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Tissue Engineered Neurovascularization Strategies for Craniofacial Tissue Regeneration

Yiming Li,
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States

David Fraser,
Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States; Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, New York 14620, United States; Translational Biomedical Sciences Program, University of Rochester Medical Center, Rochester, New York 14642, United States

Jared Mereness,
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States; Department of Environmental Medicine, University of Rochester Medical Center, Rochester, New York 14642, United States

Amy Van Hove,
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States

Sayantani Basu,
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States

Maureen Newman,
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States

Corresponding Author Danielle S. W. Benoit – Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States; Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, New York 14620, United States; Translational Biomedical Sciences Program, Department of Environmental Medicine, and Department of Biomedical Genetics and Center for Oral Biology, University of Rochester Medical Center, Rochester, New York 14642, United States; Materials Science Program and Department of Chemical Engineering, University of Rochester, Rochester, New York 14627, United States; benoit@bme.rochester.edu.

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Danielle S. W. Benoit
Department of Biomedical Engineering, University of Rochester, Rochester, New York 14627, United States; Department of Orthopaedics and Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York 14642, United States; Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, New York 14620, United States; Translational Biomedical Sciences Program, Department of Environmental Medicine, and Department of Biomedical Genetics and Center for Oral Biology, University of Rochester Medical Center, Rochester, New York 14642, United States; Materials Science Program and Department of Chemical Engineering, University of Rochester, Rochester, New York 14627, United States

Abstract

Craniofacial tissue injuries, diseases, and defects, including those within bone, dental, and periodontal tissues and salivary glands, impact an estimated 1 billion patients globally. Craniofacial tissue dysfunction significantly reduces quality of life, and successful repair of damaged tissues remains a significant challenge. Blood vessels and nerves are colocalized within craniofacial tissues and act synergistically during tissue regeneration. Therefore, the success of craniofacial regenerative approaches is predicated on successful recruitment, regeneration, or integration of both vascularization and innervation. Tissue engineering strategies have been widely used to encourage vascularization and, more recently, to improve innervation through host tissue recruitment or prevascularization/innervation of engineered tissues. However, current scaffold designs and cell or growth factor delivery approaches often fail to synergistically coordinate both vascularization and innervation to orchestrate successful tissue regeneration. Additionally, tissue engineering approaches are typically investigated separately for vascularization and innervation. Since both tissues act in concert to improve craniofacial tissue regeneration outcomes, a revised approach for development of engineered materials is required. This review aims to provide an overview of neurovascularization in craniofacial tissues and strategies to target either process thus far. Finally, key design principles are described for engineering approaches that will support both vascularization and innervation for successful craniofacial tissue regeneration.

Graphical Abstract

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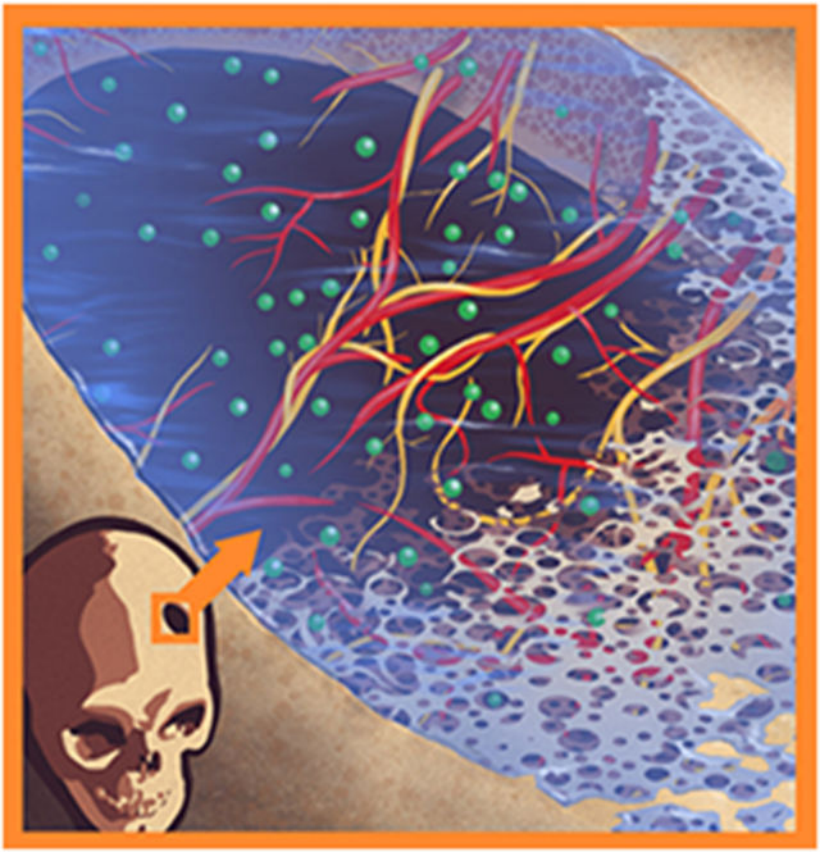

Keywords

engineered tissue regeneration; craniofacial tissue; neurovascularization; biomaterial design; growth factor; cell therapy; hydrogel

1. INTRODUCTION

The craniofacial complex is composed of various tissues including cranial, maxillary, and mandibular bones, dental and periodontal tissues, and salivary glands.[1,2] These structures provide critical functions including protection of the brain and oral cavity, mastication, defense against bacteria, and assisting in digestion.[3] Destruction or loss of craniofacial tissues has many underlying causes. Craniofacial bone defects can occur following injury, tumor resection, or as a result of dysfunctional development.[4] Dental pulp and periodontal tissues can be damaged by dental caries and periodontitis.[5,6] Xerostomia, or chronic dry mouth, occurs due to bystander damage of salivary glands during radiation treatments or destruction due to Sjögren's Syndrome.[7-9] Craniofacial tissue dysfunction significantly reduces quality of life, and successful repair of damaged tissues remains a significant challenge.[10] The current lack of approaches to restore function to cranial and oral tissues demands innovative tissue engineering and regenerative medicine approaches.

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While the field of tissue engineering has made remarkable progress, vascularization remains a significant and long-standing hurdle for engineered scaffolds including those for craniofacial tissues.[11] Additionally, craniofacial tissues are highly innervated. Nerves are found in close proximity to blood vessels and are increasingly recognized as critical coregulators of tissue regeneration.[12-14] While vascularization has been targeted with tissue engineering approaches in cranial and alveolar bone defect healing[15,16] and dental tissue regeneration,[17,18] innervation has received much less attention, and coordinated innervation and vascularization has not been directly investigated for craniofacial tissue regeneration.

Here, we review the biological processes underpinning both vascularization and innervation and their crosstalk in craniofacial tissues. We then describe methods employed to date to promote angiogenesis and innervation, either directly in the context of craniofacial tissue regeneration or in general for tissue engineering. Finally, we discuss the microenvironmental cues that may pave the way for successful neurovascular tissue engineering strategies for craniofacial tissues.

