Collagen and Leather

REVIEW

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Advancing collagen-based biomaterials for oral and craniofacial tissue regeneration

Bo Zhang[1], Yunxiang He[2], Jialing Liu[1], Jiaojiao Shang[2], Chider Chen[3,4], Tianyi Wang[1], Mei Chen[2], Yifei Li[5], Guidong Gong[2*], Jie Fang[1*], Zhihe Zhao[1] and Junling Guo[2,6,7]

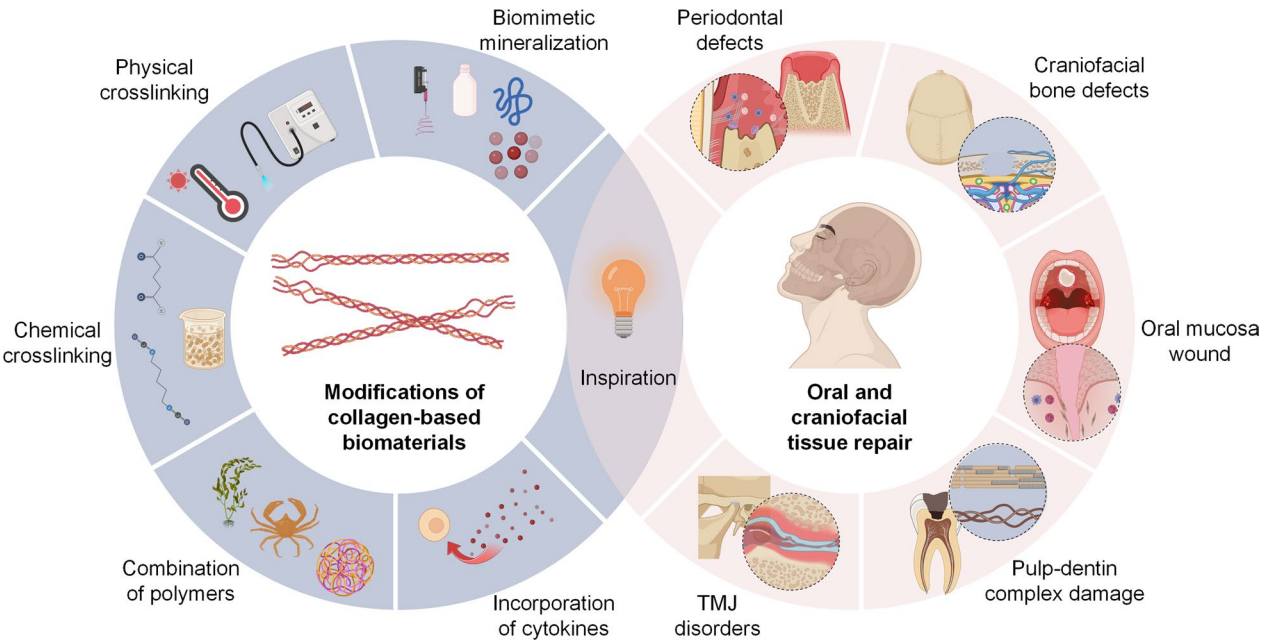
Abstract

The oral and craniofacial region consists of various types of hard and soft tissues with the intricate organization. With the high prevalence of tissue defects in this specific region, it is highly desirable to enhance tissue regeneration through the development and use of engineered biomaterials. Collagen, the major component of tissue extracellular matrix, has come into the limelight in regenerative medicine. Although collagen has been widely used as an essential component in biomaterial engineering owing to its low immunogenicity, high biocompatibility, and convenient extraction procedures, there is a limited number of reviews on this specific clinic sector. The need for mechanical enhancement and functional engineering drives intensive efforts in collagen-based biomaterials concentrating on therapeutical outcomes and clinical translation in oral and craniofacial tissue regeneration. Herein, we highlighted the status quo of the design and applications of collagen-based biomaterials in oral and craniofacial tissue reconstruction. The discussion expanded on the inspiration from the leather tanning process on modifications of collagen-based biomaterials and the prospects of multi-tissue reconstruction in this particular dynamic microenvironment. The existing findings will lay a new foundation for the optimization of current collagen-based biomaterials for rebuilding oral and craniofacial tissues in the future.

Keywords Collagen-based biomaterial, Oral tissues, Craniofacial tissues, Tissue engineering, Leather tanning process

*Correspondence:
Guidong Gong
guidong-gong@qq.com
Jie Fang
jiefangscu@qq.com
Full list of author information is available at the end of the article

Graphical Abstract



1 Introduction

The oral and craniofacial region is a complex area consisting of various types of hard and soft tissues, such as bones, cartilage, teeth, oral mucosa, and muscles. Disorders in this region will impair not only physical functions, such as mastication and speech but also psychological well-being and social acceptance. Oral and craniofacial disorders are estimated to have the highest prevalence and incidence worldwide, which calls for a concerted global health response [1]. However, current treatment modalities in clinical settings are still unable to achieve ideal therapeutic outcomes.

Tissue engineering approaches hold great promise for oral and craniofacial tissue repair. However, the incredible tissue diversity and sophisticated architectures of the region present great challenges to structural and functional tissue regeneration. Therefore, intense efforts have been devoted to the optimization of tissue-engineering biomaterials to meet the clinical demands [2–4]. Biomaterials based on natural polymers are attractive with biocompatibility and functional properties, providing a favorable milieu to deliver cells or cytokines for tissue regeneration [5, 6]. As one major organic polymer in the extracellular matrix (ECM) of both hard and soft tissues, collagen has inspired the construction of biomaterials to impart biomimetic characteristics.

Collagen serves as the biogenic building block of multiple tissues in the oral and craniofacial region. With low immunogenicity, high biocompatibility, and convenient preparation procedures from extensive sources, collagen offers a promising source of commercial ingredients for biomaterial fabrication [7]. However, insufficient mechanical strength, high biodegradation rate, and shrinkage of natural collagen limit the results in regenerative effects and clinical translation, especially in the treatment of oral and craniofacial disorders. Molecular re-engineering by crosslinking or incorporation of organic/inorganic components can accelerate the development of novel collagen-based biomaterials with higher adaptability to practical applications. In addition, the natural assembling and mineralization processes of collagen also shed light on biomimetic remineralization in craniofacial bone and dental tissue regeneration [8].

Extensive reviews are focusing on collagen materials in regenerative medicine, especially in bone regeneration; however, only few review article concentrates on oral and craniofacial tissue regeneration. Due to the unique nano-/microstructure of these tissues, the conventional engineering approaches of collagen-based materials may not be fully adaptable in this highly specific facial sector in the clinic. Therefore, we aim to provide a summary of the state-of-the-art findings in the laboratory and clinical applications of collagen-based biomaterials with a

comprehensive focus on different hard and soft tissues in oral and craniofacial regions. Based on the literature review, we highlight the challenges and prospects of further optimization of collagen-based biomaterials in rebuilding oral and craniofacial tissues, which will assist in bridging laboratory advances and clinical demands in the future.

2 Collagen-based biomaterials in the oral and craniofacial system

Collagen is a type of self-assembled protein, comprising up to 25–35% of proteins in humans [9]. As the main structural component of ECM, type I, II, and III collagens represent the lion's share of fibrous collagen in bone, cartilage, dentin, and mucosa tissues in oral and craniofacial system structures [10]. Collagen is a trimeric molecule featuring a unique tertiary structure, in which three left-handed parallel polypeptide α chains weave together into a right-handed triple helix bundle [7]. The natural hierarchical architecture of collagen fibrils and covalently intermolecular crosslinking make them stable in the tissue microenvironment and resilient to enzyme degradation [7].

To date, extracted collagen from numerous species is commercially and clinically available in dentistry [11]. However, the natural crosslinking of collagen fibrils will be damaged during extraction procedures, resulting in poor mechanical strength and stability of reconstituted collagen assemblies in vitro [12, 13]. As collagen offers exciting opportunities in tissue regeneration, researchers have reengineered collagen-inspired biomedical materials in different forms, mainly including scaffolds and particles, to achieve biomimetic regeneration of oral and craniofacial tissues with both structural and biological properties (Fig. 1).

2.1 Scaffold

Porous scaffolds are usually designed to simulate compositions and structures of hard tissues, providing biomimetic support for cell adhesion, proliferation, and differentiation. Ideal scaffolds for tissue engineering should possess favorable biocompatibility to promote cell adhesion and ECM formation, proper porosity to transfer bioactive molecules, and tunable biodegradation rate as the new tissue forms, as well as enough mechanical properties for surgical operation [14].

