin and description	Key benefits and properties	Indications	References
Barrier membrane	Jason® from Botiss Biomaterials. Smartbrane® from Regedent.	Porcine pericardium.	Easy manipulation dry or wet. Exceptionally thin (~0.15 mm). Naturally long barrier function. No stickiness after rehydration. No swelling after rehydration. Tear resistance.	Fenestration and dehiscence defects. Furcation defects (class I and II). GTR/GBR. Intraosseous defects (1–3 walls). Protection and covering of Schneiderian membrane. Ridge augmentation. Sinus augmentation. Socket preservation.	[84]
	Collprotect® from Botiss Biomaterials.	Porcine periderm.	Easy manipulation dry or wet. Exceptionally thin (~0.15 mm). Naturally long barrier function. No stickiness after rehydration. No swelling after rehydration. Tear resistance.	Fenestration and dehiscence defects. Furcation defects (class I and II). GTR/GBR. Intraosseous defects (1–3 walls). Protection and covering of Schneiderian membrane. Ridge augmentation. Sinus augmentation. Socket preservation.	
	DynaMatrix® from Keystone Dental.	Porcine small intestinal Submucosa.	Facilitates angiogenesis. Regulates cell adhesion and differentiation.	GTR/GBR. Ridge augmentation. Socket preservation.	
	Biogide® from Geistlich Pharma AG.	Porcine peritoneum.	Optimised topography for fibroblast and osteoblast attachment.	GTR/GBR. Extraction socket management. Peri-implantitis. Ridge augmentation. Sinus augmentation.	[83]
Soft tissue graft	Mucoderm® from Botiss Biomaterials.	PDM from porcine skin	Revascularization and tissue integration. Remodelling into host tissue in ~6–9 months. Easily applied and fixed by sutures. Easily cut to shape.	Gingival augmentation. Extraction socket management. Root coverage. Simultaneous approach with GTR/GBR. Soft tissue augmentation.	[78] [79]
	Mucograft® from Geistlich Pharma AG	Bi-layered graft from porcine peritoneum with collagen matrix	Compact layer and porous layer. No crosslinking.	Gingival augmentation. Root coverage. Socket seal. Vestibuloplasty.	[86] [87] [88]
Bone graft	BioOss® from Giestlich	DBBM	Hydrophilic. Osteoconductive.Similar microstructure to human bone.	Extraction socket management. Ridge augmentation. Sinus augmentation.	[90] [91] [92]
	Biocoral® from Biocoral Inc.	Marine coral-derived bone graft	Moderate porosity. No risk of viral transfer. Resorption by osteoclasts.	Extraction socket management. Ridge augmentation. Sinus augmentation. Socket preservation.	[93]

as the polyesters polycaprolactone (PCL), polylactic acid (PLA) and polyglycolic acid (PGA) can offer some advantages in this regard, albeit the *in vivo* degradation of PLA, for example, has been reported to take as long as 4 years. Since the degradation of these polyesters occur in large part due to hydrolysis [105], the ultimate degradation profile of a polymer or co-polymer can be regulated by modifying its hydrophobicity. To that end, the copolymerization of PLA with PGA (a more hydrophilic polymer) can reduce its degradation time significantly [106] and, as such, polylactic-co-glycolic acid (PLGA) barrier membranes have been shown to resorb *in vivo* in less than 6 months [107].

Recent advances in additive manufacturing processes have allowed for the design of scaffolds which mimic the complexity and structure of periodontal tissues [108]. Synthetic polymers such as PCL, PLA and PLGA are attractive materials for use in additive manufacturing processes as their thermoplastic nature allow for the printing of polymer melts using 3D printing techniques such as fused deposition modelling and melt electrowriting, a high-resolution process that utilises a moving collector to facilitate direct-writing with the capability of producing fibers in the micro- and nanometer range [109]. The principles of additive manufacturing have previously been applied indirectly to fabricate bi-phasic PGA-PCL scaffolds designed to recapitulate bone and PDL tissue compartments, respectively, whereby scaffolds seeded with BMP-7 transfected human gingival fibroblasts and human PDL cells and implanted ectopically in mice in contact with a human dentin block lead to the attachment of a newly formed ligament with the deposition of cementum-like tissue [110]. More recently, melt electrowriting was leveraged to fabricate 3D fibrous PCL scaffolds which were coated with calcium phosphate and seeded with primary human osteoblasts for 28 days in vitro to generate a tissue-engineered construct which was further functionalised with a PDL cell sheet and decellularized to form an off-the-shelf graft for periodontal regeneration [111]. Additionally, a recent study has developed a barrier membrane through a semi-interpenetrating network of high molecular weight PLA and in situ-polymerized mesh of PCL and PLGA, the unique bilayered morphology of which was achieved through self-assembly and thermally-induced phase separation resulting in distinct smooth and nanofibrous compartments optimised for epithelial occlusion and tissue regeneration, respectively [112]. Indeed, the PLA-PCL-PLGA membrane was demonstrated to outperform a commercial PLA membrane in a rat orthotopic periodontal defect model. Although the versatility of synthetic polymers allows for their processing into complex structures, they lack receptors such as cell-surface ligands which reduces their overall bio-functionality and, unlike the native ECM, polyesters such as PCL are also hydrophobic in nature, further decreasing cell attachment and cell-biomaterial interaction. These limitations can be addressed in part through surface functionalization. For example, enzymatic hydrolysis

can be leveraged to increase hydrophilicity by breaking down polymer chains on the surface of the material, while plasma treatments can alter surface energy making them more receptive to adhesives and coatings [113]. Techniques such as aminolysis can also be used to bring positive charges to the surface of a synthetic polymer, thus facilitating its subsequent functionalization with negatively charged natural polymers [114].

4.4. Natural polymers

Biomaterials fabricated from natural polymers, including those present in the ECM, have some advantages over synthetic polymers, including improved biocompatibility as well as a capacity to support cellular interactions and deliver biochemical cues to support tissue formation. Although these polymers are commonly derived from mammalian or marine tissues (i.e. xenogeneic sources), they are generally considered distinct from traditional decellularized xenografts [115]. Natural polymer biomaterials are typically fabricated from purified proteins and peptides that have been isolated and extracted from organic sources. These purified proteins then act as building blocks for the fabrication of natural biomaterials which can be combined with other macromolecules and polymerized to form 3D scaffolds that aim to mimic native ECM structures [116]. One drawback associated with the use of natural polymer biomaterials for tissue engineering applications is their relatively low mechanical properties, although this limitation can be ameliorated in part through physical and chemical crosslinking techniques which form chemical bonds between polymer chains and increase the stiffness and degradation resistance of biomaterials.

Collagen is the main component of the ECM and is the most abundant structural protein found in mammals, accounting for around 30 % of total bodily protein content [117]. Collagen can be processed using manufacturing processes such as lyophilization, electrospinning and 3D printing to form highly porous scaffolds, the architecture of which can be leveraged to modulate cell behaviour. For example, work from our lab has shown that by reducing the final freezing temperatures during the lyophilization process of collagen-based biomaterials in 10 °C increments from −10 °C to −40 °C, decreasing pore sizes ranging from 151 to 96 μm can be achieved which results in increased cellular attachment due to providing cells with an increased surface area and, therefore, a higher ligand density for binding [118]. Further research into the influence of scaffold pore size on cellular behaviour demonstrated that improved cell migration, which occurs at pore sizes >300 μm, overcomes the initial beneficial effect of cell adhesion which takes place at smaller pore sizes [119]. In periodontal tissue engineering applications, collagen type I scaffolds have been shown to support osteogenesis of bone marrow derived MSCs in vitro [120] and, furthermore, clinical studies have demonstrated a significant reduction in the recession of gingival defects treated with collagen type I biomaterials with an enhanced gingival biotype (tissue thickness) when compared to ammonium membranes also reported [121]. Collagen type I/III scaffolds have demonstrated non-inferiority when compared to the CTG in soft tissue augmentation around dental implant sites [122], with the reported volume stability of these scaffolds, achieved through crosslinking, potentially preventing shrinkage issues associated with use of grafts such as ADM [123,124]. Different trials, however, have reported an increase in bone loss with use of collagen type I/III scaffolds compared to the CTG in soft tissue augmentation procedures [125].

