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REVIEW

# Mussel-Based Biomimetic Strategies in Musculoskeletal Disorder Treatment: From Synthesis Principles to Diverse Applications

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**Abstract:** Musculoskeletal disorders are the second leading cause of disability worldwide, posing a huge global burden to the public sanitation system. Currently, tissue engineering-based approaches act as effective strategies, which are, however, challenging in limited application scenarios. Mussel-based biomimetic materials, exhibit numerous unique properties such as intense adhesion, biocompatibility, moisture resistance, and injectability, to name only a few, and have attracted extensive research interest. In particular, featuring state-of-the-art properties, mussel-inspired biomaterials have been widely explored in innumerable musculoskeletal disorder treatments including osteochondral defects, osteosarcoma, osteoarthritis, ligament rupture, and osteoporosis. Nevertheless, a comprehensive and timely discussion of their applications in musculoskeletal disorders is insufficient. In this review, we emphasize on (1) the main categories and characteristics of mussel foot proteins and their fundamental mechanisms for the spectacular adhesion in mussels; (2) the diverse synthetic methods and modification of various polymers; and (3) the emerging applications of mussel-biomimetic materials, the future perspectives, and challenges, especially in the area of musculoskeletal disorder. We envision that this review will provide a unique and insightful perspective to improve the development of a new generation of mussel biomimetic strategies.

**Keywords:** mussel, biomimetic, musculoskeletal disorder, tissue engineering, biomaterials

## Introduction

Mussels are a common marine organism, of which mussel foot protein (Mfp) is the most representative natural adhesion substance with excellent adhesion, great flexibility, superior biocompatibility, and low toxicity, which has attracted increasing attention. The development of promising mussel biomimetic adhesion materials by mimicking the molecular structure and properties of natural mussel adhesion proteins has become a research hotspot in a spectrum of research fields such as mussel biomimetic,[1] biomedical engineering,[2–4] soft robotics, electronics,[5–7] environmental science,[8–10] energy science,[11,12] and so forth. In particular, a library of mussel-inspired materials, mainly including polydopamine (PDA), PDA-coated materials, and catechol-based polymers,[13–16] have been exploited as essential building blocks to improve musculoskeletal system regeneration.

The musculoskeletal system offers mechanical support to the human body, consisting of hard (bone) and soft tissues (cartilage, muscles, tendons, and ligaments),[17] as shown in Figure 1. When injuries and disorders (especially in the musculoskeletal system) affect the human body's movement, such as osteochondral defects, osteosarcoma, osteoarthritis, ligament rupture, and osteoporosis, it is termed as musculoskeletal disorders (MSDs). MSDs are the second leading cause of disability worldwide, which has posed a huge global burden to public sanitation systems.[18,19] Surgical intervention involving device/biomaterial implantation is currently indispensable to treat MSDs but frequently displayed a short-term

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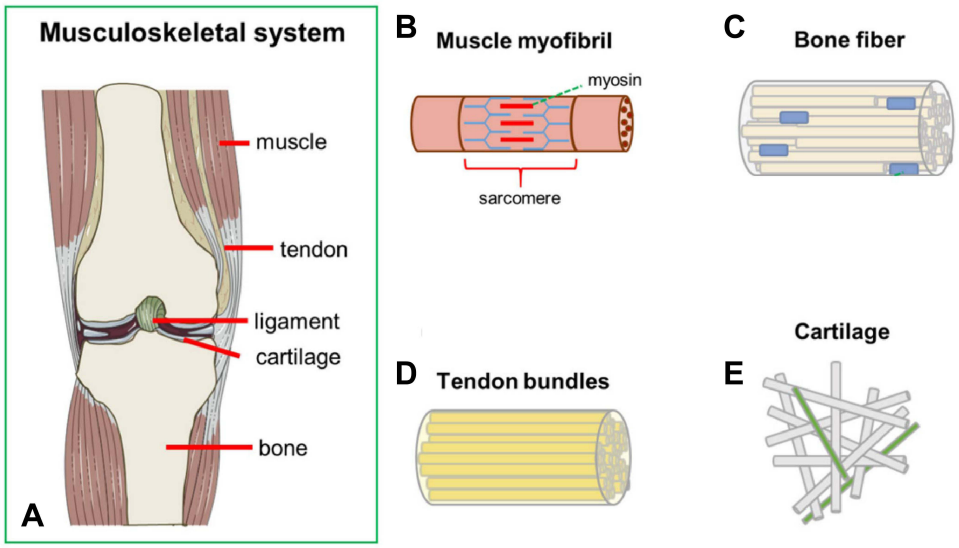