Multiple types of collagen-based scaffolds have been employed as artificial grafts for tissue repair and reconstruction. However, natural collagen scaffolds fabricated by freeze-drying or electrospinning lack mechanical strength and biostability [15], which triggers continuous efforts into physical, chemical, and biological modifications. Ultraviolet or gamma irradiation and dehydrothermal treatment (DHT) are commonly applied to collagen scaffolds as physical crosslinking methods [16]. Chemical agents, such as glutaraldehyde, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, and hexamethylene diisocyanate, achieve crosslinking of collagen by covalent amine/imine linkage [17]. However, chemical crosslinking inevitably causes cytotoxic residues in scaffolds which impairs cell growth. Thus, a mixture of other natural or synthetic polymers with collagen stands out as another strategy to overcome the drawbacks of natural collagen scaffolds. Natural polymers, such as chitosan and fibroin, and synthetic polymers, such as poly (ε-caprolactone) (PCL), polylactic acid (PLA), and poly(lactide-*co*-glycolide) (PLGA), polyethylene glycolhave (PEG) been incorporated into collagen-based scaffolds [18]. In addition, the hybridization of inorganic components, such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), can form mineralized collagen scaffolds to enhance the mechanical properties, biodegradability and osteogenic inducibility of scaffolds [19]. However, the collagen/mineral hybrid scaffolds only achieve extrafibrillar mineralization, which is different from the natural mineralization architecture in the collagen matrix of hard tissues. Therefore, strategies to drive intrafibrillar mineralization of collagen by chemical agents or proteins have recently drawn great attention in the repair of oral and craniofacial hard tissues [8].

2.1.1 Hydrogel

Hydrogels are featured by their unique ability to absorb and retain water [20]. With the capability to gel, swell, self-aggregate, and degrade, hydrogels based on collagen have been extensively applied in oral and craniofacial tissue engineering of both hard and soft tissues. The appropriate biocompatibility of collage-based hydrogels enables them to deliver various types of cells, drugs, or cytokines; and to act as platforms for the three-dimensional culture of cells together with the reconstruction of biomimetic tissues in vitro. However, high degradation rate and contraction in cell culture systems and transplantation sites greatly limit the application of pure collagen hydrogels in oral and craniofacial tissue engineering [21].

In order to optimize hydrogels, natural collagen is physically/chemically crosslinked, mixed with polysaccharides or synthetic polymers, or combined with inorganic compounds [22]. In addition, injectable hydrogels based on collagen are attractive to provide simple and minimally invasive transplantation procedures in tissue engineering. Several kinds of injectable hydrogels incorporating collagen, such as alginate/collagen hydrogel, nano-hydroxyapatite (n-HA)/collagen hydrogel, PEG-PCL-PEG copolymer/collagen/n-HA hydrogel, thiolated

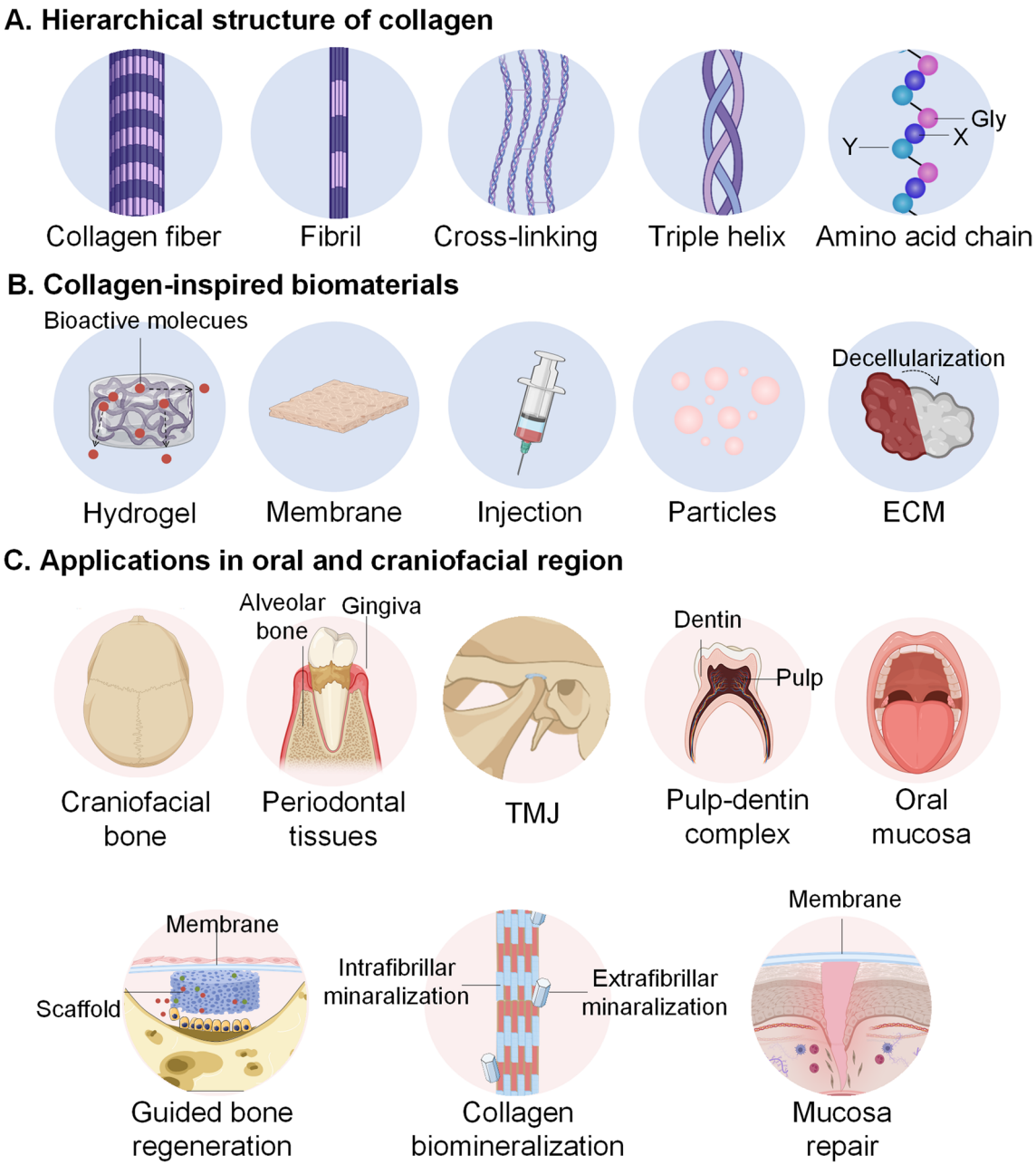


Fig. 1 Collagen-inspired biomaterials in oral and craniofacial tissue regeneration. **A** Illustration of the hierarchical structure of collagen fibers in the extracellular matrix of tissues. **B** Main forms of collagen-based biomaterials used in tissue regeneration of the oral and craniofacial region. **C** Widespread applications of collagen-based biomaterials in oral and craniofacial tissue regeneration and typical repair mechanisms

hyaluronic acid/ collagen were designed to promote cranial bone or condyle cartilage regeneration [23–25].

2.1.2 Membrane

Membranes are special forms of scaffolds widely applied in the oral and craniofacial region. Guided bone regeneration (GBR) is the most attractive strategy for applying both bone grafts and barrier membranes for oral and craniofacial bone repair [26]. Membrane biomaterials determine the clinical success of GBR by providing platforms for regeneration of bone and spatial barriers for the growth of fibrous connective tissues [26]. Therefore, GBR membranes should have sufficient mechanical strength and tunable biodegradability to provide spatiotemporal support for bone regeneration.

Non-absorbable membranes based on synthetic polymers have the disadvantages of secondary surgical removal and early exposure of membranes during healing [27]. Thus, bioabsorbable membranes based on natural polymers, especially collagen, are the most commonly used membranes in GBR for craniofacial bone regeneration [28]. Multiple strategies have been applied to enhance mechanical strength and prolong resorption time of collage membranes, including physical and chemical crosslinking, and the combination of other polymers or calcium phosphates. Additionally, bioactive molecules, such as fibroblast growth factor and bone morphogenetic proteins, can be delivered by collagen-based membranes to enhance osteoinductive effects [29].

2.2 Microparticles and nanoparticles

Collagen can also be formulated into particles with different sizes for multiple applications. The fabrication of collagen microparticles or nanoparticles is mainly based on techniques of emulsion in water/organic solvents, thermally induced phase separation, or complex coacervation [30, 31]. However, with a porous inner structure, natural collagen particles are fragile and require further crosslinking to improve their mechanical properties. Recently, the spray-drying processing strategy has been applied in the fabrication of collagen microparticles, in which diluted acid-soluble collagen solution was atomized to form a mist of thin droplets, and immediately dried by evaporation of the solvent [32].

Collagen microparticles and nanoparticles are efficient microcarriers for the delivery of drugs or proteins in tissue engineering. Multiple types of antibacterial drugs and growth factors have been encapsulated and delivered by collagen particles for bone tissue regeneration [33]. Additionally, the incorporation of apatite or β-TCP into collagen particles can also be applied to enhance cranial bone regeneration [34].