In order to better mimic the ECM structure of oral tissues, collagen can be combined with GAGs such as hyaluronic acid (HyA) and chondroitin sulfate. *In vivo,* GAGs and play a key role in maintaining tissue integrity and hydration, thereby providing resistance against pressure, and also offer sites for growth-factor binding. Collagen-GAG scaffolds were first developed to regenerate skin in burn patients [126], and have since been investigated for the regeneration of numerous other tissues including cartilage [127] and bone [128,129]. HyA-based scaffolds, specifically, have been demonstrated to support differentiation of human dental pulp stem cells (DPSCs), human PDL cells and human gingiva-derived MSCs down osteogenic and neurogenic pathways [130, 131].

Chitosan is a polysaccharide that is structurally similar to the GAGs present in the ECM [132]. Chitosan has a number of advantages such as its mucoadhesive, hemostatic, antibacterial, and antifungal properties that have made it a promising material for tissue engineering applications [133]. To that end, chitosan has been explored as a biomaterial for use as dental coatings, porous scaffolds and drug/gene delivery in dental tissue regeneration. For example, porous chitosan-collagen scaffolds loaded with plasmid and the adenoviral vector encoding human transforming growth factor (TGF)-β1 were shown to up-regulate collagen types I and III production of human PDLs cells in vitro, and furthermore, supported cell and soft tissue infiltration *in vivo* [134]. More recently, chitosan scaffolds incorporating aligned synthetic polymer nanofibers were leveraged to guide the orientation and elongation of cells in vitro which translated *in vivo* to a more organized arrangement of a regenerated PDL tissue with a more extensive formation of mature collagen fibres [135]. Additionally, the antimicrobial capacity of chitosan has been harnessed in a number of recent studies aimed at enhancing the barrier effect and osteogenic properties of membranes for GTR in periodontal tissue engineering applications [136–138].

3D bioprinting is an advanced biofabrication technique which involves the co-printing of cells with a biocompatible material also known as a bioink which is typically crosslinked after printing to improve its degradation resistance and allow for tissue deposition and maturation. Natural polymers have garnered increased interest as the main component of such bioinks due to their capacity to form hydrogels of high-water content with sites for cellular attachment. Gelatin is derived via the denaturation of collagen and can be relatively easily functionalised to support photo-crosslinking through the addition of methacrylic anhydride [139]. Recently, a cell-laden gelatin-methacrylate hydrogel modified with decellularized ECM has been shown to enhance the regeneration of periodontal tissues in dogs, with the authors reporting improved anchoring structures of the bone–PDL interface with well-aligned periodontal fibres and a highly mineralized alveolar bone [140]. Alveolar bone regeneration has also been reported with the use of cell-laden gelatin-methacrylate hydrogels in rat model of periodontal regeneration [141]. Another natural polymer commonly used as a bioink in 3D bioprinting is alginate, a polysaccharide derived from brown algae. Alginate does not contain natural binding sites but can be functionalised with molecules such as RGD (Arg-Gly-Asp) motifs to provide sites for cell attachment and is typically crosslinked through the addition of calcium ions. Recent work has demonstrated an increased amount of keratinized gingiva *in vivo* with the use of cell-laden alginate-ADM bioinks implanted in beagle dogs [142]. Cell-laden alginate bioinks can also be functionalised with growth factors such as BMP-2 and platelet derived growth factor (PDGF) to further enhance regeneration of gingival, PDL, and alveolar bone tissues [143]. 3D bioprinting also allows for superior spatiotemporal control over the release of such growth factors. For example, spatial gradients of vascular endothelial growth factor (VEGF) have been shown to promote higher levels of vessel invasion in bioprinted implants and, when combined with localised BMP-2 delivery, have accelerated large bone defect healing whilst minimizing heterotopic bone formation [144]. The properties and indications of various synthetic and natural polymer biomaterials with examples of commercially available products are presented in Table 3.

4.5. Bioceramics

Another class of biomaterial used for tissue engineering applications, and particularly in the regeneration of hard tissues are bioceramics. Like native bone tissue, bioceramics generally have high compressive properties making them attractive for load bearing applications. Additionally, calcium phosphate bioceramics, such as synthetic HA ($Ca_{10}(PO_4)_6(OH)_2$), have a chemical composition similar to that of the

Table 3
Commercial examples of synthetic and natural polymer biomaterials for periodontal and endodontic tissue engineering applications.

Polymer type	Biomaterial type	Commercial examples	Origin and description	Key benefits and properties	Indications	References
Synthetic	Barrier membrane	Cytoflex® Tefguard from Unicare Biomedical	Expanded PTFE	Microporous. Non-resorbable (Removed after 3–4 weeks). Textured surface.	GTR/GBR. Socket grafting.	[27]
		Cytoplast® TXT200 from Osteogenics	High density PTFE	Microporous. Non-resorbable (Removed after 3–4 weeks). Higher strength for larger defects.	GTR/GBR. Socket grafting.	[102]
		Resolut Adapt® from Gore and ASSOC	PLGA	Occlusive. Resorbable. Space maintenance.	GTR/GBR.	[107]
		Epi-Guide® from Curasan	PLA	Extended barrier function. High absorption capacity. Resorbable. Textured surface.	GTR/GBR	
Natural	Porous scaffold	Collaplug® from Zimmer Dental	Porcine type I collagen	Aids healing. Controls bleeding and stabilizes blood clots. Easily cut to shape. Highly porous. Short Resorption time. Wound bed protection.	Periodontal surgical wounds. Socket preservation.	
		Fibrogide® from Geistlich Pharma AG.	Porcine type I/III collagen	Increases soft tissue thickness. Porous. Volume stability.	Gingival augmentation. Root coverage. Simultaneous approach with GTR/GBR. Soft tissue augmentation.	[123] [124]
		Collaform® from Impladent Ltd	Bovine type I collagen	Aids healing. Controls bleeding and stabilizes blood clots. Easily cut to shape. Highly porous. Short Resorption time. Wound bed protection.	Extraction sites. Extraction socket management. Periodontal surgical wounds. Sinus augmentation. Socket and ridge preservation.	
	Barrier membrane	Biomend® from Zimmer Dental	Bovine type I collagen	Cell-occlusive. Easy to handle even when hydrated. Permits nutrient diffusion. Resorbable. Space maintenance. Tear resistance.	GTR/GBR. Ridge augmentation. Sinus augmentation.	
		Healiguide™ from Encoll	Animal derived collagen type I collagen	Calcified collagen. Resorbable.	GTR/GBR.	
		OSSIX® PLUS from Datum Dental	Porcine type I collagen	Excellent handling properties. Maintains barrier functionality for 4–6 months. Resistant to degradation when exposed for 3–5 weeks	Furcation defects. Intra bony defects. Recession defects. Ridge augmentation. Sinus augmentation.	

mineralized component of bone tissue. The high thermal decomposition temperature of HA (1360 °C) facilitates the sintering of its powder form allowing for the production of 3D structures [145]. Consequently, HA has been widely used as bone fillers in the form of porous scaffolds, cement or granules [146]. In dentistry, synthetic HA has been used in the treatment of periodontal defects, alveolar crest augmentation, and maxillary sinus elevation [147–149]. Drawbacks associated with synthetic HA, however, include brittleness, weak tensile properties and an extremely slow resorption rate, which may limit its application in regenerative medicine [150].

The sub-optimal resorption rates of HA has led to increased interest in other calcium phosphate bioceramics. Carbonate apatite (CAp; $Ca_{10-a}(PO_4)_{6-b}(CO_3)_c$) has a low thermal decomposition (400 °C) making it unsuitable for sintering [151,152]. This characteristic has, in large part, hindered its use as a biomaterial for bone tissue engineering applications. Recent studies, however, have described a process whereby calcium carbonate is leveraged as a precursor to generate CAp blocks through a dissolution–precipitation reaction in an aqueous solution [153–155]. These calcium carbonate biomaterials have been shown to have a faster dissolution rate than HA in acidic conditions [156]. Furthermore, mineral deposition by osteoblasts is a key feature of the bone remodelling process and human bone marrow derived MSCs seeded on CAp scaffolds were shown to demonstrate higher expression of osteoblastic markers such as type I collagen, alkaline phosphatase, osteopontin and osteocalcin, compared to MSCs seeded on HA scaffolds [157]. Another critical feature of the bone remodelling process is osteoclast resorption, and in this regard, CAp granules implanted into bone defects in rats revealed osteoclastic resorption whereas a lack of resorption was observed with the use of HA granules [158]. Recent clinical studies have also demonstrated the efficacy CAp granules in treating periodontal intrabony defects [159] and in regenerating bone for implant placement [160].