**Figure 1** (**A**) The schematic illustration shows the components of the musculoskeletal system. (**B**) Muscle myofibril is composed of endomysium, perimysium, and epimysium. Cell types: Myocytes. (**C**) Bone fiber is composed of trabecular and cortical bone. Cell types: Osteoclast; osteoblast; osteocyte (**D**) Tendon bundles are composed of endotenon, epitenon, and peritendon. Cell types: Tenocytes (**E**) Cartilage is composed of the superficial, middle, and deep zone. Cell types: Chondrocytes. Reproduced with permission from: Casanellas I, et al. Producing 3D Biomimetic Nanomaterials for Musculoskeletal System Regeneration. Front Bioeng Biotechnol. 2018;6:128. doi: 10.3389/fbioe.2018.00128.[126] Copyright 2018. Casanellas, García-Lizarribar, Lagunas and Samitier.

and temporary therapeutic effect.[20] In recent years, approaches in regenerative tissue engineering have been widely employed to treat interface injuries or fill defects (scaffolds),[21–23] exhibiting promising potential over other strategies that simply apply inert materials to assist the therapy. As one of the critical factors in regenerative tissue engineering, the selection and utilization of biomimetic materials will play a significant role. Over the last two decades, outstanding success has been achieved in mussel-inspired biomaterials, mainly from the design and synthesis of diverse mussel-inspired compounds to the exploitation of potential applications in the field of MSDs. However, hitherto, there have been only two review articles on mussel-inspired biomaterials with a sparse focus on the applications in MSDs,[24,25] to which the tremendous vigor in this emerging field displays striking contrast. Therefore, it is important to shed light on the recent progress and future trend in this field.

Herein, we initially introduce the main categories and characteristics of Mfps, as well as the fundamental mechanisms underpinning the spectacular adhesion in mussels. Subsequently, we elaborate on the diverse synthetic methods and modifications of various polymers. Moreover, the cutting-edge applications in MSDs are then highlighted, including treatments of osteochondral defects, osteosarcoma, osteoarthritis, ligament rupture, and osteoporosis. Additionally, the remaining challenges and future perspectives are discussed in depth, aiming to provide a unique and insightful perspective to improve the development of innovative mussel biomimetic strategies.

## Mussels: From Macro to Micro Scales

### Morphology and Formation Process of Mussel Byssus: The Macro Scale

The key for mussel's survival in coastal habitats is its byssal attachment which offers strong adhesive properties on diverse surfaces. Byssus, a high-performance fibrous material, is produced by mussels to withstand waves and protect themselves against predators.[26] Currently, byssus-mediated adhesion between clustered and individual mussels is thoroughly studied and widely applied to marine fixtures. Mussel foot exhibits vigorous synthetic activity to produce a thread in their ventral groove at once to form a complete byssus (Figure 2A).[27] Notably, due to the mussels' age difference, the byssus production rates range from 30 sec to 8 min (young mussels are relatively faster).[28] The thread formation is similar to liquid transfer in microfluidic devices: three main gland reservoirs, phenol, collagen, and accessory glands, quantitatively fill their contents into the ventral groove (Figure 2A).[29,30] These glands are responsible for synthesizing and storing molecular components that adhere to plaques, collagen cores, and the cuticle. Secreted