2. INNERVATION AND ANGIOGENESIS IN CRANIOFACIAL TISSUE REGENERATION

2.1. Innervation and Angiogenesis after Injury.

Peripheral nerves can regenerate after injury. Over the first 24 h following axotomy, nerve stumps retract due to dissolution of the cell membranes adjacent to the injury, and macrophages are recruited to the injury site. Distal axons undergo Wallerian degeneration (Figure 1), which is the coordinated removal of the axon and tissue debris by Schwann cells and macrophages. Schwann cells (SCs) proliferate in response to myelin debris and macrophage-secreted cytokines, then align in tubes known as Bungner bands, which express chemotactic cues including nerve growth factor (NGF) to attract and guide proximal axon reinnervation, resulting in functional recovery of their tissue targets (Figure 1).[19-22] Schwann cell proliferation can also be stimulated by target organ-derived trophic factors such as glial derived growth factor (GDGF) and brain-derived neurotrophic factor (BDNF).[22]

Angiogenesis occurs in response to tissue hypoxia, or low oxygen tension, following injury-mediated disruption of vascularization. A representation of this process is shown in Figure 2, which includes a summary of key cells and growth factors. First, cells in ischemic tissue increase production of hypoxia inducible factor 1α (HIF-1α), which induces production of vascular endothelial growth factor (VEGF) that diffuses into the nearby tissue. These factors signal to pericytes and endothelial cells (ECs) of nearby vasculature, causing detachment of pericytes and sprouting of endothelial tip cells toward the signal gradient. Tip cells then migrate in the direction of the gradient, degrading the local extracellular matrix to enable stalk cells to proliferate and form vessels. Stalk cells align in tube-like luminal structures, forming an immature vascular network. Pericytes are then recruited to the newly formed vasculature, stabilizing the immature vessels, and participating in vessel remodeling.

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Vascularization and innervation share many developmental and anatomical similarities including reciprocal signals that influence their development. To establish proper connections within the vasculature and nervous system, chemotaxis of axons or blood vessels is orchestrated by similar structures: the growth cone in axons or tip cells in vessels.[19,23,24] Endothelial and nerve cells can both secrete angiogenic and neurogenic factors during vessels and nerve regeneration. Recent studies suggest that endothelial cell paracrine factors provide critical cues for recruiting and controlling innervation.[25,26] Specifically, endothelial cells secrete artemin and neurotrophin 3 that recruit axons to track alongside vessels.[27,28] In turn, nerves secrete VEGF in a spatiotemporally controlled manner to coordinate vessel growth.[29] Further, stimulation of neuronal activity can also trigger angiogenesis.[30,31]

2.2. Coupled Innervation and Angiogenesis in Craniofacial Tissue Regeneration.

2.2.1. Craniofacial Tissues Are Vascularized and Innervated.—Craniofacial tissues, including cranial and mandibular bone, dental tissue, and salivary glands, are highly vascularized and innervated with blood vessels and nerves in close juxtaposition (Figure 3). For example, the calvarial periosteum and diploë, the cancellous bone separating the inner and outer layers of the cortical bone of the skull, are innervated by peripheral nerve fibers, including both sensory and sympathetic fibers.[33,34] Some small sensory nerve fibers depart blood vessels and wind through the periosteum, while the main sensory nerves follow blood vessels, terminating in the lining layer of periosteum or continuing along vessels into bone via Volkmann's canals.[35] Sympathetic fibers often wrap around blood vessels penetrating from the periosteum into the diploë.[35]

Dental vessels and nerves course from the inferior alveolar nerve and vessels in the mandible (Figure 3Bi) and from branches of the maxillary artery and nerve in the maxilla, entering the dental pulp primarily through the apical foramen at the tooth root end (apex) (Figure 3Bii). Arterioles in the central pulp region supply a peripheral capillary network adjacent to dentin walls.[36] Autonomic nerve fibers are found primarily in association with the vasculature, while sensory nerve fibers form a network around the pulp periphery and can enter dentin tubules in close relationship to odontoblasts.[37] Additionally, the periodontal ligament (PDL) surrounding the cementum lining the tooth root and connecting alveolar bone, is vascularized and innervated.[38] Conversely, cementum is avascular and contains no nerves.[39] Progenitor and stem cell populations in both dental pulp and PDL are closely associated with the neurovasculature[40,41] and sensory denervation can inhibit stem cell proliferation and differentiation.[42]

Vessels and nerves are also colocalized within the salivary gland (Figure 3C). Vessels enter the salivary gland from the external carotid artery and closely associate with the duct network of the salivary tissue together with nerves[43] (Figure 3C). These vessels form dense capillary networks around the terminal ends of the secretory acinar units, which are also enveloped by nerves.[44] Salivary gland innervation, similar to the pulp and PDL, is required for gland function and repair, controlling salivary secretion, and possibly maintaining salivary epithelial progenitor cell populations.[45-47] Thus, vessels and nerves colocalize and play important roles in tissue homeostasis in craniofacial tissues.

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2.2.2. Innervation and Angiogenesis Coordinate Craniofacial Tissue Regeneration.—Blood vessels and nerves synergistically coordinate tissue regeneration.[48-54] In bone, healing is initiated by hematoma and inflammation, which leads to cytokine release from inflammatory cells, followed by increased blood flow and cell migration to the injured site.[55] Mesenchymal stem cells (MSCs) and osteoprogenitors migrate to the defect area and differentiate into osteoblasts to form the ossification center.[56] Within the hypoxic wound, osteoblasts synthesize and secrete VEGF in response to elevated levels of HIF-1α, which then stimulates angiogenesis. Blood vessels sprouting from preexisting vessels to the defect center can be observed within the first week after injury in mouse cranial defect models[57,58] (Figure 4A). Inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF)-α, directly induce NGF expression and downstream nuclear factor kappa B (NF-kB) signaling in calvarial osteoblasts to stimulate nerve recruitment.[59] Reinnervation, which is associated with blood vessels, can be observed as early as 3 days postinjury in mouse cranial defects (Figure 4B).[60] Nerves play diverse roles during osteogenesis, regulating the canonical/ß-catenin Wnt signaling pathway and expression of Connexin 43 (Cx43) and N-cadherin in MSCs[61] as well as secreting vasculogenic neuropeptides, including neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), and substance P (SP), to stimulate angiogenesis.[62,63] Increased angiogenesis recruits additional osteoprogenitors to the repair site, along with nutrients, oxygen, and minerals necessary for mineralization. Concomitantly, endothelial cells produce osteogenic factors, such as transforming growth factor beta (TGF-β) and bone morphogenetic protein-2 (BMP2), to further promote osteogenic differentiation and bone mineralization.[64,65]

Dental and periodontal tissue repair also requires the orchestrated effort of vessels and nerves. Dental pulp has an inherent, albeit limited, regenerative capacity, which requires mesenchymal cell infiltration, innervation, and angiogenesis from adjacent healthy tissues into the pulp space.[66] Dental pulp injuries result in hypoxia where pulp cells respond by secreting HIF-1α to drive downstream expression of VEGF, platelet derived growth factor (PDGF), fibroblast growth factor (FGF)-2, and angiopoietins to promote angiogenesis.[67] Additionally, pulpal nerves respond to injury with sympathetic nerves releasing NPY and norepinephrine leading to vasoconstriction, while sensory neurons release neuropeptides such as SP and CGRP, which promote vasodilation and recruit immune cells.[68] Neuropeptides induce nerve sprouting adjacent to the pulpal injury, with further neuropeptides released from these sprouting fibers leading to additional immune cell recruitment, vasodilation, and continued healing.[37] The pulp chamber of mature teeth presents a particularly challenging space for tissue regeneration: new nerves and vessels must sprout from existing vessels and nerve trunks up to 15 mm away and enter through a narrow apical foramen 0.2 to 0.4 mm in diameter.[69,70]

Similar to bone, initial healing of the periodontium is characterized by the release of cytokines such as PDGF, TGF-β, VEGF, and bFGF from platelets and infiltrating immune cells, which then stimulates angiogenesis and recruitment of host cells from adjacent periodontal tissues.[71] Recombinant PDGF-BB and autologous platelet-derived factors promote periodontal wound healing and tissue regeneration[72,73] and likely stimulate