2.3 ECM

ECM is a highly organized extracellular network generated and maintained by tissue-resident cells [35]. Functioning as a specialized network of bioactive molecules, ECM is the structural and biological signaling center for surrounding cells, providing mechanical and biochemical cues for tissue homeostasis and repair [36]. Proteins in native ECM are highly conserved over species, among which collagen is the most abundant and pivotal component [35]. Researchers have successfully obtained decellularized ECM scaffolds by demineralization of hard tissues and removal of cells while retaining the overall architecture and bioactivity of natural ECM [37]. The obtained native ECM can be freeze-dried and optimized via crosslinking or mineral incorporation to generate multiple forms of biomaterials, including scaffolds and particles. Decellularized ECM can provide multiple types of matrix-associated growth factors and extracellular vesicles, promoting growth and differentiation of resident cells and providing an anti-inflammatory effect [38].

ECM-derived biomaterials have been successfully fabricated from multiple types of human or xenogeneic tissues from oral and craniofacial regions, including cartilage, dentin, dental pulp, oral mucosa, and tongue, for corresponding tissue regeneration. In addition, ECM extracted from the human dermis and amniotic membrane, xenogeneic dermis (Mucoderm®), and small intestine submucosa (DynaMatrix®) have also been applied to promote tissue regeneration in dental clinical surgeries for soft and hard tissue augmentation [39].

3 Applications of collagen-based biomaterials in oral and craniofacial tissue regeneration

3.1 Craniofacial bone regeneration

Physical and functional reconstruction of craniofacial bone defects remains a clinical challenge for maxillofacial surgeons. Transplantation of bone grafts along with barrier membranes is a common clinical treatment modality for craniofacial bone defects [40]. The challenging situations of the clinical use of natural bone grafts encourage the investigations on artificial alternatives with bioresponsive features to boost the formation of new bone [41].

Cranialfacial bone exhibits hierarchically staggered architecture with sophisticated integration of both organic and inorganic phases at multiscale [42, 43] (Fig. 2A). As the major organic components, type I collagen fibrils are critical in templating and guiding mineral sequestration, nucleation, and growth to form mineralized collagen fibrils [44]. Notably, though bone tissues at different anatomical sites share similar structures and components, craniofacial bone contains a higher profusion of collagen than long bone [45]. Therefore, collagen-based scaffolds, hydrogels, and membranes have been essential components in biomaterials for craniofacial bone regeneration. Ideal collagen-based biomaterials for craniofacial bone regeneration should possess enough stiffness to support mechanical loading, bioactive characteristics to promote osteogenesis and angiogenesis, and biomimetic microarchitecture similar to native bone tissue as well.

Refining the mechanical properties and biodegradation rate of collagen-based biomaterials is critical for repair outcomes. In order to overcome the poor mechanical properties and structural stability of unmodified collagen-based grafts and membranes in craniofacial bone reconstruction, multiple types of natural or synthetic polymers have been blended

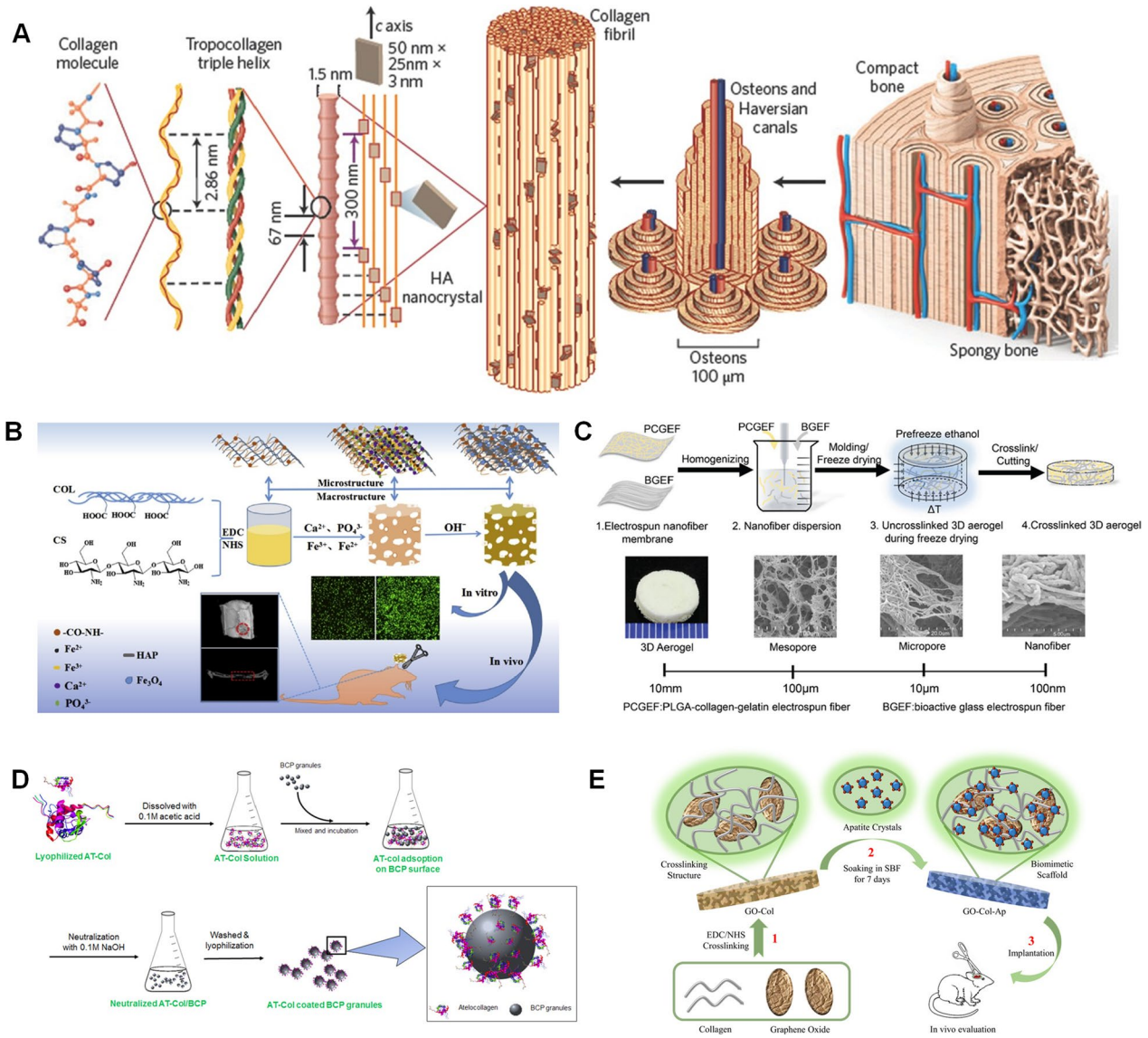


Fig. 2 Collagen-based biomaterials in craniofacial bone regeneration. **A** Scheme of bone structure. Reproduced with permission from [42]. **B** Illustration of the fabrication of the chitosan/collagen (CS/Col) composite scaffold incorporated with the nano-hydroxyapatite (n-HA) and Fe_3O_4 for cranial bone reconstruction. Reproduced with permission from [46] **C** Scheme of the formation of the 3D hybrid nanofiber aerogels composed of PLGA-collagen-gelatin (PCG) and Sr–Cu codoped bioactive glass (BG) fibers, and the scanning electron microscopy images of the structure. Reproduced with permission from [51]. **D** Schematic illustration of the preparation of atelocollagen-coated biphasic calcium phosphate granules. Reproduced with permission from [53]. **E** Schematic illustration of the fabrication of graphene oxide-functionalized collagen scaffold for cranial bone regeneration. Reproduced with permission from [69]

with collagen for modifications, such as chitosan [46–48], alginate [49], PCL [50], PLGA [51], bioceramics, β-TCP, and HA [52–54] (Fig. 2B–D). Entrapping bioactive molecules in scaffolds is an alternative strategy for the optimization of collagen-based grafts. Collagen-based scaffolds can achieve sustainable release of multiple osteoinductive and angioinductive biomolecules, such as bone morphogenetic protein-2, stromal cell-derived factor-1, and vascular endothelial growth factor [49, 55–59]. The above methods can be combined to exert synthetic effects respectively. In a recent study, Verma et al. designed a composite scaffold with N,O-carboxymethyl chitosan (NOCC), and type I collagen cross-linked by glutaraldehyde as a supporting matrix [60]. The subsequent grafting of epigallocatechin gallate (EGCG) and entrapping of adenosine in the matrix enabled the scaffold to sustainably deliver the bioactive components. The optimized osteogenic

scaffold provided a microenvironment for cell migration and osteogenesis in vitro, and promote cranial bone regeneration in vivo [60].