Another calcium phosphate bioceramic that has been explored in dental tissue engineering applications is β-tricalcium phosphate (β-TCP; $\beta\text{-}Ca_3(PO_4)_2$) [161]. Similarly to CAp, and contrary to sintered HA, β-TCP is resorbed by osteoclasts, provoking a local acidification that results in β-TCP dissolution [162]. Indeed, when implanted into mandibles in minipigs, β-TCP scaffolds demonstrated almost complete

resorption at 8 weeks and promoted more bone formation than DBBM controls [163]. Bioactive glasses are another group of synthetic bioceramic materials based on silica, calcium, and disodium oxide [164]. Bioactive glasses facilitate bonding and integration with bone tissues through the formation of a layer of silica gel which acts to promote proliferation and differentiation of osteoblast cells thereby enhancing deposition of organic bone matrix [165]. As a result, bioactive glasses have had widespread applications in dentistry including in periodontics, orthodontics, endodontics and maxillofacial surgery. However, as with other bioceramics, the mechanical limitations of these bioactive glasses, in particular their inherent brittleness and low fracture toughness, are drawbacks which may be further exacerbated when considering their potential interaction with softer more delicate tissues such as those present in the periodontium [166]. Mineral trioxide aggregate (MTA) is a bioceramic that consists mainly calcium and silicate elements. MTA has become one of the most widely studied materials in endodontics due in large part to its biocompatibility and sealing ability, with its sealing properties (expansion and contraction) reported to be similar to that of native dentin tissue resulting in a resistance to fluid leakage and microbial invasion into the root canal [167]. The use of MTA has been associated with high success rates for VPT in both human [168] and animal [169] studies. Nevertheless, limitations such as the long setting time (2–3 h) and colour mismatch have motivated increased interest in alternative bioactive endodontic cements that aim to address these issues by utilising, for example, calcium chloride to accelerate reaction time and by replacing bismuth oxide with zirconium oxide to reduce discoloration [170–172].

4.6. Composite scaffolds

Increasingly, the field of tissue engineering is moving away from the use of “hard” bioceramic scaffolds and towards composite “softer” scaffolds which combine bioceramics with natural polymers. For example, the addition of a stiff compound such as HA to a protein such as collagen results in a synergistic effect, whereby the ductile properties of collagen act to improve the poor fracture toughness of HA [173]. This method also allows for the fabrication of 3D scaffolds with greater degrees of porosity than can be achieved with block bioceramics. Numerous studies from the authors have implemented this model, whereby lyophilized collagen-based scaffolds have been reinforced with bioceramic particles including HA [174,175] and marine coral [94] which have been shown to improve a range of material, mechanical and biological characteristics including enhanced stiffness and permeability, and more robust osteogenesis via calcium ion signalling. For the treatment of infected bone defects, composite collagen-bioceramic scaffolds can also offer greater control over antibiotic release kinetics through the formation of amide bonds between amino groups in antibiotics such as vancomycin and gentamicin, and carboxyl groups in collagen, achieved via crosslinking [176]. Although such antibiotics are often used to combat microbes and mitigate bacterial infections, their excessive administration has led to an increase in bacterial resistance [177]. To address this challenge, the use of alternative substances possessing antimicrobial properties have been proposed and, to this end, metallic compounds and their oxides have been leveraged as antimicrobial nanoparticles within composite scaffolds. For example, the incorporation of copper-doped bioglass nanoparticles within collagen-based scaffolds demonstrated effective antibacterial activity against *S. aureus* [178] and also supported bone regeneration *in vivo* [179]. Furthermore, magnesium oxide nanoparticles incorporated within PLGA microspheres have demonstrated antibacterial activity against periodontal pathogens *F. nucleatum* and *P. gingivalis* [180], and, when delivered within electrospun PLA-gelatin scaffolds, also effectively guided periodontal tissue regeneration in a rat periodontal defect model [181]. Beyond antimicrobial activity, metallic-bioceramic compounds such as cobalt-doped bioglass have also been shown to promote angiogenesis [182]. The properties and indications of various bioceramic and composite biomaterials with examples of commercially available products are presented in Table 4.

5. Cells for periodontal and endodontic tissue engineering

Mesenchymal stem/stromal cells (MSCs) are attractive cell sources for tissue engineering applications due to their capacity to undergo numerous population doublings in vitro without loss of phenotype and their ability to differentiate down a range of tissue-specific lineages. However, they have yet to come into widespread use in dentistry, due in part to challenges associated with cell survival and donor/batch variability. MSCs harvested from non-craniofacial structures, such as the iliac crest and tibia, develop embryonically from the mesoderm-derived mesenchyme while MSCs harvested from craniofacial structures arise either primarily from the ectomesenchyme, a unique embryonic tissue derived from the neural crest, or from a mixed mesoderm/neural crest origin. This section outlines some of the MSC populations that can be leveraged in tissue engineering applications to promote regeneration of the periodontium and endodontium.

5.1. Bone marrow derived mesenchymal stem cells

The possibility that an osteogenic precursor cell resided in the bone marrow was alighted on in the 1960s when a number of *in vivo* studies revealed the capacity of cells within the bone marrow to generate osseous tissues when transplanted [188–190]. Subsequent work carried out in 1974 developed a method to isolate fibroblast-like cells from the bone marrow, based on their ability to adhere to tissue culture plastic, which were defined as colony-forming units fibroblastic cells that were fibroblastic, nonphagocytic and clonogenic in nature [98,191,192]. In 1991, these cells were named MSCs and work postulated that the isolation, expansion, and site directed delivery of MSCs could govern the repair of skeletal tissues [193],with ensuing studies demonstrating the capacity of bone marrow derived MSCs to undergo osteogenic, chondrogenic and adipogenic differentiation in vitro [194–196].

The relative ease with which bone marrow MSCs can be harvested, and their ability to undergo osteogenesis, have resulted in their exploration as cell sources for bone tissue engineering applications. The osteogenic phenotype of bone marrow derived MSCs can be modulated via biophysical stimuli such as fluid flow [197]. Furthermore, biomaterial characteristics such as substrate stiffness [198] and surface topography [199] can also be leveraged to regulate osteogenesis. The in vitro osteogenic differentiation of bone marrow derived MSCs can be promoted through culture with dexamethasone, ascorbic acid, and β-glycerophosphate, whereby dexamethasone induces expression of the osteogenic transcription factor Runx2, ascorbic acid increases the secretion of collagen type I and β-glycerophosphate acts as a source of phosphate for HA [200]. The in vitro osteogenic priming of bone marrow derived MSC-seeded scaffolds has previously been demonstrated to repair bone when implanted in mandibular defects in dogs [201,202]. However, in vitro osteogenic priming of cell-seeded scaffolds can also lead to extensive matrix mineralization, sealing the pores of the scaffold thereby inhibiting host cell remodelling and vascularisation upon implantation and ultimately resulting in core degradation of the construct [203].

Bone marrow derived MSCs are typically harvested from the iliac crest, femur or tibia. While this harvesting procedure is well-established, it causes a challenge for the oral surgeon in that it requires an additional invasive procedure. Bone marrow derived MSCs harvested from alveolar bone circumvents this need for an additional procedure outside the oral cavity [204]. Unlike bone marrow derived MSCs harvested from the iliac crest, femur or tibia, which arise from the mesoderm-derived mesenchyme, alveolar bone marrow derived MSCs arise from a mixed mesoderm/neural crest origin, which may result in some phenotypic differences. For example, when human alveolar bone marrow derived MSCs were compared to iliac bone marrow derived MSCs, comparable

Table 4
Commercial examples of bioceramic and composite biomaterials for periodontal and endodontic tissue engineering applications.