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angiogenesis during this process. PDL nerves produce low levels of neuropeptides during tissue homeostasis[74] yet retain the ability to remodel and regenerate in response to external stimuli.[75,76] The PDL responds to orthodontic force with nerve fiber sprouting, increased production of both sensory (SP, CGRP) and sympathetic (NPY, tyrosine hydroxylase) neuropeptides, and increased capillary density together with transient local bone resorption.[77-79] PDL nerves also express the high affinity neurotrophin receptor tropomyosin receptor kinase B (TrkB)[80] and high levels of NGF receptor p75-NGFR and growth associated protein-43 (GAP-43), factors associated with neuroplasticity.[81] Neurotrophins and neurotrophin receptors are also expressed by periodontal ligament cells,[82] and cells within healing periodontal defects, including infiltrating endothelial cells, express TrkB.[83] The epithelial rests of Malassez (ERM) and associated nerves may also play a key role in periodontal wound healing,[84] as sensory denervation results in a reduction in the size and number of ERM[85] and ankylosis of tooth to bone.[86]

There are few studies examining the role of vessels and nerves in salivary gland regeneration, despite studies indicating their importance in secretory acinar cells regeneration. During gland development, signaling from $CD31^+$ endothelial cells via vascular endothelial growth factor receptor 2 (VEGFR2) is required for proper tissue patterning by helping maintain Kit^+ progenitor cells and promoting branching morphogenesis.[43] Additionally, secretion of vasoactive intestinal peptide (VIP) by innervating ganglia is necessary for duct growth and lumen formation during branching morphogenesis,[87] and parasympathetic innervation promotes SRY-Box transcription factor 2 (SOX2) expression by progenitor cells in the developing gland.[88] Expression of SOX2 is essential for the production of secretory acinar cells, but not duct cells, and is maintained in a subset of cells in adult gland,[89] which has been shown to replace acinar cells under homeostatic conditions.[89,90]

2.3. Failures in Angiogenesis or Innervation Result in Deficient Craniofacial Tissue Regeneration.

Innervation and vascularization are both necessary for successful craniofacial tissue regeneration. For example, a significant decrease in ossification of calvaria has been observed in conditional VEGF knockout mice or those with impaired FGF signaling due to inadequate angiogenesis.[91,92] Inhibition of VEGFR2 or depletion of endothelial cells embryonically leads to loss of secretory acinar cells.[43] Additionally, deletion of NGF leads to dramatic reductions in nerve sprouts, angiogenesis, and delayed regeneration of cranial defects.[60] Sensory denervation also leads to alterations in osteoclasts, which subsequently delay cranial bone defect healing,[93] bone formation during mandibular repair,[94] orthodontic tooth movement,[95] and mineralization of new bone within the periodontium.[96,97] Denervation also leads to decreases in pulp cell proliferation[98] and increased susceptibility to pulpal necrosis after bacterial exposure.[99] Sympathectomy or treatment with sympathetic antagonists during tooth movement suppresses osteoclast activity but not bone formation[79] and also leads to periodontal bone loss via increased production of inflammatory cytokines in the periodontal tissues and subsequent osteoclast activity.[100] Moreover, denervation[90] or disruption of innervation prevents salivary gland regeneration in

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ductal ligation models, despite progenitor cell maintenance,[101-103] suggesting a critical role for innervation.

Altogether, these studies emphasize the necessity of both angiogenesis and innervation for successful craniofacial tissue regeneration and point to the possibility of superior integration with the host tissue and minimum long-term complications for regenerative approaches that target both processes.

3. CURRENT CRANIOFACIAL TISSUE REGENERATIVE APPROACHES THAT TARGET INNERVATION OR VASCULARIZATION

3.1. Growth Factor Delivery.

3.1.1. Growth Factor Delivery to Stimulate Reinnervation.—The growing appreciation of the role of reinnervation in tissue regeneration has resulted in several studies exploiting delivery of neuronal growth factors and neuropeptides to promote craniofacial tissue regeneration. These growth factors include NGF, BDNF, SP, galanin, and neurturin (NTRN). For example, NGF has been incorporated into bone scaffolds to treat rat cranial defects, showing an increase in innervation but limited new bone formation.[104,105] NGF delivery via alginate hydrogels has also been used to increase bone and cementum formation in periodontal defects.[106] Local injection of SP promoted bone formation during mandibular distraction osteogenesis in rats,[94] and BDNF delivery from collagen sponges[107,108] or using hyaluronic acid hydrogels[83,109-111] led to increased bone, PDL, and cementum formation compared to scaffold controls. Galanin-loaded collagen sponges promoted bone formation in inflammatory periodontal defects.[112] Overexpression of NTRN prior to irradiation was protective of salivary gland innervation and function,[113] and laminin matrices with entrapped NTRN promoted neurite outgrowth from isolated parasympathetic submandibular ganglia (PSG), reduced neuronal apoptosis, and increased the number of end buds, progenitor cells, and innervation in mouse submandibular glands exposed to irradiation.[101] Additionally, salivary gland cell sphere cultures combined with mesenchyme and PSG in matrices containing NRTN became innervated and underwent branching similar to development.[114]

3.1.2. Growth Factor Delivery to Promote Vascularization.—A common approach to achieve vascularization is delivery of angiogenic proteins including VEGF, FGFs, and PDGF.[115,116] For example, VEGF,[117,118] FGF-2,[15] and PDGF[16] delivery enhanced local angiogenesis and osteogenesis in some cranial defect models. However, another study showed vascularization and new bone regeneration after scaffold-mediated VEGF led to similar results as a control group, with only 26% of the defect covered by newly formed bone 12 weeks after injury,[117] suggesting that VEGF-mediated vascularization alone is insufficient to support a robust regenerative response. Previous studies have also demonstrated the ability of VEGF and FGF-2 to promote dental pulp angiogenesis.[119-121] The delivery of VEGF (together with dental pulp stem cells (DPSCs)) from heparin-conjugated gelatin microspheres in tooth roots also supported formation of vascularized pulp tissue.[122]

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3.1.3. Delivery of Multiple Growth Factors to Stimulate Innervation or Vascularization.—

Combinatorial approaches of neurogenic and angiogenic and, in some cases, osteogenic growth factors have also shown promise. Recent studies suggest delivery of multiple pro-angiogenic proteins can result in therapeutically relevant and long-lasting vascularization, which is necessary for regeneration.[123-126] For example, combined delivery of VEGF and BMP-2 promoted osteogenesis and angiogenesis in cranial defects.[127,128] Additionally, the combined delivery of VEGF or FGF2 with NGF and BMP-7 to dental pulp chambers led to angiogenesis, recellularization, and new dentin formation.[129] NGF has also been delivered by alginate hydrogels together with BMP-2, resulting in synergistic effects on periodontal bone and cementum formation.[106] Additionally, fibrin hydrogel-mediated delivery of pro-angiogenic VEGF and FGF9, which recruits vessel stabilizing mural cells and maintains neuronal cell viability and function,[130,131] enhanced salivary gland regeneration and saliva production in a gland injury model.[132]