Biomimetic mineralization provides a novel avenue for modifications of collagen-based biomaterials. The traditional methods to incorporate mineral contents by electrodeposition, co-precipitation, or immersion in the mineral-forming fluid can merely enhance extrafibrillar collagen mineralization [61, 62]. Therefore, researchers have taken advantage of natural non-collagenous proteins (NCPs) or their analogs for biomimetic mineralization of collagen grafts and membranes, which involves both intrafibrillar and extrafibrillar precipitation of HA. Poly(acrylic acid) (PAA) is the most widely investigated substitute for natural NCPs mineralization [63, 64]. Liu et al. harnessed the role of PAA and constructed a collagen-based scaffold with multiscale hierarchy and self-assembly resembling the bone matrix. The incorporation of PAA promoted hierarchical intrafibrillarly mineralization of collagen fibrils after SBF soaking scaffold [65, 66]. The intrafibrillar mineralized scaffold significantly enhanced the osteogenesis of stem cells and mandibular bone regeneration [66] (Fig. 3A–C). Li et al. designed self-mineralizable membranes by covalently attaching high-molecular weight polyacrylic acid (HPAA) to collagen membranes. Simulating the function of NCPs, HPAA induced intrafibrillar mineralization of collagen, thereby increasing the stiffness of the membrane and promoting osteogenesis of mesenchymal stem cells and cranial bone formation [67]. Additionally, surface silanized nano-bioactive glasses and graphene oxide have also been introduced to promote biomimetic biomineralization of collagen scaffolds for cranial bone regeneration [68, 69] (Fig. 2E). Amorphous silica could serve as an alternative to carbonated apatite in the mineralization of collagen-based scaffolds for bone regeneration. The infiltration of collagen matrices with silica could form a three-dimensional intrafibrillar silicified collagen scaffold with hierarchical structures, which represented good biodegradable, osteoinductive, angioinductive, and immunomodulatory properties to promote cranial bone regeneration in vivo [70–72].

Biomimetic structural modifications of collagen-based biomaterials could also provide therapeutic benefits for craniofacial defects. Yu et al. took a different method for biomimetic craniofacial bone regeneration. They simulated the micropattern of the bone structure by constructing a multilayer cell-collagen scaffold with an angle-ply structure. The scaffold presented improved osteogenic properties under mechanical loading [73] (Fig. 3D).

3.2 Alveolar bone regeneration

Alveolar bone refers to the unique intraoral bone tissue supporting teeth. Collagen-based membranes and bone grafts serve as promising candidates for clinical alveolar bone augmentation [74, 75].

Implantation of natural collagen membranes are the standard surgery procedure for the majority of GBR indications to increase the volume of alveolar bone [76]. However, the poor mechanical properties of natural collagen scaffolds have driven researchers to apply crosslinking strategies and incorporate mineral content or bioactive molecules in collagen scaffolds to enhance their effects on alveolar bone regeneration [34, 77–80]. Some clinical trials have reported enhanced alveolar bone regeneration by implantation of crosslinked or inorganic compound-modified collagen matrix [81, 82]. However, according to other reports, crosslinked collagen scaffolds presented inferior ability in alveolar bone regeneration to natural collagen matrix due to foreign body reaction and prolonged biodegradation time [83].

Given the spreading of bacterial pathogens in the oral cavity, antimicrobial properties of biomaterials are also expected for alveolar bone repair. Collagen-based biomaterials can serve as platforms for the sustainable release of antibiotics, such as metronidazole and minocycline [84, 85]. In addition, silver nanoparticles (AgNPs) were also used to enhance the antibacterial and anti-inflammatory effects of collagen-based scaffolds [86]. Qian et al. coated the surface of electrospun PLGA/PCL scaffolds with polydopamine, AgNPs, and type I collagen, constructing a multifunctional scaffold with antibacterial and osteoinductive properties for alveolar bone regeneration [87].

A further challenge for functionally repairing alveolar bone comes from the complex relationship between bone and tooth, which is connected by periodontal ligament fibers to form the periodontium. Functional healing of periodontium is expected to achieve the synchronized repair entailing osteogenesis, cementogenesis, and reattachment of aligned periodontal ligaments [88], which leads to the advocation of biomimetic scaffolds with multiphasic structures [89]. In a recent study, Ye et al. developed a hierarchical bilayer scaffold based on collagen for periodontium regeneration [90]. Collagen fibrils and nano-HA were assembled to form the porous mineralized layer, which was then combined with the parallel-arranged layer of unmineralized collagen-reinforced concentrated growth factor fibrils [90]. In vivo, the bilayer collagen-based scaffold successfully achieved complete periodontium regeneration of alveolar bone, periodontal ligaments, and cementum via stem cell recruitment and Smad3 activation [90].

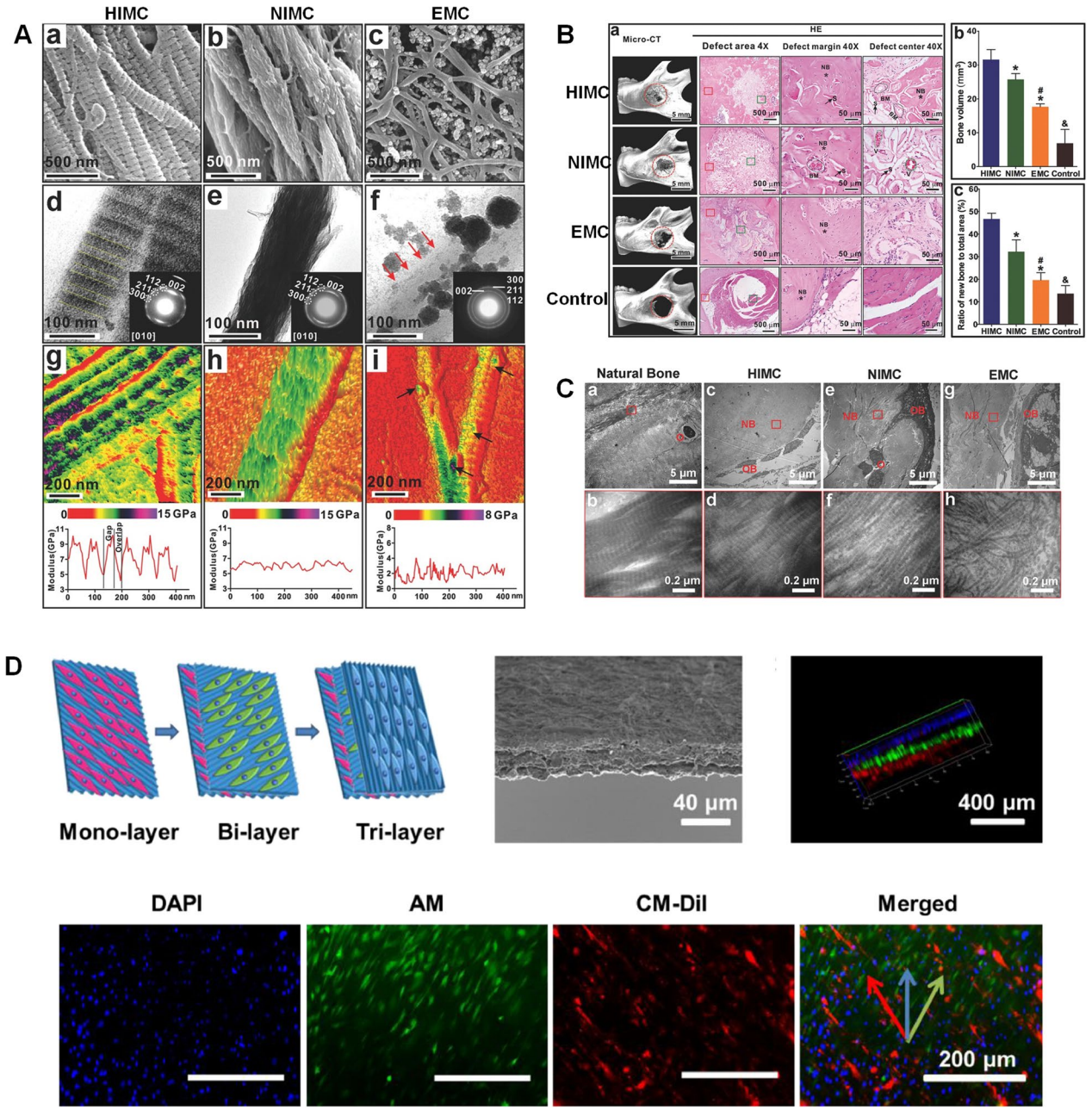


Fig. 3 Biomimetic collagen-based biomaterials for craniofacial bone repair. **A**. Hierarchically intrafibrillarly mineralized collagen scaffold for mandibular bone regeneration. Images of scanning electron microscopy, transmission electron microscopy, and anatomic force microscopy showed the nanotopography and nanomechanical properties of hierarchically intrafibrillarly mineralized collagen (HIMC) scaffold, nonhierarchical, intrafibrillarly mineralized collagen (NIMC) scaffold, and extrafibrillarly mineralized collagen (EMC) scaffold. Reproduced with permission from [66]. **B** Images of micro-CT, Hematoxylin and Eosin staining and transmission electron microscopy presented the effect of in vivo mandibular bone regeneration promoted by different collagen scaffolds. Reproduced with permission from [66]. **C** Transmission electron microscopy images of natural bone and newly formed bone by different collagen scaffolds. Reproduced with permission from [66]. **D** Scheme of biomimetic laminated cell-collagen scaffold with angle-ply structure and its feature presented by scanning electron microscopy and confocal laser scanning microscope. Reproduced with permission from [73]