Biomaterial type	Commercial examples	Origin and description	Key benefits and properties	Indications	References
Bioceramic	ENGIpore® from Finceramica. Apaceram® from HOYA Technosurgical.	HA	Micro, macro and interconnected porosity. Osseointegration. Osteoconductive. Similar composition to inorganic component of bone. Very slow resorption rate.	Maxillofacial reconstruction.	[186]
	Cytrans® Granules from GC Biomaterials. Osteogen® calcium apatite particulate from Impladent Ltd.	CAp	Hydrophilic. Osteoconductive. Resorbed by osteoclasts. Rough surface topography. Same composition as inorganic component of bone.	Intrabony defects. Ridge preservation. Sinus augmentation.	[158] [159]
	Ceros® TCP from Thommen Medical AG.	β-TCP	Osteoconductive. Porous. Resorbed by osteoclasts.	Bone augmentation. Sinus augmentation.	[161]
	Novabone® from Novabone Dental.	Bioactive glass	Porous. Promote osteogenesis and osteostimulation. Slow resorption. Supports vascularisation.	Fenestration/Dehiscence Defects. Peri-implantitis. Ridge augmentation. Sinus augmentation.	[187]
	ProRoot MTA from Dentsply.	MTA	Radiopacity. Sealing ability.	Apexification. Apicoectomy. VPT.	
Composite	BioOss® Collagen from Giestlich Pharma AG.	Porcine collagen scaffold with DBBM.	Addition of collagen improves handling. High porosity. Maintains haemostasis.	Bone augmentation. Extraction Socket Management. Intrabony defects. Sinus augmentation.	
	Osteogen® plug from Impladent Ltd.	Bovine collagen type I scaffold with CAp particulate.	High porosity. Supports keratinized tissue development.	Bone augmentation. Extraction Socket Management. Intrabony defects. Sinus augmentation.	

levels of osteogenesis were reported [205]. Interestingly, however, when chondrogenic and adipogenic capacities were assessed, human alveolar bone marrow derived MSCs demonstrated reduced differentiation potential when compared to iliac bone marrow derived MSCs, a trend which was replicated when canine, as opposed to human, cells sources were used. A recent study has also shown enhanced osteogenic capacity of alveolar bone marrow derived MSC sheets compared to iliac bone marrow derived MSC sheets in vitro, as evidenced by increased mineralization and elevated osteogenic gene expression, and *in vivo*, as demonstrated by greater bone volume and trabecular thickness upon implantation in rabbit calvarial bone defects [206] highlighting the potential of this cells source for bone tissue engineering within the oral cavity.

5.2. Gingiva-derived mesenchymal stem cells

Gingiva-derived MSCs, which can be readily obtained from clinically healthy gingival tissue, were first isolated and described in 2009 [207]. Gingiva-derived MSCs arise primarily from the ectomesenchyme, with 90 % having been demonstrated to originate from cranial neural crest cells while 10 % were demonstrated to derive from the mesoderm [208]. These cells demonstrate key stem cell characteristics, including self-renewal, clonogenic potential, and the ability to differentiate into multiple cell lineages. Importantly, gingiva derived MSCs also exhibit strong immunomodulatory properties and have been shown to suppress peripheral blood lymphocyte proliferation and upregulate a broad range of immunosuppressive factors—such as IL-10, indoleamine 2,3-dioxygenase, inducible nitric oxide synthase, and cyclooxygenase-2—in response to pro-inflammatory signals like interferon-gamma [207]. Unlike some other stem cell sources, gingiva derived MSCs have not shown spontaneous tumour formation either in vitro or *in vivo*, supporting their favourable safety profile [209]. Also of interest is that inflamed gingival tissue can yield MSC-like populations with regenerative properties comparable to those from healthy tissue, making it a viable and accessible source for clinical applications [210]. Given their multipotent differentiation capacity and potent anti-inflammatory and immunoregulatory functions, gingiva derived MSCs and their cell-free derivatives—such as conditioned media (CM) and extracellular vesicles—have been increasing explored as therapeutic agents in regenerative dentistry [211].

Studies have demonstrated that both systemically and locally delivered gingiva derived MSCs can migrate to periodontal defects and actively participate in tissue repair. Systemic administration has been observed to result in homing of gingiva derived MSCs to sites of alveolar bone damage, where they contribute to osteogenic differentiation and new bone formation, with human-derived cells detected within the regenerated tissue structures [212]. Complementary findings from local delivery models confirm that direct application of gingiva derived MSCs to periodontally compromised sites enhances histological architecture, increases alveolar bone fill, and promotes PDL fibre orientation and attachment, indicating comprehensive periodontal tissue regeneration [213]. One preclinical study which focused on combining gingiva derived MSCs with IL-1Ra-releasing HyA synthetic ECM demonstrated that it resulted in significant periodontal regeneration across multiple parameters including clinical attachment loss, probing depth, gingival recession, periodontal attachment level, cementum regeneration and bone regeneration [214].

The integration of gingiva derived MSCs into biocompatible scaffolds provide the cells with essential mechanical support while promoting survival, proliferation, and differentiation. To better replicate the natural tissue microenvironment, advanced 3D culture systems have been developed using materials such as PLA, alginate/HyA composites, and bovine pericardium membranes. The success of these scaffold-based 3D models in regulating MSC fate has driven their increased adoption,

marking a significant advancement in the practical application of gingiva derived MSCs for dental tissue engineering [215].

5.3. Periodontal ligament stem cells

First identified in 2004 [216], periodontal ligament stem cells (PDLSCs) reside within the PDL and contribute to the maintenance and repair of the periodontium. They are easily accessible during non-invasive dental procedures such as scaling. Like gingiva derived MSCs, PDLSCs exhibit classic MSC characteristics, including clonogenicity, self-renewal, and multilineage differentiation. They express MSC surface markers such as STRO-1, CD90, CD105, and CD146, while lacking hematopoietic markers such as CD34 and CD45. PDLSCs originate from the neural crest, which underlies their unique ability to differentiate not only into mesodermal lineages—such as osteoblasts, cementoblasts, chondrocytes, and adipocytes—but also into ectoderm-derived cell types [217].

Under defined culture conditions, PDLSCs have been shown to differentiate into neural-like cells, spontaneously expressing neural markers including Nestin and GAP-43. The activation of key signalling pathways, such as PKCα/GAP-43 and ERK1/2, governs their neurogenic progression, alongside cytoskeletal rearrangements that mirror early neural morphogenesis. These cells have also demonstrated the ability to differentiate into Schwann cells, endothelial cells, and even cardiac myocytes, expressing lineage-specific markers like cardiac troponin T. *In vitro* studies further suggest the possibility of generating islet-like cells and retinal ganglion-like cells from PDLSCs, highlighting their plasticity. Despite this broad differentiation potential, their most well-established application remains in the context of bone and periodontal tissue regeneration [218].

PDLSCs have demonstrated consistent efficacy in preclinical models when delivered locally in conjunction with biomaterials such as HA/TCP, collagen sponges, or decellularized periodontal scaffolds. These constructs have facilitated the regeneration of alveolar bone, cementum, and oriented PDL fibres which is necessary for restoring the structural and functional integrity of the periodontal complex [219]. PDLSCs modulate inflammation and promote tissue repair through paracrine signalling and the release of regenerative microRNAs, including miR-2861 and miR-210, which support angiogenesis and osteogenesis during the early phases of bone healing. Notably, miR-210 has been implicated in upregulating VEGF, enhancing angiogenic responses essential for tissue regeneration [220]. Clinical studies have demonstrated the safety and efficacy of PDLSCs in the regeneration of periodontal tissues, showing an increase in alveolar height, increased clinical attachment levels, decreased periodontal probing depth, and resolution of intrabony periodontal defects [221–223]. Furthermore, a systematic review and meta-analysis indicated that PDLSCs were among the most effective stem cells for periodontal tissue regeneration, outperforming other types like gingiva derived MSCs in terms of new bone and cementum formation [224].

5.4. Dental pulp stem cells

DPSCs are recognized group of oral stem cells arising from the ectomesenchyme which possess similar properties to other MSC populations in terms of surface markers and proliferation/differentiation capacity. When loaded onto hydroxyapatite/tri-calcium HA/TCP scaffolds and employed in a subcutaneous implantation model, DPSCs demonstrated dentine-like formation with a collagen matrix perpendicular to the odontoblast-like layer resembling the native dentine-pulp complex [225]. This study was the first to characterise DPSCs as clonogenic, highly proliferative postnatal stem cells, that accounted for about 2 % of the pulpal cellular content, that were also capable of tissue regeneration. Notably, DPSCs also demonstrate immune-evasive and anti-inflammatory properties, secreting chemokines that modulate host response, further supporting their suitability for allogeneic application [226–228]. DPSCs are attractive to dentists, scientists and medics as alongside stem cells of human exfoliated deciduous teeth (SHED) they are readily available within 'high-street' dental practices. However, despite extensive scientific research using DPSCs and promising preclinical research, *ex vivo* expansion of DPSCs through good manufacturing processes and subsequent transplantation has yet to be implemented into clinical practice [229].

DPSCs have also been explored in combination with other regenerative cell populations to enhance angiogenic and odontogenic responses. Combining DPSCs with human umbilical vein endothelial cells (HUVECs) has resulted in pulp-like tissue with organized collagen alignment, vascular network formation, and evidence of reparative dentine, outperforming both acellular scaffolds and empty root canal controls *in vivo*. Moreover, DPSC and stem cells of the apical papilla (SCAP) co-implantation has demonstrated the ability to generate a well-vascularised pulp-like tissue that fills the canal space and supports dentine formation, though without reestablishment of a tubular structure (DPSCs & HUVECs: [230]; DPSCs & SCAPs [231]). These findings highlight the potential of multi-cellular approaches in regenerative endodontics and reinforce the critical role of vascularisation and scaffold integration in successful tissue engineering strategies.