3.1.4. Peptides as Alternatives to Growth Factors for Vascularization.—

Protein delivery approaches can suffer from poor long-term outcomes due to insufficient protein stability and rapid clearance[133-135] as well as challenges associated with precise control over growth factor release kinetics.[11,136] Therefore, therapeutic peptides have recently gained interest as an alternative to proteins. Their smaller size[137] gives them more versatile synthetic schemes than proteins and allows peptides to be delivered at higher concentrations to target tissues when applied locally. Additionally, peptides often do not require complex tertiary structures for bioactivity, increasing *in vivo* stability.[138] For example, VIP-conjugated hydrogels have been reported to enhance cranial bone defect repair, [139] where VIP not only stimulated tube formation and VEGF expression but also promoted bone marrow stem cell (BMSC) differentiation by activating the Wnt-β-catenin signaling pathway. Self-assembling peptide hydrogels for pulpal regeneration were synthesized to contain a pro-angiogenic peptide sequence, QK, derived from VEGF or dentonin, an odontogenic peptide.[140] Roots treated with hydrogels without bioactive peptides or containing only the odontogenic peptide formed disorganized connective tissue, while hydrogels containing QK showed formation of pulpal tissues with new odontoblast-like cells, blood vessels, and nerves. A recent study delivered dimethyloxalylglycine, a glycine derivative that inhibits prolyl hydroxylase to activate HIF-1α, via nanosilicates entrapped within poly(L-lactide-*co*-glycolide) (PLGA) scaffolds, to promote angiogenesis and tissue regeneration in periodontal defects.[141]

3.2. Implantation of Prevascularized or Innervated Scaffolds.

Several techniques have been employed to develop prevascularized constructs.[142-150] These approaches exploit both fully differentiated as well as progenitor cell types. For example, DPSCs were precultured in endothelial differentiation media to form Von Willebrand factor (vWF) and CD31-positive reticular structures, which supported formation of vascularized pulp tissue and differentiated odontoblasts.[151] Additionally, a preformed endothelial network was incorporated into bone scaffolds to promote vascularization and osteogenesis in a rat cranial defect model.[152] However, only 25% of increased bone volume was observed despite increased blood vessel volume after 8 weeks, a result that may be due to no or poor innervation.[152] Prevascularization strategies face challenges to ensure stable tissue formation

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and anastomosis within host tissues. EC-only derived vasculature is commonly unstable, lasting only a few days *in vitro*. Cocultures of ECs and vessel-stabilizing MSCs or other pericyte-like cells can extend vascular network stability for >60 days *in vitro* in engineered extracellular matrices and facilitate tissue integration *in vivo*.[153,154] As an example, spheroids composed of BMSCs and human umbilical vein endothelial cells (HUVECs) were encapsulated in fibrin scaffolds to form vascular networks prior to implanting the scaffolds in rat cranial defects.[155] The preformed vascular networks survived and anastomosed with host tissue within 1 week of implantation but ultimately did not significantly enhance bone regeneration compared to controls.[155]

Innervated tissue engineering approaches have been utilized in a few applications to recapitulate Wallerian degeneration to guide nerve integration and promote healing. Though not specific to craniofacial tissues, preinnervated tissue engineered muscle was formed using a coculture of myocytes and motor neurons on aligned nanofibrous scaffolds. The presence of neurons enhanced the differentiation and maturation of skeletal myocytes *in vitro* and significantly increased satellite cell migration, microvessel formation and revascularization, and neuromuscular junction density *in vivo*.[156] Though not a direct preinnervation approach, incorporating sensory nerve tracts in bioceramic-based scaffolds has been reported to enhance both neurogenesis and bone formation.[157]

4. DEVELOPMENT OF TISSUE ENGINEERING APPROACHES FOR NEUROVASCULARIZATION

Tissue engineering approaches that address both innervation and vascularization hold great potential to promote craniofacial tissue regeneration[158] as opposed to targeting only vascularization[159-161] or innervation.[162-165] These approaches can be adopted from traditional tissue engineering approaches and include cells,[166,167] synthetic[168-170] and natural[166,171,172] scaffolds, growth factors,[173,174] and combinations therein,[127,175] which are detailed in the following sections.

4.1. Cells for Neurovascular Tissue Regeneration.

A variety of cell types have been used to promote neurovascularization for craniofacial tissue regeneration. These include stem cells, such as MSCs, DPSCs, and induced pluripotent stem cells (iPSCs), SCs, and ECs. Cells participate in regeneration via many mechanisms, including tissue-specific matrix deposition as well as secretion of growth factors, to facilitate tissue recruitment and neurovascular tissue development. For example, SCs can direct axon migration and regulate their proliferation via neurotrophic factor expression (Figure 4);[176] ECs can mediate angiogenesis and osteogenesis by producing paracrine factors[177] and proliferation, migration, and assembly into tubular structures[178] (Figure 2). Therefore, SCs[166,179-181] and ECs[167,182-184] have been incorporated in tissue engineering constructs to promote peripheral nerve regeneration and angiogenesis during bone repair, respectively. Other systems have utilized cocultured stem cells/SCs[175,185,186] and stem cells/ECs.[187-192] MSCs have been shown to differentiate into osteoprogenitors as well as Schwann-like cells[193,194] and may give rise to neurons[186] and enhance axonal regeneration.[185] Though controversial, some studies have also reported that MSCs can

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differentiate into endothelial cells.[195,196] Additionally, MSCs cocultured with ECs have been reported to act as pericytes during angiogenesis *in vitro*[197] and *in vivo*,[198] where MSCs localize along the endothelial tubes and encourage vascular network formation by secreting angiogenic growth factors such as VEGF and bFGF.[199,200] Human DPSCs have been reported to enhance HUVEC migration and VEGF secretion as well as promote ECM deposition and mineralization during dental pulp regeneration.[201] Hence, the integration of cocultured SCs/ECs or SCs/ECs/stem cells into cellular approaches may improve neurovascularization for craniofacial tissue regeneration. However, the clinical application of many cell types has been limited by source of human cells and lack of *in vitro* expansion capacity.[202,203] In this regard, iPSCs, which can be reproducibly differentiated into myriad cell types including ECs[204] and neurons,[205] are promising alternatives. Previous studies have demonstrated that iPSC-derived ECs significantly increase vascularization *in vivo*.[206,207] Moreover, iPSC-derived neural crest stem cells (NCSCs) and NCSC-SCs have been reported to encourage nerve regeneration *in vivo*, where they interacted with host axons and produce neurogenic factors (NGF and BDNF).[208] Though the application of iPSCs for craniofacial neurovascularization has not been reported, its potential has been discussed.[209-211]

4.2. Design of Biomaterials for Neurovascularization.

Biomaterials used in craniofacial tissue engineering must be designed to support peripheral nerves and vessels. Biomaterial design, therefore, must take into account many complex design requirements including biophysical and biochemical cues.[212,213] Moreover, biomaterials should be biodegradable and may also need to provide control over release of therapeutic factors to encourage cell migration, axonal growth, and vessel infiltration.[214-216] In the following sections, we summarize various biomaterials classes and design criteria enabled by new chemistries and fabrication techniques for the regeneration of neurovascularized tissues.