3.3 Joint disk and cartilage regeneration in TMJ

The TMJ, consisting of the mandibular condyle, TMJ disc, and glenoid fossa-articular eminence, is a type of ginglymoarthrodial joint responsible for the complex movement of the mandible in the craniofacial system. The regeneration of TMJ tissues after surgical removal

remains clinically challenging due to the complexity of TMJ structures, dynamic mechanical stimulus, and avascular microenvironment [91]. Therefore, collagen-based biomaterials are expected to have enough physical properties to bear dynamic mechanical loading, and biomimetic configuration for functional repair.

3.3.1 TMJ disc

The TMJ disc is a biconcave and fibrocartilaginous structure located between the condyle and glenoid fossa-articular eminence region [92]. It functions as a cushion of mechanical loading during mandible movement, working in a dynamic mechanical microenvironment, including compression, tension, and shear [93]. Therefore, grafting biomaterials are expected to possess the mechanical properties of native TMJ discs to achieve the long-term functional repair. With native microstructure and tissue-specific composition, decellularized ECM is a favorable choice for TMJ disc regeneration. Juran et al. [94] pretreated decellularized ECM of porcine TMJ discs by laser micropatterning, improving compressive modulus by 1.5 times higher than native disc (3 MPa). Liang et al. [95] also utilized ECM of porcine TMJ disc but processed it into injectable multiporous hydrogels by pepsin digestion in disc regeneration. In addition, an ECM scaffold derived from small intestinal submucosa could also promote the infiltration of host cells and the formation of TMJ disc-like fibrocartilage tissue with peripheral muscular and tendinous attachments [96]. Notably, mimicking the anisotropic collagen fiber orientation and inhomogeneous fibrocartilaginous matrix distribution of TMJ disc is critical for functional repair, which requires further investigation in the optimization of collagen-based scaffolds.

3.3.2 Mandibular condyle

The mandibular condyle originates from the mandibular ramus, located adjacent to the articulating surface of the TMJ disc. Different from other synovial joints with hyaline cartilage cover on the articular surface, the structures of the condyle include a layer of fibrous tissue, articular cartilage, which is made up of collagen-abundant fibrocartilage, and subchondral bone consisting of cortical and trabecular bone [97].

Collagen-based porous scaffolds displayed positive results in TMJ condyle regeneration with the ability to promote chondrocyte adherence and maintain cell differentiated phenotype [98]. Embree et al. have found that ectopic transplantation of native bovine collagen sponge (Helistat) loaded with condyle-derived fibrocartilage stem cells could achieve the formation of cartilaginous-like tissue after three weeks of transplantation, and transitional tissue with bone and cartilage tissues after four weeks of transplantation respectively [99]. Crosslinking and incorporation of HA could promote mechanical strength and improve resilience to hydrolytic and enzymatic degradation of collagen-based scaffolds for functional regeneration of TMJ condylar cartilage regeneration movement [100, 101].

The biomimetic concept is also adopted due to the hierarchical structure of the mandible condyle. Wang et al. designed a bilayer scaffold based on thiolated hyaluronic acid (HA-SH)/type I collagen hydrogel and biphasic calcium phosphate (BCP) ceramics for osteochondral regeneration of mandible condyle [25]. The upper layer of the hydrogel loaded with bone marrow mesenchymal stem cells or chondrocytes formed the fibrocartilage layer of the condyle, while the BCP layer mimicked bone structure [25]. The implantation of the scaffold successfully repaired osteochondral defects in rabbits by forming complete condyle-like newborn tissues [25] (Fig. 4).

3.4 Pulp–dentin regeneration

Dental caries is an extremely common oral health condition causing defects of tooth hard tissues, which will ultimately lead to irreversible inflammation in pulp tissue [102]. Currently, clinical treatment modalities of dental caries and pulpitis, including fillings of caries cavity and endodontic treatments, all rely on synthetic materials. Recent advances in regenerative medicines have directed paradigm shifts in the development of treatment modalities for tooth decay.

3.4.1 Biomimetic remineralization of dentin collagen

Dentin forms the main bulk of teeth. Conventional treatments of dentin damage done by caries can lead to trauma of healthy dentin, develop microleakage between dentin and filling materials, and provoke dentin hypersensitivity [8]. The apparent drawbacks of current treatment options have fueled the growing interest in dentin remineralization. However, dentin lacks self-regenerative capacity, which makes dentin regeneration particularly challenging.

Similar to bone tissues at the nanoscale, dentin is characterized by mineralized hierarchical architecture consisting of the inorganic phase and organic matrix [103]. Collagen molecules formed by odontoblasts account for about 90% of the organic matrix, with NCPs constituting the other 10% [104]. The self-assembled collagen fibrils play a central role in natural dentin remineralization by providing the template and mechanical support for NCP localization, and crystal nucleation and growth [105].

The essential role of NCPs in the regulation of mineral crystallization and stabilization in dentin collagen has attracted considerable attention. NCP-inspired peptides, such as 8DSS peptide, P26, and peptides derived from dentin matrix protein 1 and cementum protein 1,