More recently, translation research has shifted towards delivering DPSCs as three-dimensional spheroids rather than monodispersed cells. These spheroids retain their native ECM, preserve cell–cell interactions, and exhibit enhanced survival, differentiation, and angiogenic gene expression. In contrast to enzymatically isolated single-cell suspensions, spheroid-based delivery improves phenotypic stability and resistance to apoptosis, offering a more physiologically relevant approach to pulp tissue engineering. Furthermore, DPSC spheroids demonstrate upregulation of trophic factors and show improved regenerative outcomes *in vivo* compared with dissociated cell populations, particularly when preconditioned with hypoxic or osteogenic stimuli [232–238].

Beyond cell transplantation, cell-homing approaches using DPSC-derived CM and extracellular vesicles have emerged as promising alternatives [239,240]. These derivatives retain the bioactive secretome of DPSCs, including anti-apoptotic, angiogenic, immunomodulatory, and neurotrophic factors, enabling regeneration without the logistical and regulatory challenges of stem cell delivery. CM from DPSC spheroids has been shown to enhance odontogenic gene expression [241], promote pulp-like tissue formation, and support vascularisation in both ectopic and orthotopic models [240,242]. In particular, $CD31^{-}$ side population) DPSC-CM has demonstrated superior regenerative outcomes compared with CM from bone marrow or adipose stem cells [229,240], and SHED-derived CM has shown similar pro-angiogenic effects [232]. These findings support the development of novel, cell-free platforms for clinical translation, although further work is needed to optimise CM standardization and delivery [239,243].

5.5. Induced pluripotent stem cells

A disadvantage associated with the use of MSCs for tissue engineering applications is the issue of standardization arising from donor/batch variability. Furthermore, even well-characterized MSCs undergo senescence following extensive populations doublings making large-scale manufacturing challenging. Induced pluripotent stem cells (iPSCs) were first described in 2006 when dermal fibroblasts were reprogrammed and dedifferentiated into embryonic-like stem cells via the forced expression of a cocktail of transcription factors [244]. The self-renewal ability of iPSCs, in addition to their capacity to give rise to all lineages of the mature organism, therefore offer much promise for tissue engineering strategies [245,246]. However, iPSC potential is increasingly being understood to be dependent on the initial cell source, with immature cells typically demonstrating enhanced reprogramming potential over mature cells. Moreover, it has been suggested that iPSC reprogramming efficiency is dependent on the degree of stem cell-related genes inherent in the source [247]. Dental MSCs would

appear to be an attractive cell source for iPSC reprogramming, as they can be harvested from tissues in younger individuals that would otherwise be treated as biomedical wastes, such as for example, exfoliated primary teeth and extracted third molars. Indeed, SHED, SCAP and DPSCs, have demonstrated a higher reprogramming efficiency when compared to fibroblasts derived from either the gingiva or the foreskin [248]. Furthermore, the capacity of iPSCs to give rise to cells of both mesoderm and neural crest origins [249,250] points towards their possible use as therapeutic agents in the treatment of periodontic-endodontic lesions and even as foundational building blocks in the engineering of functional bioteeth [251]. iPSCs, however, still lag even MSCs in terms of clinical translation with further investigations into their characterization, reprogramming/dedifferentiation protocols, and genomic stability required to accelerate their implementation towards clinical application. The harvest procedures, advantages/disadvantages and potential regenerative applications of the various stem cells for dental tissue engineering are summarized in Table 5.

6. Biologics for periodontal and endodontic tissue engineering

Biologics, including growth factors, recombinant proteins and autologous blood products are therapeutic agents that can be harnessed to help promote periodontal and endodontic regeneration and healing. These therapeutic agents act by augmenting the wound healing process through regulation of key processes such anabolic bone formation, angiogenesis, cementogenesis, osteoblast/odontoblast differentiation, mitosis and chemotaxis [252]. Although biologics can be administered directly via injection, biomaterial scaffolds are increasingly being leveraged as delivery vehicles for biologics to ensure the application of sustained therapeutic doses. This section describes the key biologics and delivery vehicles utilised in periodontal and endodontic tissue engineering applications.

6.1. Enamel matrix derivative

Enamel matrix proteins are secreted by Hertwig's epithelial root sheath during root development and are composed primarily of amelogenins, a family of hydrophobic proteins that account for more than 95 % of the organic constituent of the enamel matrix [253]. Early studies observed that these amelogenins are deposited on the surface of developing tooth roots prior to cementum formation [254,255], suggesting a role for enamel matrix proteins in promoting cementogenesis and the development of periodontal tissues. This motivated work leading to the purification of the enamel layer of developing porcine teeth resulting in an acidic extract that was given the working name enamel matrix derivative (EMD).

Since its discovery, the capacity of EMD to regulate the activity of periodontal cells has been explored in a number of in vitro studies. For example, EMD has been shown to enhance proliferation, protein production and mineral nodule formation of PDL cells [256]. Furthermore, EMD was demonstrated to up-regulate hyaluronan synthesis in gingival fibroblasts [257]. Additionally, PDL cells exposed to EMD were observed to increase their proliferation and metabolic activity and also secreted several growth factors, including TGF-β1, IL-6 and PDGF into the surrounding media [258]. Interestingly in this study, although intracellular cyclic AMP signalling was upregulated in both PDL and epithelial cells, a differential effect on cell activity was observed with proliferation and growth of epithelial cells observed to diminish, indicating that EMD favours mesenchymal cell growth over epithelial cell growth. When a more recent study examining the effect of human recombinant amelogenin on oral keratinocytes was performed, a dose and time dependent reduction in the proliferation and metabolic activity of keratinocytes

Table 5
Comparison of stem cells for periodontal and endodontic tissue engineering applications.

Stem Cell Source	Harvest procedure	Advantages	Disadvantages	Differentiation capacity	Potential applications in dentistry
Extra-oral bone marrow derived MSCs	Highly invasive and potentially painful harvest from the iliac crest, femur or tibia.	Well-characterized with extensive research history. High proliferation and differentiation capacity.	General anaesthesia/ hospitalization required. Donor site morbidity. Risk of infection.	High osteogenic, chondrogenic and adipogenic potential.	Bone defect repair.
Intra-oral bone marrow derived MSCs	Invasive harvest from the maxilla/mandible under specialized surgical procedure.	Dental-relevant niche. Good proliferation and differentiation capacity.	Limited quantity. Donor site morbidity.	High osteogenic potential. Reduced chondrogenesis and adipogenesis compared to extra oral bone marrow MSCs.	Ridge augmentation. Sinus augmentation. Periodontal bone defects.
GMSCs	Minimally invasive harvest during gingivectomy/biopsy.	High proliferation capacity. Immunomodulatory properties.	Aesthetic concerns arising from harvest.	High osteogenic, chondrogenic and adipogenic potential. Notably high neurogenic potential arising from neural crest origin.	Gingival augmentation. Soft tissue augmentation Alveolar bone defect repair.
PDLSCs	Harvested during tooth extraction.	Periodontium-relevant niche Role in regeneration of the cementum, PDL, and alveolar bone.	Limited to patients with extracted teeth. Limited quantity.	High cementogenic, osteogenic and fibrogenic potential.	Periodontal defect regeneration. Tooth transplantation support.
DPSCs	Harvested from waste tooth tissue (e.g. impacted third molar teeth or premolars for orthodontics).	High proliferation and differentiation capacity Immunomodulatory properties.	Limited to patients with extracted teeth. Small cell population in normal pulp, approximately 2 %.	High odontogenic, osteogenic, neurogenic, adipogenic, myogenic and angiogenic potential.	VPT. Cell-based REPs.
iPSCs	Can be derived from any somatic cell harvested from tissues such as skin, bone, fat, dental tissues etc.	Unlimited self-renewal capacity Not limited by tissue availability.	Risk of tumorgenicity. Complex reprogramming/ differentiation protocols. Expense.	Pluripotent; Can be directed to differentiate into any cell type.	Periodontic-endodontic lesions. Biotooth engineering. Dental disease modelling. Cell-based REPs.

was demonstrated [259]. Taken together, these in vitro studies indicate a complex interaction between various cells within the oral cavity and EMD.