4.2.1. Biomaterial Classes for Neurovascularization.—

Because of excellent biocompatibility, natural polymers, such as collagen,[171,217-219] chitosan,[172,220-222] and silk,[166] have been utilized to promote neurovascularization *in vivo*. For example, chitosan has been reported to support ~50% regeneration and tissue reinnervation in a rat critical nerve gap model.[222] Neovascularization has also been observed in chitosan scaffolds after 12-weeks of implantation *in vivo*.[223] Additionally, cell/growth factor-loaded collagen-based scaffolds have been reported to promote nerve regeneration[224] and vascularization[225] *in vivo*. However, the use of natural polymers is hindered by their complex chemical structures, uncontrolled degradation, and thermal sensitivity.[226] Alternatively, synthetic polymers can be tailored to match biophysical and biochemical properties demanded by vascularization and innervation and enable delivery of cells and bioactive factors. Previous studies have demonstrated that polymers such as poly(glycolic acid) (PGA),[227,228] poly(lactic acid) (PLA),[229-231] PLGA,[232-235] and poly(caprolactone) (PCL),[236-238] combined with cells[168] and growth factors,[169] can encourage peripheral nerve regeneration *in vivo*. However, application of synthetic polymers in nerve repair still remains a clinical challenge.[239,240] Even biomaterials approved by the FDA for specific applications, such as NeuraGen,[241] Neuromaix,[242] and NEUROLAC,[243] provide only limited repair for nerve defects longer

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than 3 cm. Synthetic polymers, such as PGA,[244,245] PLA, and PLGA,[161,246,247] have also been developed as delivery vehicles of angiogenic growth factors to promote neovascularization *in vivo*. Nevertheless, the effects of these scaffolds on angiogenesis can be hindered because release profiles of the incorporated growth factors are difficult to control and often do not match what is required to achieve regeneration.[248]

Various hydrogel biomaterials have also been explored in neural and vascular tissue engineering. Hydrogels have great utility in tissue engineering in general due to high water content, ability to be tailored via functionalization by exogenous biochemical cues, incorporation of cross-linkers degradable by various modes and rates, and incorporation and control over growth factor release.[32,249-254] Poly(ethylene glycol) (PEG)[255] and gelatin-based hydrogels[256] promoted the regeneration of rat sciatic nerves, as evidenced by increased axon number and diameter. Gelatin hydrogels have been used in multiple studies to promote angiogenesis during bone repair through the delivery of various growth factors.[248,257-259] PEG-based hydrogels have also been used to deliver growth factors[159] and cells[260,261] to improve angiogenesis during bone regeneration *in vivo*. Despite promise, hydrogel-based materials have not yet been effectively used to promote both angiogenesis and innervation in the regeneration of craniofacial tissues.[262,263]

4.2.2. Biomaterial Physical Cues for Neurovascularization.—Biomaterials designed for neurovascularization should provide a 3D microenvironment with proper biophysical cues, including pore size/porosity, stiffness, and degradation dynamics, to support endothelial and nerve cell growth and migration. Previous studies have demonstrated that a pore size of 35–100 μm with at least 50% porosity is optimal for blood vessel formation.[264,265] Cells may rapidly migrate from scaffolds with pore sizes too large, and smaller pore size can hinder oxygen and nutrition diffusion and cell migration, resulting in unstable vessels.[266] The optimal pore size for innervation was reported to be in the ~5–30 μm range with >80% porosity to enable nutrient and waste exchange and neuron infiltration.[267-269]

The morphology, organization, and function of endothelial[270] and nerve tissues[271] have also been reported to be influenced by substrate stiffness. In 3D culture systems, which have greater relevance for tissue engineering than 2D studies, more robust neurite outgrowth was observed in softer matrices (0.5 kPa) than stiffer matrices (1.4 kPa,[272] 2.1 kPa[273]). Encapsulated nerve cells also showed higher gene expression level of neural differentiation and neuron maturation markers including Synapsin1, βIII-tubulin (TUBB3), and Neuronal nuclear antigen (NeuN) in softer matrices.[272] Similarly, greater spreading and branching of microvessels formed by ECs were observed with decreased matrix stiffness: from 17 to 7 kPa[274] and from 0.5 Pa to 0.2 kPa.[275] Additionally, stiffer matrices (~0.5 kPa) encourage EC spreading and branching versus softer matrices (~0.1 kPa).[275,276] Though absolute stiffness ranges may vary due to divergent design parameters, generally more compliant matrices favor vascularization and innervation.

Cell migration and sprouting not only depend on the original matrix stiffness but also its degradation mode and rate.[277-279] For example, our previous study found that matrix metalloproteinase (MMP)-degradable hydrogels better support EC sprouting

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than hydrolytically degradable hydrogels with a similar initial modulus (~10 kPa).[280] Additionally, endothelial[281,282] and nerve [283,284] tissues can sense their surrounding mechanical environment and secrete enzymes, such as MMPs, to degrade and remodel ECM dynamically. Indeed, softer matrices (~2 kPa) upregulated nerve cell expression of MMP-2 and MMP-3 compared to stiffer matrices (~3.5 kPa).[285]

An additional challenge for some craniofacial tissues, including cranial and alveolar bones, is the requirement for structural stability during tissue regeneration. Many current approaches include a stiff scaffold component that slowly resorbs as new bone is deposited and matures.[286] For instance, design criteria for periodontal tissue scaffolds often include a “bone” component with a distinct design from PDL and cementum portions of the scaffold.[287] Even if each component of such multiphasic scaffolds is porous and interconnected, ingrowth of host neurovasculature may be hindered by complex, slowly degrading structures. Thus, composite scaffolds that combine sufficiently porous or soft, degradable structures required for optimal neurovascularization together with stiffer, dense components that can direct bone growth and stability may be required in certain craniofacial locations.

4.2.3. Biomaterial Biochemical Cues for Neurovascularization.—Given the critical role of cell-secreted growth factors (GFs) in driving transplanted cell bioactivity, therapeutic factors can be used to promote neurovascularization. For example, delivery of NGF,[288-290] GDNF,[291-293] and BDNF[294,295] from synthetic nerve conduits improves axon regeneration *in vivo*. Previous studies have also demonstrated enhanced vascularization and bone regeneration by singular and dual delivery of VEGF,[160,161] PDGF,[296] and VEGF/BMP2.[127,297] Furthermore, FGF delivery has been reported to improve neurogenesis,[298] angiogenesis,[299] and bone regeneration.[300,301] Consequently, therapeutic cues for tissue engineered neurovascular approaches will likely include combinations of proangiogenic and neural growth factors, which necessitates further investigation to identify the critical growth factors and define the appropriate doses and temporal availabilities to achieve regenerative success.

While GFs can be physically encapsulated/immobilized into or absorbed on the surface of biomaterials, these approaches are susceptible to a fast or burst release of factors immediately after contact with physiological fluids.[302] For example, burst release of VEGF and BMP-2 from poly(L-lactic acid) (PLLA) scaffolds was observed only after 24 h postimplantation *in vivo*, and >80% of these growth factors were released after 14 days (Figure 6A).[303] This temporal profile is unlikely to match any native GF release patterns, and GF bioactivity may be compromised by unstable release profiles.[248] For example, in cranial defects, angiogenesis and reinnervation do not occur until 3–7 days after injury and then continue for up to 6 weeks (Figure 4). Covalent immobilization of GFs to biomaterials through carbodiimide, [304,305] thiol–ene, [250,252,253,306,307] and enzymatic[307,308] conjugations can eliminate the possibility of initial burst release and has emerged as a promising approach for improved GF delivery kinetics. In this case, GF release depends on biomaterial degradation or hydrolytic or enzymatic cleavage of the bond between GFs and the biomaterial.[32,250] Additionally, inspired by the natural interactions between ECM and GFs, bioaffinity tethering approaches have been applied for more controlled delivery

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systems. For example, due to the interaction between GFs (e.g., BMP2, VEGF, and FGF-2) and heparin sulfate of the natural ECM, biomaterials have been decorated with heparin or heparin sulfate-mimetic molecules to bind GFs.[290,309,310] The higher affinity of heparin-GF binding not only contributes to more extended and stable release profiles but also facilitates localized and spatially regulated signaling.[309,311]