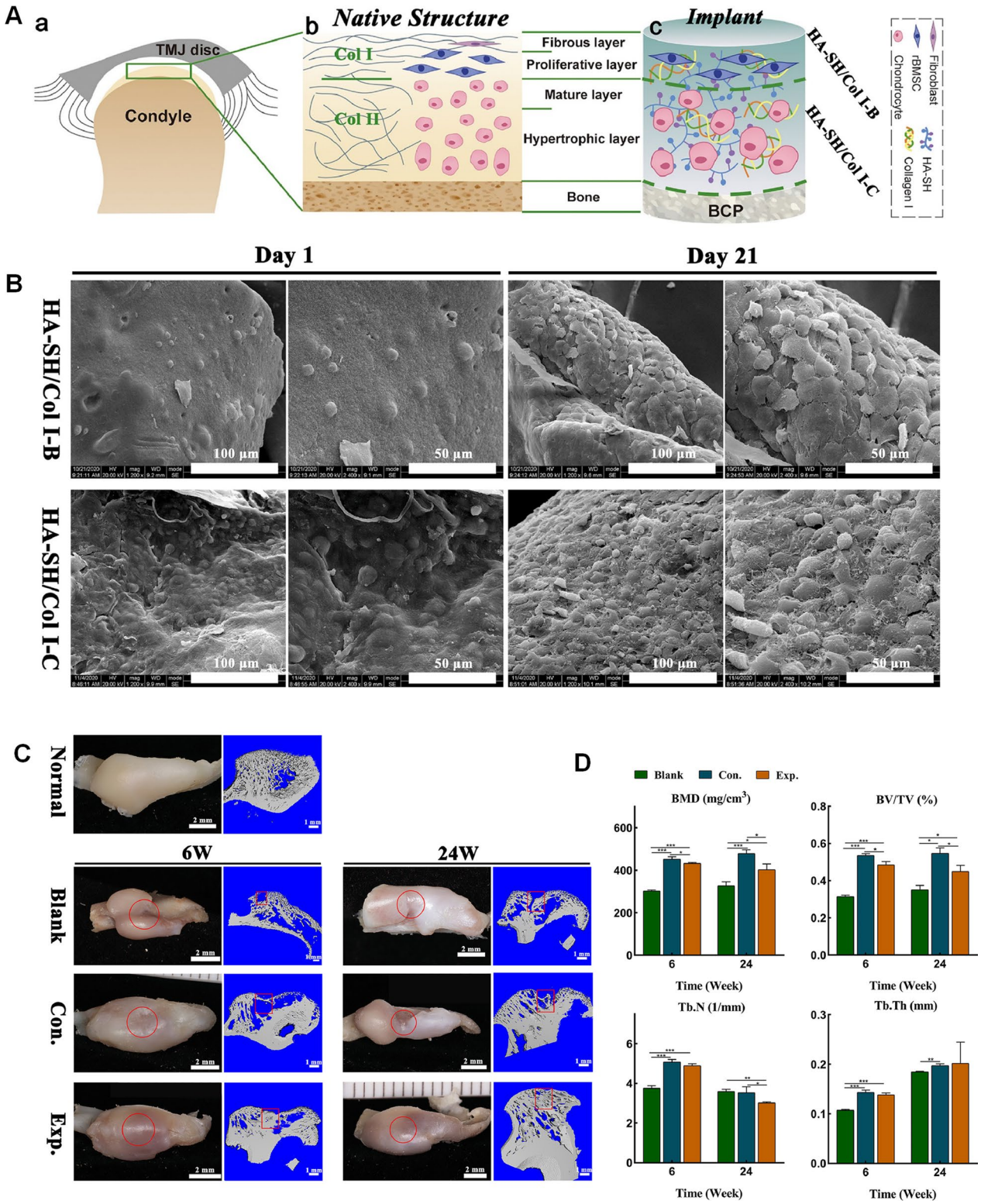


Fig. 4 Injectable blend hydrogel-BCP ceramic scaffold for TMJ condylar osteochondral repair. **A** Scheme for preparation of bilayer scaffold. **B** Scanning electron microscopy images of rabbit bone mesenchymal stem cells (rBMSCs) and chondrocytes cultured in injectable self-crosslinking thiolated hyaluronic acid (HA-SH)/type I collagen (Col I) hydrogel. **C** Gross morphology and representative sagittal images of condylar defects after the implantation of the hybrid scaffold. **D** Micro-CT analysis of condylar osteochondral regeneration. Reproduced with permission from [25]

were reported to promote collagen mineralization [103, 106–108]. Polymer NCP analogs, such as poly(amido amine) (PAMAM) dendrimers and polydopamine, have also been extensively studied to induce amorphous calcium phosphate formation and collagen remineralization in dentin [109]. PAMAM could be modified by different terminal functional groups, such as –COOH, $–PO_3H_2$, $–NH_2$, to enhance in situ remineralization of dentin through attracting calcium and phosphate ions through electrostatic forces and chelation, and stabilizing amorphous calcium phosphate [110–112]. In addition to peptides and polymers, some small molecules could also promote collagen remineralization. For instance, methacryloyloxydecyl dihydrogen phosphate (MDP) in the collagen-bound state could form a huge collagenous phosphoprotein (HCPP), expanding the intrafibrillar space and trapping calcium phosphate precursors by electrostatic attraction [113]. Succinic acid could also interact with collagen via a hydrogen bond and facilitate the attraction of calcium ions, thereby accelerating collagen intrafibrillar mineralization [114].

Collagen stabilization remains a hurdle to the clinical application of remineralization templates. Therefore, some researchers focused on strategies to stabilize the dentin collagen matrix to improve dentin remineralization. Tao et al. took advantage of natural NCPs in maintaining structural integrity and stability of the collagen matrix, and fabricated multifunctional particles by modifying PAMAM with natural NCPs and galardin. The particles combined the properties of promoting amorphous calcium phosphate formation and intrafibrillar mineralization (PAMAM). They also facilitated collagen crosslinking and stabilization (NCPs), and inhibited protease to preserve collage structure and NCP function (galardin) [115]. The multifunctional particles successfully induced dentin remineralization in the presence of collagenase and demonstrated anti-dentin caries function in vivo (Fig. 5A–C). Peptide P_{11}-4 was also reported to stabilize the dentin collagen matrix [116]. In addition to peptides, tannic acid was also reported to mediate crosslinking of dentin collagen, thereby enhancing collagen resilience to collagenase degradation tissue [117].

3.4.2 Regeneration of pulp–dentin complex

Vital pulp therapy (VPT) is a biologic-based treatment option in endodontic treatments to preserve the vitality of pulp tissue and promote regeneration of the pulp–dentin complex in immature teeth [118]. The therapeutic outcomes depend on the clinical situation of pulp inflammation and pulp capping materials. Current available clinical materials, such as Biodentine and mineral trioxide aggregate (MTA), are mostly based on calcium silicate, which has numerous drawbacks, including limited pulp regeneration capacity, slow rate of dentin repair, and discoloration of tooth. Recently, bioactive tissue ECM has emerged as a substitute biomaterial for pulp–dentin complex regeneration.

The treated dentin matrix (TDM) from demineralized, sterilized, and atelopeptidized natural dentin is a type of porous native collagen scaffold with the physical characteristics of dentin [119]. TDM can serve as a reservoir of multiple growth factors and NCPs to induce pulp–dentin complex regeneration. Demineralized TDM particles/sheets with or without atelopeptidization were reported to promote dentin-pulp tissue regeneration when they were loaded with dental pulp stem cells or dental follicle cells [120, 121]. TDM particles could also be mixed with sodium alginate solution to form a hydrogel, which could promote dentin regeneration as a direct pulp capping material [122]. Chen et al. developed a kind of TDM paste by mixing demineralized TDM powder with aqueous TDM extracts. The paste promoted the proliferation and odontogenesis of dental pulp stem cells and induced continuous reparative dentin bridge in the caries model [123]. Jiao et al. reported that cryopreservation treatment could preserve the activity of dentinogenesis-related proteins in TDM [124]. Loaded with dental follicle cells, the cryopreserved TDM could form new biomimetic dentin-pulp-like tissues with dentinal tubules, dentin, collagen fibers, nerves, and blood vessels in vivo [124]. Biological modifications by peptides and liposomes could further improve the regenerative capacity of TDM [125, 126].

The ECM of the dental pulp is another candidate for the regeneration of the pulp–dentin complex. Song et al. reported that the collagen-abundant pulp ECM could support the growth and differentiation of stem cells of the apical papilla, serving as collagenous scaffolds for pulp–dentin complex regeneration [127]. An in vivo study also suggested that the pulp ECM scaffold could enhance the regeneration of the pulp–dentin complex in root canals [128]. In addition, decellularize pulp ECM could be freeze-dried, crosslinked, and fabricated into hydrogels,

(See figure on next page.)

Fig. 5 Applications in repair of pulp–dentin complex. **A** Scheme of the preparation of PAMAM-NGV@galardin (PNG) and the mechanisms for dual effects on collagen stabilization and remineralization. Reproduced with permission from [115]. **B** Transmission electron microscopy images of collagen fibers. Addition of PAMAM-NGV (PN) increased the diameter of collagen fiber compared with the negative control group. Reproduced with permission from [115]. **C** Transverse-section scanning electron microscopy images of intrafibrillar remineralization of dentin promoted by PAMAM and PNG. Reproduced with permission from [115]. **D** The preparation procedure and histological features of decellularized pulp ECM. Reproduced with permission from [129]