The amelogenins in EMD aggregate at a physiological pH range and at 37 °C, thus they require dissolution in a medium/material of acidic or alkaline pH and at low temperature [260]. Early work demonstrated PGA to be effective in promoting precipitation of amelogenins, thereby facilitating exposure of PDL cells to EMD and allowing resultant cell-matrix interactions to occur [261]. Consequently, the first marketed EMD was presented in a lyophilized form to be mixed with PGA immediately prior to use. To reduce time and minimize errors during the mixing process, the product was subsequently provided pre-mixed in PGA at a concentration of 30 mg/mL (Emdogain® by Straumann). Emdogain® has since become one of the most extensively studied biologics in dentistry and is used clinically in treatment of intrabony defects, furcation involvements and gingival recessions [252,262,263].

6.2. Platelet derived growth factor

PDGF is regarded as one of the principal wound healing hormones and its ability to promote periodontal regeneration was first demonstrated in 1989 when its application was shown to enhance regeneration of bone, cementum and PDL in periodontitis-affected teeth in beagle dogs [264]. The PDGFs are a family of growth factors that exert biologic effects by activating two tyrosine kinase receptors (the PDGF-α and PDGF-β receptors) [265]. Traditionally, PDGF-AA, PDGF-BB, and PDGF-AB were believed to the only PDGF ligands, but at the turn of the century two additional members of the PDGF family (PDGF-CC and PDGF-DD) were identified [266,267]. In examining the biological effect of different PDGF isoforms, PDGF-AA was shown to have no chemotactic activity or ability to induce reorganization in human fibroblasts [268], whereas PDGF-BB was shown to stimulate the proliferation of osteoblasts and fibroblasts [268,269]. Furthermore, the expression of PDGF-β receptors was demonstrated in regenerated periodontal tissues whereas the expression of PDGF-α receptors was not identified. This suggests that the PDGF-β receptors are likely to contribute in periodontal healing and regeneration to a greater extent as compared to PDGF-α receptors. Given that PDGF-β receptors bind PDGF-BB with high affinity, PDGF-AB with lower affinity, and PDGF-AA with no considerable affinity [270], together these studies pointed towards PDGF-BB as the isoform with the most potential for therapeutic effect in dental applications. In this context, a recent study demonstrated that PDGF-BB signalling via PDGFR-β regulated maturation of blood vessels generated upon the vasculogenic differentiation of human DPSCs [271]. Additional work also demonstrated that over-expressing PDGF-BB in human DPSCs enhances proliferation and odontoblastic differentiation thereby improving stem cell-mediated dentin-pulp complex regeneration *in vivo* [272].

Although enhancement of periodontal tissue regeneration has been shown with the use PDGF-BB delivered via injection of the growth factor solution [273], the short half-life of the biologic (<4 h) is considered a limitation and has motivated the search for an appropriate delivery vehicle to ensure sustained therapeutic dosage. GEM 21 S® by Lynch Biologics LLC is a recombinant human PDGF-BB product approved for the in treatment of intrabony defects, furcation defects and gingival recessions and is provided with a β-TCP matrix component. In a multicentre human clinical trial involving 180 patients, β-TCP matrices loaded with PDGF-BB were shown to induce greater linear bone gain and defect fill at 6 months, as well as higher clinical attachment levels, than non-loaded β-TCP controls [274]. Nonetheless, the sequestration of growth factors such as PDGF-BB within β-TCP matrices may still be sub-optimal and subject to a burst-release pattern. Indeed, when examining release kinetics of GEM 21 S®, elution of PDGF-BB was found to occur rapidly from β-TCP both in vitro and *in vivo*, with almost 100 % of the PDGF-BB recovered from β-TCP after 90 min in vitro whilst approximately 90 % of PDGF-BB was depleted from rat calvarial defect sites within 3 days [275]. One potential method of reducing burst release of a cationic growth factor such as PDGF-BB is to leverage ionic interaction through the use of an anionic biomaterial. To that end, the incorporation of negatively charged chondroitin sulfate within chitosan scaffolds loaded with PDGF-BB was observed to retard release of the growth factor whilst maintaining its bioactive capacity as demonstrated by increased osteoblastic proliferation [276].

6.3. Bone morphogenetic protein

BMPs are members of the TGF-β super-family and perform essential functions during osteogenesis and chondrogenesis, skeletal development, and homeostasis, and transduce signals through SMAD-dependent and -independent pathways [277]. Their activity was first observed in the mid-1960s when demineralized bone matrix implanted in muscular tissues were shown to induce ectopic formation of cartilage and bone tissues with bone marrow [67,278]. To date, over 15 BMPs have been identified in human and rodents [277] with BMP-2 and BMP-7 receiving the most interest as therapeutic agents for bone tissue engineering applications.

The INFUSE® Bone Graft by Medtronic is a recombinant human BMP-2 product delivered using a collagen sponge and is approved for use in certain spinal and orthopaedic procedures as well as in sinus and ridge augmentations. Despite the strong osteogenic properties of BMP-2 as demonstrated in a numerous studies [279–282], when used in periodontal applications some studies have also indicated that BMP-2 can induce adverse healing events such as ankylosis and root resorption [283,284]. More worryingly, in the spinal field, the INFUSE® bone graft has been associated with complications including osteolysis, ectopic bone formation, infection, and cancer risk [285–290]. These complications, suggested to be the result of the uncontrolled release of supra-physiological levels of BMP-2 from the collagen sponge carrier [291], have led to increased interest in biomaterial technologies that aim to control BMP-2 delivery while retaining its potent osteogenic capacity. HA crystals offer non-covalent binding sites for proteins via the $–COO^-$ functional group [292,293] and potentially the –OH and $–NH_2$ functional groups [294]. Work from the authors have leveraged the HA component within collagen-based scaffolds to better control the delivery of pro-osteogenic and pro-angiogenic growth factors [295]. When utilising BMP-2 as the protein of choice, this approach was successful in demonstrating critically sized bone defect repair using 30 times less protein than the INFUSE® product [296]. Other groups have harnessed BMP-2 functionalised calcium phosphate particles embedded within HyA hydrogels to achieve enhanced vertical alveolar bone augmentation in a beagle dog model [297]. Another means of controlling BMP-2 release is through its encapsulation within a polymeric delivery system which facilitates release upon degradation of the polymer. To that end, both natural (alginate) and synthetic (PLGA) polymeric beads have been harnessed within collagen-based scaffold systems to control BMP-2 delivery [298]. Alginate hydrogels loaded with BMP-2, and covalently coupled with the arginine-glycine-aspartic acid peptide to facilitate cell adhesion, have also been shown to promote the regeneration of bone with mechanical properties approaching that of native bone [299] and have even achieved levels of bone defect repair higher than those achieve using the INFUSE® system [300].

In addition to optimising the dosage and release profile of BMPs, some studies have sought to enhance their therapeutic efficacy through their co-delivery with a pro-angiogenic growth factor such as VEGF [238,301,302]. This approach seeks to recapitulate the *in vivo* phenomenon of osteogenic-angiogenic coupling whereby VEGF and BMPs work in synergy during bone repair to first induce angiogenesis and vascularisation and subsequently facilitate osteogenesis and bone formation [303,304]. Interestingly, however, co-delivery of VEGF with BMP-2 has also been shown to suppress odonto/osteoblastic differentiation of human DPSCs when compared to the delivery of VEGF alone [305]. Recently, a co-delivery approach has been leveraged using BMP-2

with PDGF-BB. In this work, a composite scaffold consisting of a gelatin/chitosan cryogel loaded with BMP-2 and a poly-*l*-lactic acid nanofiber structure encapsulating PDGF-BB, was shown to exert a synergistic effect on osteogenesis and greatly accelerate bone healing in a rat calvarial defect model [306]. Additional work examining co-delivery of these two biologics via chitosan microspheres coated on titanium scaffolds demonstrated enhanced osteogenic differentiation compared to single-factor scaffolds [307].

6.4. Fibroblast growth factor

Fibroblast growth factor (FGF) was first identified in 1974 as a protein capable of promoting the proliferation of fibroblasts from bovine pituitaries [308]. In the following decade, acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2) were determined as two proteins with different acidic and basic isoelectric points [309]. Since then, 22 FGF genes in total have been identified in humans with FGF-2 garnering particular attention as a therapeutic candidate for regenerative medicine [310].