During regeneration, integrin transmembrane receptors mediate cell–substrate binding, which is critical for adhesion and migration.[312,313] Apart from forming focal adhesions, binding between integrin subunits (α and β) and ECM ligands alters actin cytoskeleton structures and actively transduces biochemical and signaling cascades.[314] Therefore, biomaterials have been functionalized by ECM protein mimetic peptides specifically to encourage neurogenesis and angiogenesis. Laminin mimetic peptides (CDPGYIGSR or CSRARKQAA-SIKVAVSAD,[315] and YIGSR[316]) immobilized within chitosan hydrogels have been reported to promote nerve regeneration *in vivo*. Additionally, the peptide, RGD, which is ubiquitously found within myriad extracellular matrix proteins, has been incorporated into poly(caprolactone)-based materials to promote SCs outgrowth *in vitro*[317] and axonal regeneration and functional recovery *in vivo*.[318] Laminin (YIGSR,[319] SIKVAV[320]) and collagen (e.g., GFOGER[159] and P15 (PQGIAGQRGVV)[321]) mimetic peptides, along with RGD[322] have also been applied to stimulate angiogenesis *in vitro* and *in vivo*. Additionally, fibronectin-derived peptide REDV (GREDVY),[323] osteopontin-derived peptide SVVYGLR,[324] and VEGF-binding domain-derived peptide PR1P (DRVQRQ-TTTVVA)[325] have been used to functionalize biomaterials to enhance angiogenesis *in vivo*.

4.2.4. New Approaches to Meet Biomaterials Design Requirements for Neurovascularization.—

Recently, various techniques have been applied to fabricate complex, multicomponent biomaterials to better meet the demands for neurovascularization. For example, synthetic polymers, such as poly(caprolactone) (PCL), poly(dimethylsiloxane) (PDMS), and hydrogels can be fabricated into vascular[326,327] and neuronal[328,329] scaffolds using three-dimensional (3D) printing techniques. Perfusable 3D-printed vascular networks and porous neural scaffolds have been reported to support angiogenesis[330-332] and neurogenesis,[328,333] respectively, *in vitro*. A 3D printed PCL scaffold doped with tricalcium phosphate (TCP) supported vascularized new bone formation in a rat calvarial defect model,[334] where the microchannels in the scaffold facilitated diffusion of nutrients to printed cells, overcoming the diffusion limit of 100–200 μm for cell survival in engineered tissues.[335] 3D printing has also been used to fabricate scaffolds for alveolar bone and periodontal tissue regeneration, primarily to localize growth factors and transplanted cells and guide cell orientation during healing.[336] 3D printing technology is also being explored for salivary gland regeneration, focusing on secretory and duct cell patterning and organoid printing.[337-340] The integration of nerves and vasculature is likely to be a key step in the full integration and successful regeneration of salivary gland tissue using these methods. Therefore, 3D bioprinting has promise for fabricating scaffolds for bone and dental tissues regeneration, which provide features targeting vascularization and innervation.

A combination of favorable biochemical and biomechanical cues can be achieved by designing materials to support and respond to tissue infiltration as required during neurovascularization and tissue regeneration. In particular, MMP-degradable hydrogels

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are promising materials from which to develop neurovascularization strategies.[341] Both endothelial cell migration and vessel extension during angiogenesis and axonal outgrowth and pathfinding during innervation occur via degradation of the surrounding ECM by MMPs.[342,343] MMP-degradable hydrogels can be optimized to support host tissue recruitment and integration by modifying the degradation kinetics of the MMP-susceptible linkages.[167,240,344-346] Moreover, the potential of MMP-degradable hydrogels to improve both angiogenesis and neurogenesis has been investigated *in vitro*[347,348] and *in vivo*.[349,350] Indeed, our recent study demonstrated that a tissue engineered periosteum composed of MMP-degradable hydrogels improved allograft healing by promoting rapid innervation and vascularization (Figure 5).[280] We have also found that MMP-degradable hydrogels improve the organization, apicobasal polarization, and retention of salivary gland acinar cell phenotype in tissue-mimetic culture systems.[351,352]

As control over growth factor delivery from polymeric scaffolds is still challenging,[303] various fabrication techniques, such as microsphere formation[353] and electrospinning,[354,355] have been investigated. The GF release kinetics from microspheres can be adjusted by altering the molecular weight and composition of the copolymer.[356] A sustained 4-week release of NGF[357] and up to 80-days of steady release of BDNF and GDNF[358] (Figure 6B) from PLGA microspheres have been reported, where the release of NGF significantly enhanced neurite outgrowth *in vitro*. The *in vivo* release profile of BMP-2 from PLGA microspheres has been shown to be an S-shaped curve over 84 days without any observed burst release at early time points (Figure 6C).[359] PLGA microspheres were also developed to exhibit minimal initial *in vitro* release of VEGF in the first 7 days after loading and then reaching a plateau at day 20.[355]

Another fabrication method to prolong the release of entrapped GFs is via electrospinning. Electrospinning techniques can manufacture scaffolds with ECM-like structure including variable degrees of porosity and adjustable mechanical properties.[360] Growth factor release can be controlled by the extruded materials' orientation and geometries.[361] Electrospun PLGA nanofibers have been reported to slow the release of FGF-2[354] and VEGF[355] *in vitro*, showing a 28-day sustained *in vitro* release profile of VEGF (Figure 6D).

5. PERSPECTIVES ON NEUROVASCULARIZATION STRATEGIES FOR CRANIOFACIAL TISSUE REGENERATION

Despite great progress in the fundamental understanding of neurovascularization during development and regeneration and biomaterials design and fabrication, progress in implementing these innovations for the repair of craniofacial tissue defects is still in its infancy. Given the complex nature of craniofacial tissues, the integration of multiple tissues remains a critical barrier. For example, during craniofacial bone regeneration, osteogenic, neurogenic, and endothelial cells may require different microenvironments to holistically integrate to coordinate healing.[158,362] Challenges in manipulating multiple cell types, particularly those originating from different tissues, as well as spatial regulation of complex cell-cell interactions, remain unaddressed.[363] Additionally, the clinical translation of cell-based therapies can be hindered by complicated cell isolation processes, long-term

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loss of viability, regulatory hurdles, and adverse host responses,[364] some which may be overcome through the use of iPSCs and their offer of nearly infinite patient-specific cells and cell types.[365] Successful neurovascularization strategies are also likely to require spatially and temporally regulated growth factor/bioactive peptide release. Considering the multifactorial and differential effects of growth factors on various cell types, a significant challenge is determining and delivering optimal combinations and concentrations of growth factors with appropriate temporal availabilities to coordinate successful craniofacial tissue regeneration.[366] Nevertheless, recruitment of host neurovascular tissues can be modulated within tissue engineering approaches through careful design of biomaterial mechanics, degradation rate and mechanism (hydrolytic or enzymatic), and adhesive ligand concentration.[148-150,367-370] MMP-degradable hydrogels,[341] incorporation of critical growth factors or iPSCs-derived target cells, prevascularization, and preinnervation strategies, as well as new tissue engineering techniques such as 3D printing, have promise for the development of biomaterials that can improve the regeneration of craniofacial tissues by promoting neurovascularization.