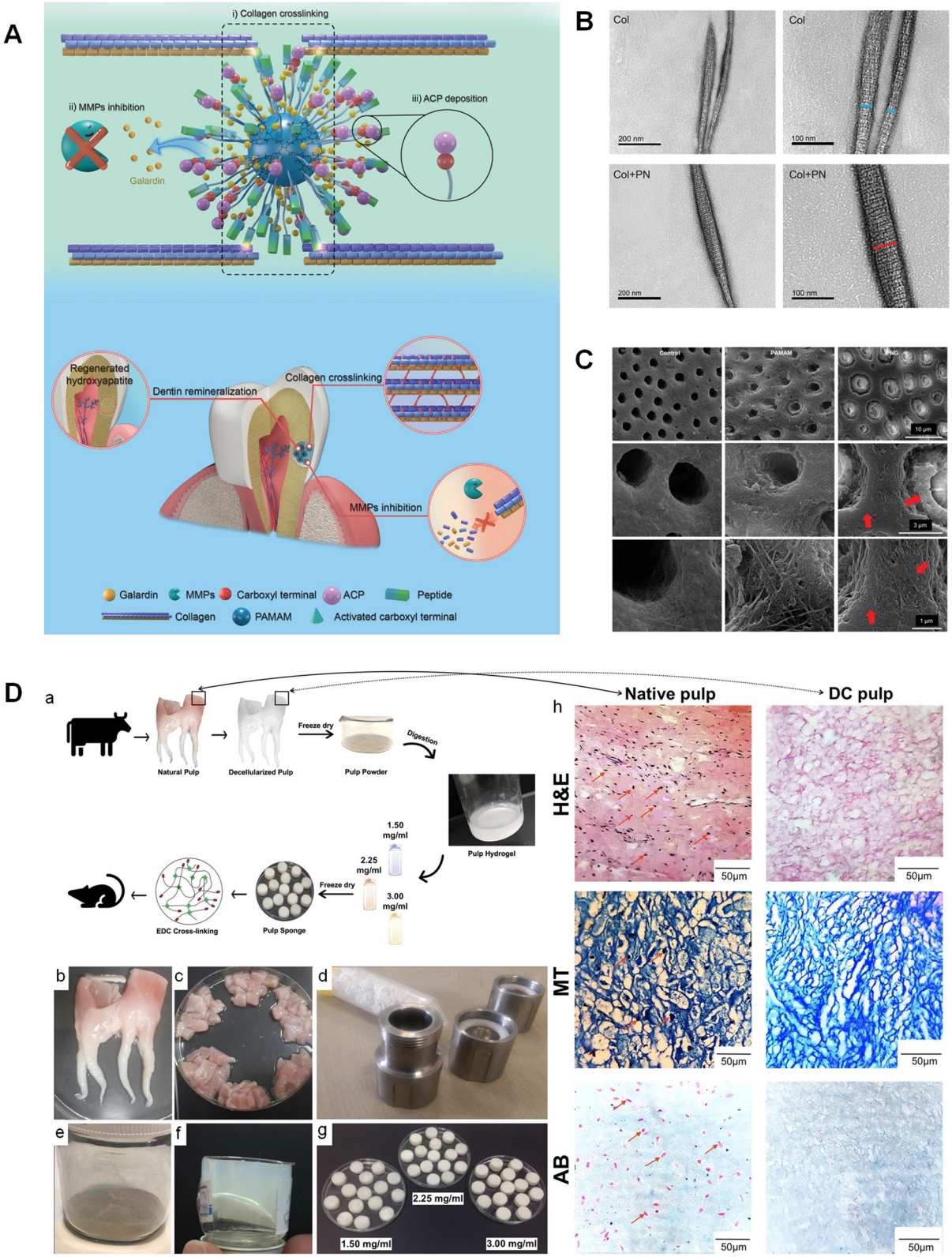


Fig. 5 (See legend on previous page.)

which could promote the expression of DMP-1 and collagen-I in bone marrow mesenchymal stem cells [129] (Fig. 5D).

3.5 Intraoral soft tissues

3.5.1 Oral mucosa

Oral mucosa functions as the barrier against the exogenous stimulus and pathogen invasion [130]. Though oral mucosa wound usually heals faster than the skin, some large oral mucosa defects will turn into chronic wounds due to the bacteria-laden environment and constant mechanical abrasion in the oral cavity [131] (Fig. 6A). The gold standard treatment for oral mucosa defects is the transplantation of autologous mucosal or skin grafts, which is frequently confronted with the trauma of healthy tissues, the shortage of oral mucosa, and the infection of skin grafts. Using biomaterial-based tissue reconstruction to promote oral mucosa healing has gained increasing support in recent years [131]. Collagen-based biomaterials for oral mucosa reconstruction are required to have high tensile strength for surgical operation, enough stability to support new tissue formation, and optimal biodegradation rate to avoid secondary surgical removal and early exposure of the biomaterials. In terms of biological properties, the abilities to promote both cell proliferation and epithelialization to form the full-thickness regeneration of oral mucosa are required.

The repair of keratinized gingiva is the focus of oral mucosa reconstruction due to the high prevalence of gingival recession. Multiple types of collagen-based scaffolds have been examined in the regeneration of keratinized gingiva and the augmentation of soft tissue volume. Decellularized ECM from human dermis is a clinical choice for gingiva tissue augmentation at tooth or implant sites. Clinical data have reported promising results in both horizontal and vertical gingiva augmentation by acellular dermal matrix [132, 133]. However, a long-term observation reported a significant relapse of the gingival recession in patients treated with ADM [134], which might be due to the lack of keratinization of the regenerated gingiva [135]. Xenogeneic collagen matrices are other choices for gingival recession and soft tissue augmentation. A non-crosslinked bilayered xenogeneic collagen matrix has been widely applied in clinical settings. The layer of collagen fibers in a compact arrangement can facilitate suturing and graft protection, while the thick porous spongy layer supports blood clot maintenance and tissue formation [136]. Clinical grafting of the bilayer collagen matrix can increase the width of keratinized gingiva with favorable aesthetic outcomes and reduced surgical and recovery time [137–139]. Another kind of crosslinked volume-stable collagen matrix presented a promising ability to maintain gingiva volume stability in clinical settings [140, 141]. In addition, xenogeneic collagen matrices from small intestine submucosa or dermal tissue can also promote gingiva regeneration [39]. However, repaired gingiva based on the xenogeneic collagen matrices is still thinner than free mucosa grafts [142].

The collagen-based repair of oral mucosa also attracts the construction of in vitro models as artificial substitutes for physical and pathological studies. Natural collagen gel or its combination with other natural polymers has been widely used for the three-dimensional culture of keratinocytes and fibroblasts to form mucosal epithelial and subcutaneous connective tissue in vitro [143, 144]. It is reported that the non-crosslinked membrane based on types I and III collagen (Bio-Gide®) showed the best ability for oral mucosa reconstruction in vitro among other commercial collagen membranes collagen [145]. However, natural collage gel contracts over time of culture, and the majority of 3D oral mucosa models based on collagen matrix are non-keratinized tissues [146–148]. Recently, engineered keratinized oral mucosa was generated based on crosslinked electrospun collagen scaffold. The 3D keratinized mucosa model even presented favorable attachment to dental implants in vitro [149].

3.5.2 Tongue

Apart from serving as the barrier, dorsal tongue mucosa is responsible for taste detection with taste buds located in the epithelium. Therefore, functional repair of tongue mucosa should also consider the possibility of taste bud reconstruction. Tissue ECM from porcine small intestinal submucosa could provide a scaffold for functional taste bud regeneration and reinnervation layer [150]. Decellularized tongue ECM is another candidate for taste recovery (Fig. 6B). Lee et al. reported that 2D coating of tongue ECM could maintain functional phenotypes of taste cells and achieve signal transmission between the taste cells and neurons [151]. Meanwhile, the 3D hydrogel of tongue ECM could form a stable structure with collagenous nanofibrils and enable the functional reconstruction of taste buds in vitro [151] (Fig. 6C–E).

Injuries can penetrate tongue mucosa and cause trauma in the muscle layer, that seems to have an inferior ability to regenerate to limb and trunk muscles [152]. Collagen gel could support myofibroblasts to form muscle-like tissues in the hemiglossectomy model [153, 154]. ECM of porcine small intestinal submucosa loaded with MSCs could also promote tongue muscle regeneration with reduced contraction and fibrosis in critical-sized myomucosal defect models [155].