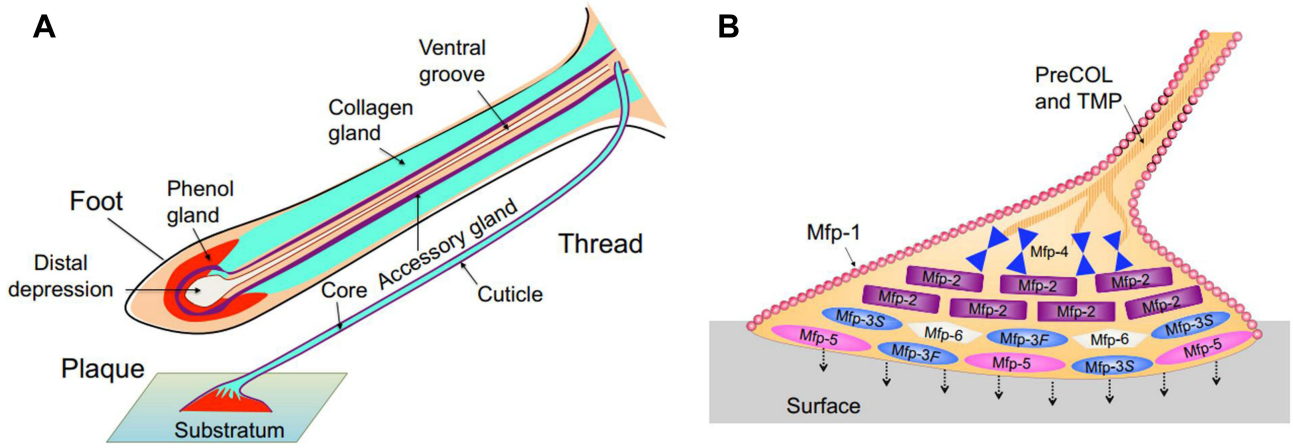


**Figure 2** (**A**) Schematic illustration shows the holistic appearance of the mussel and the structure of the mussel's foot and substratum. The formation of byssus is similar to the reminiscent of reaction injection molding, which is explained in the text in detail. (**B**) The schematic illustration shows the location of different types of Mfps and other known proteins in the plaque and distal thread. Adapted with permission from: Waite, J.H. Mussel adhesion - essential footwork. J Exp Biol. 2017;220(Pt 4):517–530. doi: 10.1242/jeb.134056.[32] Copyright 2017. The Company of Biologists Ltd.

proteins produced by these glands are injected from the top to the bottom of the ventral groove to form the initial byssus. The ventral groove on the mussel foot is the mold for the byssus generation, while its distal depression is the location for plaque formation (Figure 2A).

Finally, just before the thread departs from the groove, the assembled structure is coated with an approximately 5-μm-thick layer of the cuticle from accessory glands, so the new thread is used for load bearing purpose. Although the characteristics of byssus have not been completely elaborated, there are more than 20 known protein components, most of which display a highly localized distribution (Figure 2B). Mussel foot proteins, especially Mfp2, 3, 4, and 5, originate from the phenol gland, and distribute mainly in the plaque, playing a significant role in its adhesive functions.

## The Representative Categories of Mfps: The Micro Scale

Mfps are divided into six subcategories according to their distribution in the foot,[28,31–33] as shown in 2B and Table 1, of which Mfp3 and Mfp5 are the most studied. They are located at the bottom of the foot plaque, acting as the main proteins for intense bio-adhesion.[34,35] Mfp3 is the smallest but most polymorphic Mfp identified thus far, with 30–35 variants, which are classified into fast-type Mfp3f and slow-type Mfp3s based on the electrophoresis rate. Mfp5 contains positively charged amino acid residues (approximately 20 mol% positive residues) and a phosphoserine residue with an extra-frontal negative charge (approximately 10 mol% negative residues). Other Mfps also play a significant role in mussel foot filament morphology maintenance and mussel adhesion. Mfp1 is composed of 80 tandem repeat decapeptides, which mainly protect the foot silk core and foot silk plaque against certain hard

**Table 1** Biochemical Comparison of the Mfps in the Adhesive Plaques and Threads Regarding Mass, pI, DOPA Content, Localization of Proteins in the Mussel Byssus, Sequence, and Metal Binding

| Protein | Mass (kDa) | PI | DOPA (mol%) | Location | Sequence Motifs (Number of Repeats) | Metal Binding | Ref. |
|---|---|---|---|---|---|---|---|
| Mfp1 | 108 | 8~10 | 15 | Proximal and distal thread | Decapeptide (75) | $Fe^{3+}$ | [38,46,127–130] |
| Mfp2 | 45 | 10 | 2~3 | Plaque core | EGF domain (11) | $Fe^{3+}/Ca^{2+}$ | [129,131] |
| Mfp3f | 6 | 8~10 | 20 | Plaque interface | DOPA -Arg/Lys (6) | — | [43,132–135] |
| Mfp3s | 6 | 7~8 | 5~10 | Plaque interface | Gly- DOPA (8) | — | [135–137] |
| Mfp4 | 70 | 8.4 | 5 | Plaque core | Dodecapeptide (4) | $Cu^{2+}$ | [135,138] |
| Mfp5 | 10 | 9.8 | 30 | Plaque interface | DOPA -Lys (16) | $Mg^{2+}/Ca^{2+}$ | [46,139–142] |
| Mfp6 | 12 | 9.3 | <5 | Plaque interface | Cys (3), Tyr-Lys (5) | — | [143] |