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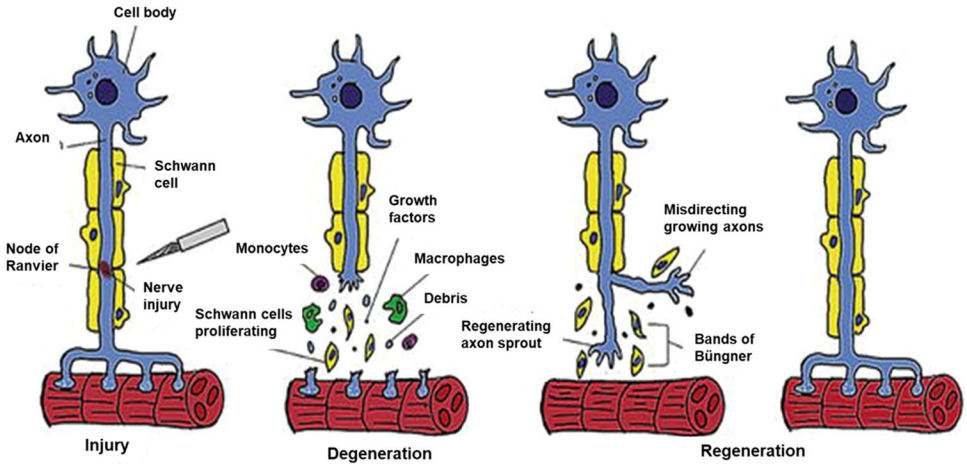

Figure 1.

Depiction of Wallerian degeneration [Reproduced with permission from ref 21. Copyright 2017 IntechOpen].

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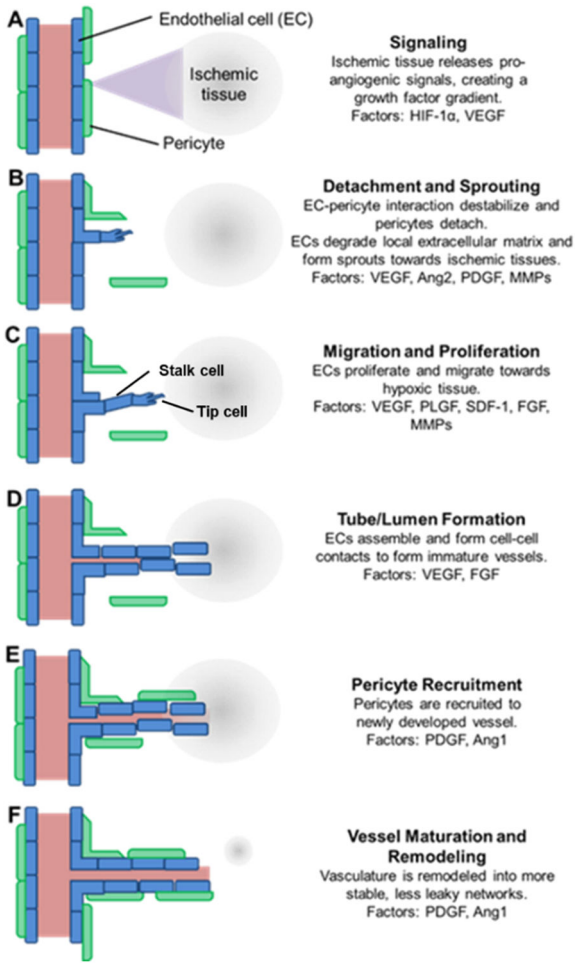

Figure 2.

Angiogenesis is a tightly controlled process involving numerous cells and factors. (A) Ischemic tissue increases production of hypoxia inducible factor 1α (HIF-1α), which induces production of vascular endothelial growth factor (VEGF) that (B) signals to pericytes (green) and endothelial cells (ECs, blue), resulting in detachment of pericytes and sprouting of endothelial tip cells toward the VEGF gradient. (C) Tip cells (blue) then migrate, degrade the matrix, and (D) enable stalk cells (blue) to proliferate and form vessels via alignment into tube-like luminal structures, followed by (E) pericyte recruitment and (F) further remodeling and maturation. HIF-1α, hypoxia inducible factor 1α; VEGF, vascular endothelial growth factor; Ang2, angiopoietin 2; PDGF, platelet derived growth factor; MMPs, matrix metalloproteinases; PLGF, placenta growth factor; SDF-1, stromal cell-derived factor 1; FGF, fibroblast growth factor; Ang1, angiopoietin 1 [Reproduced with permission from ref 32. Copyright 2015 Frontiers].

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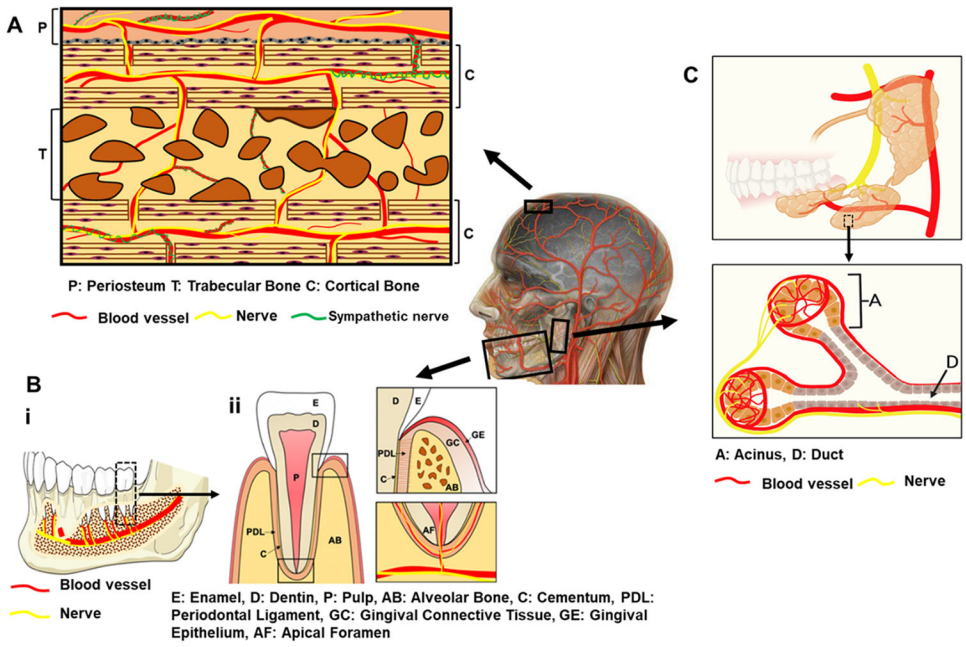

Figure 3.

Anatomy of vascularized and innervated craniofacial tissues (A) cranial bone, (B) (i) mandibular bone (ii) and tooth, and (C) salivary glands. Part C was created with BioRender.com, agreement number: MB22XPLPSX.

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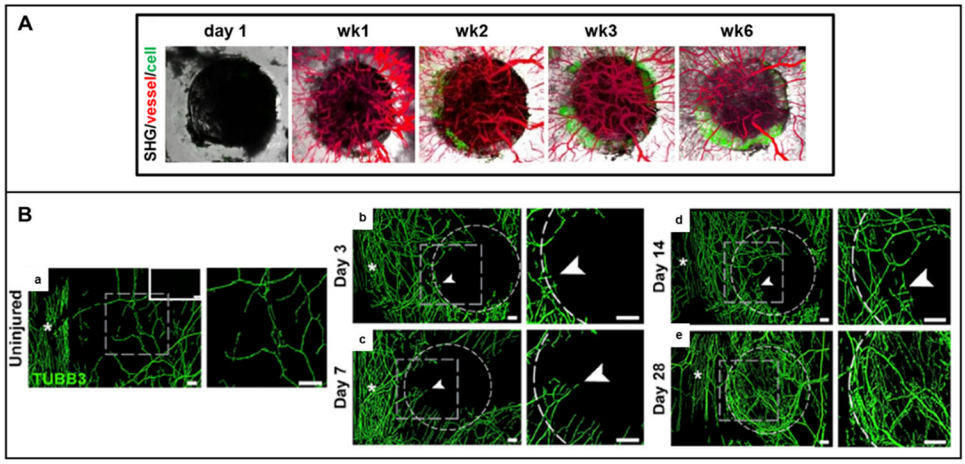

Figure 4.