In vitro, FGF-2 has been shown to promote proliferation of human PDL cells and to suppress their osteogenic differentiation via regulation of Runx2 expression [311]. Whilst FGF-2 has also been demonstrated to induce the proliferation of gingival epithelial cells, this effect was inhibited in gingival epithelial cells in the presence of fetal calf serum but synergistically enhanced in PDL cells [312]. Taken together, these studies indicated a potential differential response by these cells to FGF-2 administration *in vivo,* and suggested a role for FGF-2 in supressing epithelial downgrowth in periodontal regeneration through up-regulation of a competitive inhibitor in PDL cell growth. Indeed, pre-clinical trials carried out in beagle dog and non-human primate models found significantly improved periodontal regeneration with the use of FGF-2 compared to control groups, as evidenced by enhanced bone and cementum formation [313,314]. Notably, no instances of epithelial downgrowth, ankylosis or root resorption in response to FGF-2 application were observed in these *in vivo* studies. In subsequent clinical trials, recombinant human FGF-2 was demonstrated to induce periodontal regeneration [315,316] leading to the approval of its use in Japan as the active agent in REGROTH® (Kaken Pharmaceutical Co., Ltd.) which has been shown to be superior to Emdogain® in the treatment of intrabony defects [317]. Furthermore, in a recent clinical trial examining the combined therapy of REGROTH® with CAp granules (Cytrans® granules), enhanced alveolar bone formation and clinical attachment level, in addition to reduced tooth mobility, were demonstrated compared to preoperative values, although no improvements in the width of keratinized gingiva or gingival recession were observed [318].

6.5. Autologous blood products

An alternative approach to the use of exogenous growth factors and recombinant proteins in regenerative applications is to leverage the endogenous factors present in a patient's own blood. During the wound healing process, platelets play a key role in the initial inflammatory phase and also subsequently regulate MSC proliferation and differentiation and thus have been proposed as a potential therapy for use in regenerative medicine [319]. Platelet rich plasma (PRP) is a concentrate of platelets within a small volume of plasma which is typically prepared via centrifugation using a two-step method with an anti-coagulant to prevent clotting. In this two-step process, differential centrifugation is leveraged to separate platelet poor plasma from erythrocytes and PRP and to isolate PRP from erythrocytes [320]. Upon activation by an agonist such as thrombin, PRP releases a range of inflammatory factors and growth factors including; Connective Tissue-Activating Peptide III, FGF-2, PDGF, TGF-β1 and VEGF [321,322]. Recently, there has been an increase in case reports describing the use of PRP in endodontic healing, with one patient with an under developed root and an open apex demonstrating increased thickening of the root walls, root development and apical closure of the root apex three years post-treatment with PRP [323]. A significant increase in root length was also reported with use of PRP in the regeneration in non-vital immature permanent teeth when compared to blood clot controls, although no differences in bone density or lesion size were observed [324]. In periodontal applications, PRP has typically been used in combination with graft materials with mixed outcomes reported. For example, in a systematic review assessing the effect of PRP in the treatment of periodontal defects and gingival recessions, the authors concluded that PRP may be beneficial in the treatment of intrabony defects but not for gingival recessions [325]. Other work examining the use of PRP in GTR in combination with bone grafts found no statistical improvement in the treatment of intrabony defects when compared to non-PRP controls [326]. Differences in preparation methodologies, graft materials used, treatment courses and patient-specific factors go some way towards explaining the variations that arise when assessing the efficacy of PRP in regenerative therapies.

Platelet rich fibrin (PRF) is a second-generation platelet concentrate therapy whereby a one-step centrifugal process is leveraged to induce physiologic clot formation and fractioning without the requirement of additives such as anticoagulants [327]. The result is a fibrin scaffold containing platelets, leukocytes, and plasma proteins which acts as a reservoir of growth factors [328]. In addition to being a truly autologous blood product in not requiring external anticoagulants or activators, PRF also releases its growth factors in a more controlled, sustained manner when compared to PRP which ultimately results in a greater overall release of protein over a prolonged period [329]. *In vitro,* PRF has been shown to increase proliferation of oral bone marrow MSCs [330], gingival fibroblasts [331], PDL cells [332], and dental pulp cells [333,334]. Additionally, PRF has been shown to enhance alkaline phosphatase activity (an early marker of osteogenesis) in oral bone marrow MSCs [335], PDL cells [332] and dental pulp cells [336]. In a systemic review of clinical studies examining the potential of PRF in treating intrabony periodontal defects, the authors concluded that PRF resulted in better clinical/radiographic outcomes than open flap debridement, and also augmented the therapeutic effects of bone grafts [337]. Furthermore, in a clinical study assessing the capacity of PRF in combination with autologous grafts to treat gingival recessions, enhanced root coverage was reported with the use of PRF albeit at the short follow-up time of 3 months [338].

One of the main limiting factors of in the use of PRF in dental tissue regeneration is its fast resorption rate, which has been characterized to occur within 2–3 weeks and which renders PRF unsuitable for use as a barrier membrane in GTR/GBR [339,340]. Recently, however, studies have sought to extend resorption time and improve volume stability by heating platelet-poor plasma (PPP) containing roughly 60 % albumin to 75 °C for 10 min to facilitate denaturation and the breaking of hydrogen bonds within its protein molecule [341]. Subsequently, the proteins are then reorganized into a denser protein structure, with the resorption time of this heated PPP/albumin gel being reported to extend out to 3–4 months [342,343]. In order to account for the loss in biological capability resulting from the denaturation process, a platelet-rich layer from the buffy coat (i.e. liquid PRF) is then mixed back in upon sufficient cooling and the resultant product has been given the working term albumin-PRF. Studies have demonstrated a slow and gradual release of growth factors such as TGF-β1 and PDGF from albumin-PRF over a 10 day period as well as increased proliferation and collagen type I gene expression in fibroblasts treated with albumin-PRF CM [344]. Furthermore, in a recent randomized control trial comparing the capacities of albumin-PRF and CTG to modify gingival phenotype, albumin-PRF was shown to increase gingival thickness, although CTG demonstrated a greater enhancement in keratinized tissue width [345]. Although such results are encouraging, it is generally accepted that further studies are necessary to support the use of PRF and albumin-PRF in routine dental practice with high clinical efficacy and long-term stability.

7. State of the art and future trends

Over the past few decades, the shift away from traditional surgical techniques towards minimally invasive procedures has had a significant impact across many medical fields. This shift has perhaps been most pronounced in the field of orthopaedics, where developments in arthroscopic surgical techniques have been driven by technological advances focussed around improved instrumentation and enhanced imaging techniques complemented by automated assistance which may contribute to a lower rate of postoperative infection [346,347]. This trend is increasingly becoming evident in dentistry where aesthetic concerns are a major factor in moves towards reducing the damage caused to tissues in the process of surgical procedures. In periodontology, for example, the Pinhole® Surgical Technique has been developed as a minimally invasive procedure for the treatment of gingival recessions which circumvents the need for scalpel incisions and suturing [348]. In this procedure, a specialized dental instrument is used to create a pin-sized hole in the gum and the instrument is then manoeuvred to loosen the tissue and reposition the gum line so that it covers the exposed root of the tooth while a biomaterial (typically thin strips of collagen) is implanted to stabilize the repositioned tissue (Fig. 6). Advances in injectable biomaterials with, for example, optimised shear thinning properties, in situ crosslinking capacities and enhanced formulations, offer the potential of more effective filling of the difficult to access spaces that are created in the process of these procedures. To that end, chitosan hydrogels incorporated with curcumin and α-tocopherol-loaded liposomes, with tailored formulations to guide the biological performance of human DPSCs and human gingival fibroblasts have recently been described as antimicrobial injectables with multi-functional features for endodontic and periodontal tissue engineering applications [349]. Furthermore, the crosslinking of these chitosan injectables can be modulated via exposure to visible light and body level temperatures [138]. Such a photo-curable approach to in situ crosslinking has also recently been demonstrated using layered double hydroxide-HyA-composite hydrogels which possess antimicrobial properties and the capacity to promote growth factor-free bone regeneration [350]. The development of second order injectable hydrogels [351], that is, ECM-based materials functionalised with one or more cell types with associated cytokines and capable of promoting key biological processes such as vascularisation would therefore appear to be a key area of focus in future dental tissue engineering therapies. In the endodontic field a salient example is that of VPT which is gaining popularity as an as a more regenerative biological based treatment approach for the management of cariously exposed vital pulp tissue. However, as described above even this seemingly wholly positive development yet remains to be taken on as the gold standard practice. This is for various reasons including the basic underlying technologies, which are still in the pre-clinical/clinical phases, but also because in many cases, these treatments would be carried out in general dentistry clinics, where changes to specialized procedures are often take time to gain traction. The recent updates to the European Medical Device Regulation (MDR) highlight the importance and utility of pulp preservation strategies, taking a patient-centred perspective. However, approval routes, resource limitations for small operators, and a lack of sufficient infrastructure for approval can again pose challenges to translation.