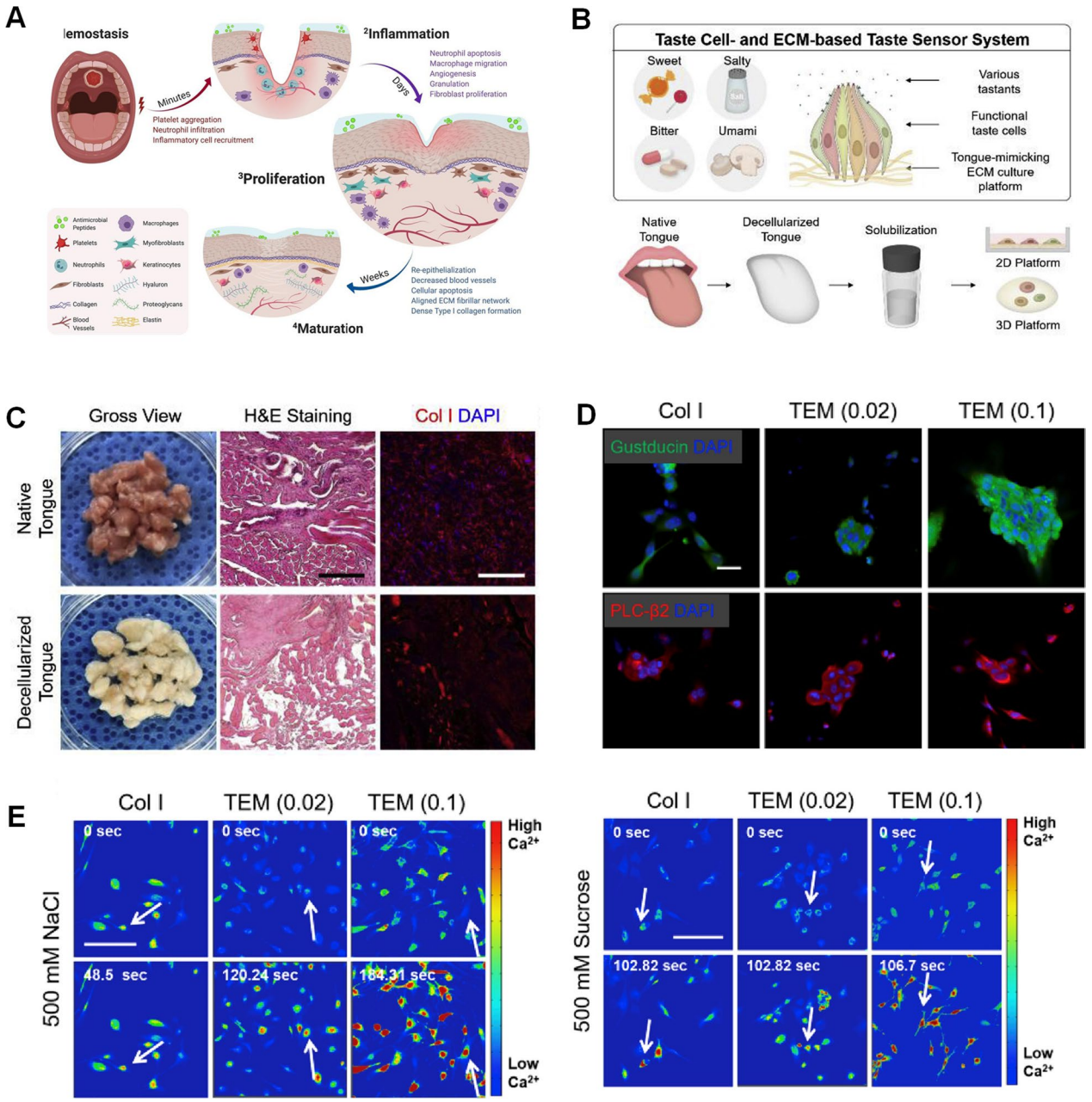


Fig. 6 Applications of collagen-based biomaterials in oral mucosa repair. **A** Schematic illustration of the timeline of oral wound healing and mucosa remodeling. Reproduced with permission from [131]. **B** Characterization of tongue tissue matrix before and after decellularization. Reproduced with permission from [151]. **C** Images of gross view and histologic staining of decellularized tongue tissue. Reproduced with permission from [151]. **D** Immunostaining images showing the upregulated expression of taste cell-specific markers gustducin and PLC-β2 in taste cells after culture in the microfluidic device with tongue extracellular matrix-coated microchannels. Reproduced with permission from [151]. E. Fluo-4-mediated visualization of taste cell function presented by cytosolic Ca^{2+} influx before and after tastant treatments. Reproduced with permission from [151]

4 Discussion

Collagen-based biomaterials are versatile due to their practical applications and present great promise for tissue regeneration in the oral and craniofacial region. Despite the plethora of literature on the potential applications of collagen-based biomaterials in oral and craniofacial tissue regeneration, only a limited number of reported materials were recommended for clinical use. This striking contrast between academic research

and clinical outcomes requires further refinements and optimizations on collagen-based biomaterials.

In terms of improvements in mechanical properties and biostabilities, the pre-tanning process in leather manufacturing might inspire the re-engineering of collagen-based biomaterials. During the pre-tanning process, metal–polyphenol-mediated crosslinking is applied to improve the collagen resistance to heat and microbial-related enzymatic degradation and enhance the mechanical strength and flexibility of the leather. The tanning process shares similarities with the optimization of collagen-based biomaterials by crosslinking to improve mechanical properties and biodegradation rates. Indeed, several types of polyphenols, such as EGCG, proanthocyanidin, and quercetin, have gained significant interest in crosslinking of dentin collagen and stabilization of decellularized xenografts [156, 157]. Further studies are required to explore the potential of polyphenol-mediated optimization of collagen-based materials in oral and craniofacial tissue regeneration.

There remains a gap between preclinical experiments and clinical applications of collagen-based biomaterials in oral and craniofacial region. This might result from the difficulties in the balance of the mechanical strength and biocompatibility during crosslinking or other modification processes. The crosslinking processes will inevitably impair biocompatibility of collagen-based biomaterials, leading to enhanced host immune reaction. In addition, the inability to achieve tissue functional repair also leads to unsatisfactory clinical outcomes. The tissue diversity strongly requires multi-tissue regeneration to achieve long-term functional repair of the oral and craniofacial complex. In most studies today, only one type of tissue can be regenerated. From a biomimetic standpoint, future collage-based biomaterials are tailored to possess the anisotropic mechanical and biological properties for multi-tissue repair. Furthermore, collagen can be combined with different polymers to mimic the spatial gradient of matrix composition and topography similar to the natural interface structure. The "bottom-up" layer-by-layer biomaterial strategy is effective to simulate the complex architecture of native tissues. Recently, 3D bioprinting technologies provided rapid and robust approaches to multi-tissue regeneration and interface reconstruction. It is strongly desirable to bioprint anisotropic collagen-based scaffolds with optimized mechanical properties, adequate structural fidelity, tunable biodegradation, and ideal porosity for functional multi-tissue regeneration. 3D bioprinting can also assist in the making of scaffolds with precisely customized shapes for the regeneration of tissues with irregular morphology, such as the TMJ and the periodontium.

Apart from the complex structures, the mechanical microenvironment in the oral and craniofacial region should also be considered. Different bodily movements, such as chewing and talking, will produce continued exogenous mechanical signals to oral and craniofacial tissues. In addition to exogenous stress, mechanical and physical properties of the ECM, mainly including substrate stiffness and topography, are the origins of endogenous stress of oral and craniofacial tissues. Therefore, future collagen-based biomaterials with biomimetic mechanical and topographic features are expected to transduce mechanical loading and enhance multi-tissue repair with matched stiffness.

Despite the low immunogenicity, the collagen can induce material-dependent inflammation once implanted, which hinders tissue repair and subsequently leads to failures of implant surgeries [27]. Therefore, novel collagen-based biomaterials are expected to reduce the resulting inflammation and enhance the pro-resolving biological outcomes to accelerate oral and craniofacial tissue regeneration. The incorporation of anti-inflammatory cytokines and antioxidant components is a potential strategy for rebalancing tissue inflammation and repair. Moreover, the exact biological mechanisms of inflammatory responses caused by collagen-based biomaterials remain to be investigated to guide future modifications of biomaterials.

The biological attributes and the customizable nature of collagen fit the demand for regenerative medicine in the oral and craniofacial region. Even though the mechanical and biological properties of collagen-based biomaterials remain a significant challenge in the clinical setting, innovations based on nature-derived structures and microenvironments of oral and craniofacial tissues can revolutionize the future of collagen-mediated therapeutics.

5 Conclusion

Extensive studies have been devoted to demonstrating the promising prospects of collagen-based biomaterials in oral and craniofacial tissue regeneration. However, a comprehensive review of this particular clinical sector is absent, while the challenges of collagen-based biomaterials usage remain. This review contributes to the research of collagen-based biomaterials focusing efforts on oral and craniofacial tissue regeneration. In this review, we introduced the recent collaborative efforts in the applications of collagen-based materials for hard and soft tissue reconstruction in the oral and craniofacial region. We also discussed the future directions for re-engineering collagen-based materials to achieve structural and functional repair in the specific region. Despite a promising outlook, collagen-based materials will undoubtedly face

numerous scientific and engineering challenges in future development and implementation. This review can provide integrated knowledge and interesting perspectives on the development of artificial materials for oral and craniofacial tissue regeneration.

Abbreviations

TMJ	Temporomandibular joint
ECM	Extracellular matrix
DHT	Dehydrothermal treatment
PCL	Poly(ε-caprolactone)
PLA	Polylactic acid
PLGA	Poly(lactide-*co*-glycolide)
PEG	Polyethylene glycolhave
HA	Hydroxyapatite
β-TCP	β-Tricalcium phosphate
n-HA	Nano-hydroxyapatite
GBR	Guided bone regeneration
NCPs	Non-collagenous proteins
NOCC	N,O-carboxymethyl chitosan
EGCG	Epigallocatechin gallate
CS/Col	Chitosan/collagen
PCG	PLGA-collagen-gelatin
BG	Bioactive glass
PAA	Poly(acrylic acid)
PCLMA	Polycaprolactone methacryloyl
HPAA	High-molecular weight polyacrylic acid
HIMC	Hierarchically intrafibrillarly mineralized collagen
EMC	Extrafibrillarly mineralized collagen
AgNPs	Silver nanoparticles
TMD	TMJ disorders
HA-SH	Thiolated hyaluronic acid
BCP	Biphasic calcium phosphate
rBMSCs	Rabbit bone mesenchymal stem cells

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Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]State Key Laboratory of Oral Diseases and National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, Sichuan, China. [2]BMI Center for Biomass Materials and Nanointerfaces, College of Biomass Science and Engineering, Sichuan University, Chengdu 610065, Sichuan, China. [3]Department of Oral and Maxillofacial Surgery and Pharmacology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. [4]Center of Innovation and Precision Dentistry, School of Dental Medicine, School of Engineering and Applied Sciences, University of Pennsylvania, Philadelphia, PA 19104, USA. [5]Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education (MOE), Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu 640041, Sichuan, China. [6]Department of Chemical and Biological Engineering, Bioproducts Institute, University of British Columbia, Vancouver, BC V6T 1Z4, Canada. [7]State Key Laboratory of Polymer Materials Engineering, Sichuan University, Chengdu 610065, Sichuan, China.

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