(A) Longitudinal tracking of cranial bone defect healing in Col2.3GFP transgenic mice over a 6-week period illustrates osteogenesis and angiogenesis. Vessel, red; osteoblasts, green [Reproduced with permission from ref 57. Copyright 2018 Springer eBook]. (B) Reinnervation during cranial bone defect repair: representative whole-mount tile scans (left) and high-magnification images (right) of TUBB3 (beta III tubulin)-stained cranial defects (b–e) from days 3 to 28 postinjury compared to uninjured controls (a); TUBB3+ nerve fibers appear green; dashed white circles indicates margins of defect; white asterisks indicate midline suture and white scale bar, 200 mm [Reproduced with permission from ref 60. Copyright 2020 Elsevier].

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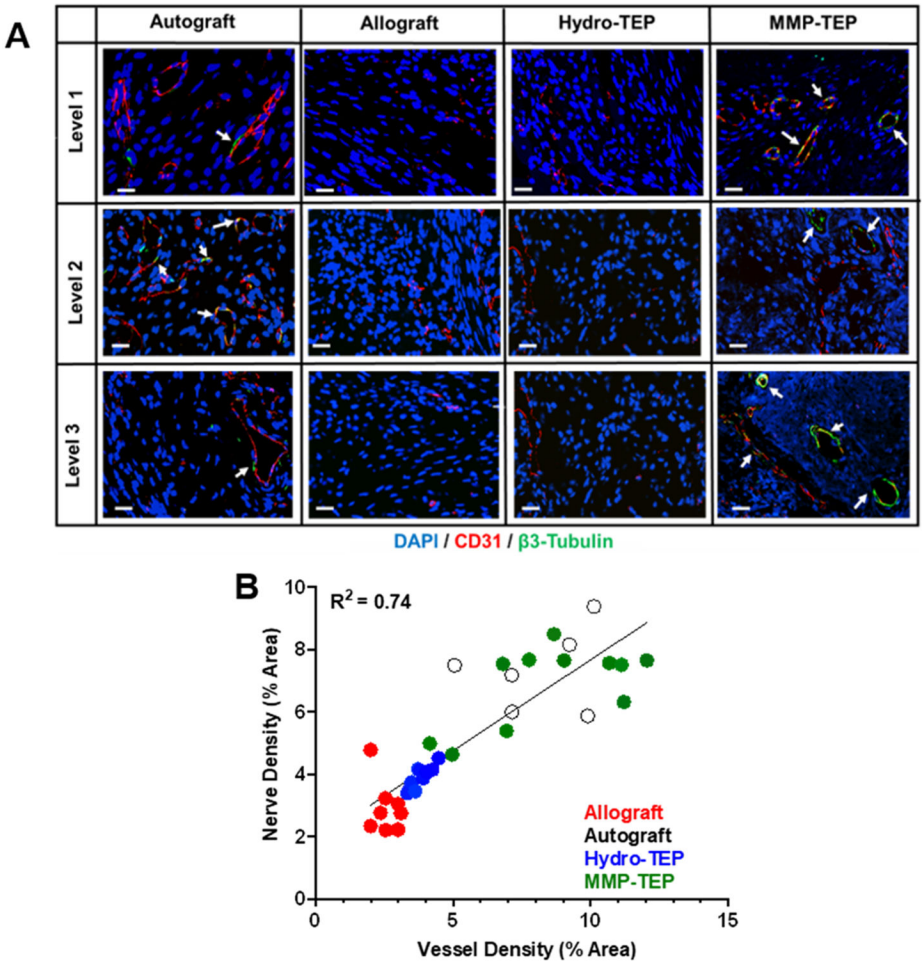

Figure 5.

(A) Representative confocal images of costained of CD31 (blood vessels, red) and β3-tubulin (nerves, green) on the cross sections of autografts, allografts, allografts modified by hydrolytically or MMP degradable tissue engineered periosteum (Hydro-TEP, MMP-TEP) at levels proximal (1), medial (2), and distal (3) in relation to the femoral head (scale bar = 20 μm) at 3-week postsurgery. (B) Blood vessel density-dependent effects on nerve density, where regression analysis demonstrates a linear relationship (R^2 = 0.74) between revascularization and reinnervation, indicating their synergistic coordination during bone defect healing [Reproduced with permission from ref 280. Copyright 2021 Elsevier].

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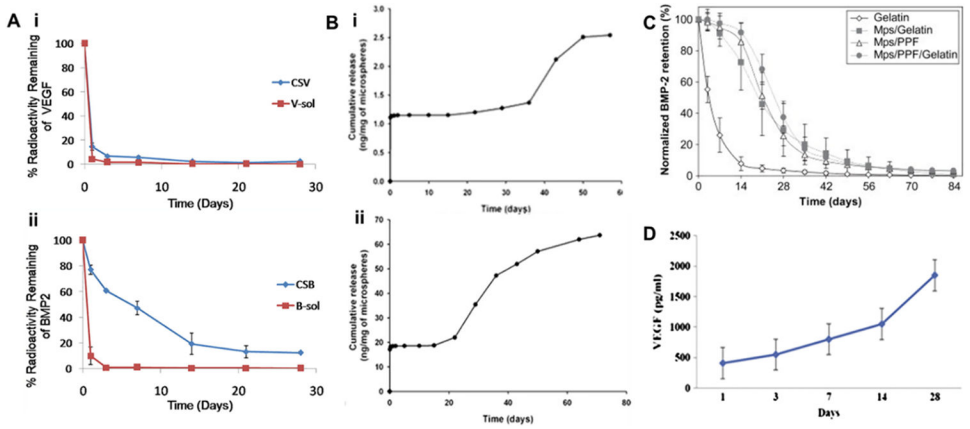

Figure 6.

(A) *In vivo* release profiles of (i) VEGF and (ii) BMP-2 were obtained after implantation of scaffold into the subcutaneous tissue mice for 28 days,[303] where CSB and CSV represent nanocomposite fibrous scaffold (CS) loaded with BMP2 (B) and VEGF (V), respectively [Reproduced with permission from ref 303. Copyright 2018 Elsevier]. (B) Release kinetics of PLGA microspheres steady release of neurotrophic growth factors was detected for at least 60 days (i, BDNF) and 80 days (ii, GDNF) [Reproduced with the permission from ref 358. Copyright 2010 Springer Nature]. (C) Normalized *in vivo* release profile of BMP-2 from the four different implants in a rat subcutaneous implantation model, where Mps = PLGA microparticles loaded with BMP-2, and PPF = poly(propylene fumarate) [Reproduced with the permission from ref 359. Copyright 2008 Elsevier]. (D) Cumulative release of VEGF from the biohybrid scaffold with PLGA nanofibers, which displays a sustained release of VEGF over 28 days [Reproduced with the permission from ref 355. Copyright 2014 Elsevier].