Another clear trend in the development of biomaterials within the dental healthcare space is a move towards personalised scaffolds tailored to a patient-specific geometry. This approach has a number of advantages including reduced surgical time, greater stability of grafts and a decrease in micromovement. Related is a shift in implant planning work flow away from the traditional method, whereby the initial positioning of an implant within the available bone determines crown placement, towards a prosthetic-driven approach in which an ideal implant position is planned, increasingly aided by advances in artificial intelligence and machine learning [352],factoring in the form, fit and function of final restoration. A critical factor in these developments has been the widespread adoption of intra-oral scanners within the dental community, the universal nature of which has been evidenced in a recent survey of over 1000 dentists in which over 75 % of respondents were reported to use intra-oral scanners on a daily basis [353]. The ubiquitous presence of such high-resolution scanning technology, in which thousands of images can be easily stitched to form 3D models and subsequently be exported as STL, PLY or OBJ files, potentially places dentistry at the vanguard of sectors within the broader healthcare system that may be ideally positioned to exploit the opportunities offered by advanced fabrication techniques such as 3D bioprinting. Indeed, intraoral scanning and additive manufacturing is already making an impact in reducing the time in the chair for patients requiring orthodontic treatments such as clear aligners, splints, Hawley retainers, or occlusal guards and prosthodontic treatment such as full or partial

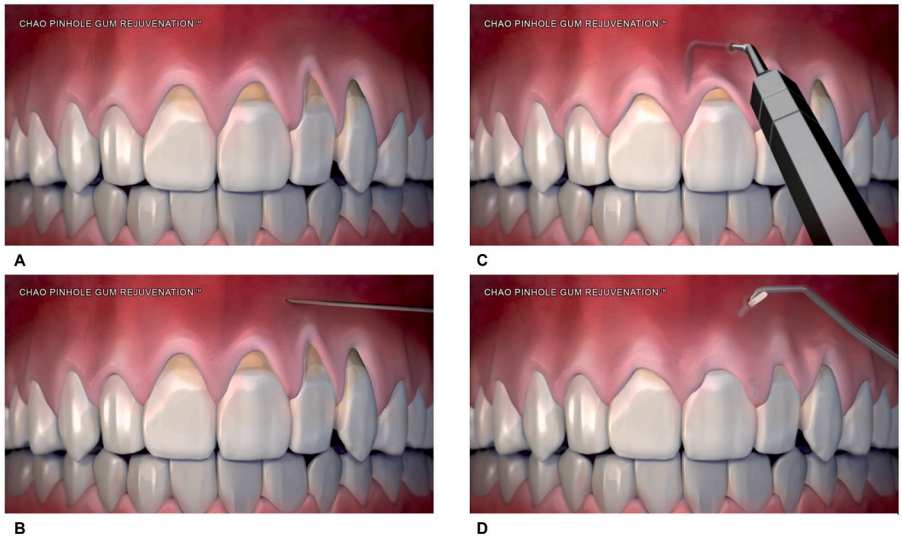

Fig. 6. Schematic of the Pinhole® Surgical Technique. (A) Illustration of multiple gingival recessions. (B) A pin-sized hole is created in the gum tissue above the recessions. (C) A specialized dental instrument is inserted through the pinhole to gently loosen the tissue and the gingival margin is then repositioned to cover the exposed root structure. (D) Thin strips of collagen are typically placed under the gums to stabilize the repositioned tissue. Used with permission. © Dr. John Chao. Pinhole® is a registered trademark. All rights reserved.

dentures. Leveraging combinations of cells, bioinks and biologics to 3D bioprint customized scaffolds for the regeneration of periodontal defects, treatment of multiple complex gingival recessions and advanced GTR therapies is envisaged to make a significant step forward for regenerative medicine within the oral cavity and, to that end, recent studies have explored co-printing of human PDLSCs with natural polymer bioinks [354,355] with the aim of regenerating periodontal tissues whilst meltelectrowriting has also been harnessed to generate composite PCL-nano HA scaffolds which were subsequently shown to enhance the metabolic activity and osteogenic capacity of seeded human PDLSCs [356]. The 3D bioprinting of gingival fibroblasts encapsulated within ADM-gelatin-alginate bioinks has also been demonstrated as an effective means of increased gingival keratinized tissue width when implanted into beagle dogs [142].

Despite advances in biomaterial delivery systems, the short half-life of recombinant proteins and growth factors used in regenerative medicine remains a limitation. Whilst perhaps less of a concern for acute wounds within the oral cavity, the application of such biologics to treat larger, more complex defects may be problematic due to issues arising from the administration of high therapeutic doses, including abnormal tissue growth and off-target effects. Consequently, there is increased interest in the use of genes as therapeutic agents for more complex regenerative applications within the oral cavity, as such an approach may allow for the over-expression of a target gene for a longer duration than can be achieved with traditional biologics, whilst also potentially offering improved spatiotemporal control by targeting specific cells and reducing issues owing to biologic diffusion away from the defect site. To that end, viral vectors encoding PDGF genes have been shown to promote regeneration of calvarial bone defects [357], regulate cementogenesis of tissue engineering constructs [357] and enhance dentin-pulp complex formation [357]. However, some safety concerns have been described with the use of viral vectors for gene therapy applications, with retrovirus and adenovirus vectors in particular reported to be the cause of leukemia-like disease [358,359] and fatality [360], in patients participating in clinical trials. Non-viral vectors reduce the risk of mutagenesis and exhibit lower toxicity than viral vectors, although a related reduction in gene-delivery efficiency indicates a need for enhanced vector design and targeted delivery strategies [361]. In this regard, there have been significant advances recently in the use of non-viral vector technologies for hard and soft tissue regeneration, including development of polymeric nanoparticles, such as chitosan and alginate in addition to inorganic (e.g. HA) and, lipid-based nanoparticles [362,363], which may have further applications in the endodontic and periodontal fields. Related are developments in microRNA-based therapies, specifically scaffold-based delivery of synthetic microRNA activators and inhibitors [179,364,365], which offer additional exciting therapeutic opportunities for regenerative medicine in these fields through the modulation of key processes in dental stem cell biology [366].

Both the endodontium and the periodontium are integrated units comprising interfaces between hard and soft tissues. Such hierarchical multi-tissue units propose a challenge for the design of biomaterials for regenerative applications as an effective scaffold strategy may necessitate the recapitulation of a number of different tissues to achieve a native architecture. In the periodontium, for example, a hard-soft-hard tissue interface is present in the cementum-PDL-alveolar bone complex whilst there is also a soft-hard tissue interface between the gingiva and the cementum/alveolar bone. To address these challenges, researchers have sought to fabricate multi-layered scaffolds within which various phases contain differences in composition, porosity and biochemical cues [367]. Manufacturing processes for fabricating multi-layered scaffolds and membranes include iterative freeze-drying [368], electrospinning [369], additive manufacturing [370] and covalent bonding [371]. Imperative to the advancement of such multi-layered scaffolds for tissue engineering applications is the achievement of good integration between layers in order to avoid delamination during and post-implantation of constructs [372]. To that end, the fortification of layered scaffolds with a common framework or skeleton may lead to an integrated scaffold unit more resistant to delamination. The reinforcement of collagen-HyA scaffolds with an optimised PCL framework, for instance, resulted in an increase in tensile modulus and allowed for superior suture fixation [373]. A similar approach has also recently been leveraged to fabricate bi-layered scaffolds containing a common PCL framework for pulp-dentin regeneration, in which the inclusion of HyA within the pulpal layer led to an increase in hydrophilicity and an associated enhancement in cell adhesion while the presence of bioactive glass in the dentin layer enhanced mechanical properties and surface roughness as well as bioactivity of human DPSCs [374].

To conclude, our knowledge of the potential of different combinations of scaffolds, cells and biologics required to regenerate the complex tissue units present in the oral cavity is rapidly expanding within the scientific and clinical community. Although significant challenges remain, the shift that is already occurring towards minimally-invasive, patient-specific solutions complemented by 3D scanning and modelling puts the dental field is in a strong position to capitalize on the potential of advancements in tissue engineering applications.

CRediT authorship contribution statement

Eamon J. Sheehy: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Niamh Coffey:** Writing – review & editing, Writing – original draft. **Ross M. Quigley:** Writing – review & editing, Writing – original draft. **Henry F. Duncan:** Writing – original draft. **Oran D. Kennedy:** Writing – review & editing, Conceptualization. **Fergal J. O Brien:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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