**Abbreviations**: pI, Isoelectric point; EGF, epidermal growth factor.

substances such as rocks. Mfp4 mainly mediates the morphological transformation of the byssus from the thread to the plaque.[36,37] Mfp2 is located among various Mfps (Mfp4, Mfp3, Mfp5, and Mfp6), serving as the most abundant adhesion protein in the plaque, accounting for approximately 25% of the total proteins. The Mfp2 contains 6~7 mol% Cys residues, and includes 11 tandem epidermal growth factor-like motifs, which are intramolecularly connected by the disulfide bonds, suggesting a high stability improvement in the byssus.[36,38,39] Mfp6 locate at the bottom of the mussel foot plaque together with Mfp3 and Mfp5 in which Cys content is even higher (11 mol%). It can form a Cys-DOPA cross-linking bond with Mfp3 and Mfp5 to avoid 3,4-dihydroxyphenylalanine (DOPA) oxidation, and the sulfhydryl group in Cys is employed to reduce dopaquinone to DOPA to enhance the adhesion of Mfp3 and Mfp5 to the substrate.[36]

### The Mechanism Behind the Mystery of Mussel Adhesion

Mfp is able to anchor to various organic or inorganic surfaces without quick tearing, mainly due to its intense adhesion and cohesion.[40–42] In the adhesion process, DOPA in Mfp can attach to different substrates through various interactions, including hydrogen bond, metal-catechol coordination bond, π-π/π- cation interaction, and others with the schematic illustrations and details shown in Table 2.[39] Taking the interaction between DOPA and $TiO_2$ surface as an example, catechol on the DOPA side chain can form hydrogen bonds with the $TiO_2$ surface, and the connection between catechol and $O^{2-}$ is transformed from a bidentate hydrogen bond to a bidentate coordination bond with $Ti^{4+}$ accompanied by pH increase.[43] In terms of cohesion, the attraction between neighboring parts is a manifestation of the molecular forces. For instance, the interaction between DOPA in Mfp and cation -π in Lys greatly promotes Mfp cohesion so that it lays a solid foundation for the superior adhesion of mussels.[36] In addition, other aromatic amino acid residues (eg, Phe and Tyr residues) also contribute to the intense cation -π interactions by providing cohesion. Based on the adhesion mechanisms discussed above, it is expected that diverse innovative materials and devices would be proposed by mimicking the Mfp structure and properties.

## Mussel Biomimetic Materials: From Structure Design to Synthetic Optimization

Currently, there are mainly three ways to obtain mussel-biomimetic adhesive materials: first, extract and isolate adhesive proteins directly from marine mussel byssus, which is the most convenient, straightforward, and effective approach.[44] However, it is unsuitable for large-scale sample preparation due to the limited mussel size, minimal adhesive protein secretion, the complex extraction process, extremely low yield, and high cost. Second, gene engineering is utilized to recombine relevant genes into Escherichia coli or yeast for specific protein expression.[45–47] Compared with the first method, the yield of adhesive protein is remarkably increased, but the adhesion performance fails to meet the standard of natural mussels.[33] Third, a synthetic polymer with a catechol adhesive group is used to mimic the adhesion property of marine mussels by incorporating DOPA into the side chain or the end of the polymer skeleton.[48] It is the most studied and widely used strategy to create mussel-biomimetic adhesive materials. According to the diverse polymer skeletons, it is typically divided into three subtypes that are described as follows.

### Catechol-Adhesion Polypeptide Copolymer

Mfp5 is one of the most important proteins in the byssal adhesive plaque of the mussel,[49] which mainly consists of glycine, L-lysine, and DOPA.[50] The high ratio of DOPA (~30 mol %) and its specific distribution (near the plaque−substrate interface) indicate its significance in the bio-adhesion.[51] By mimicking the composition of Mfp5, mussel-biomimetic adhesive copolymers (polypeptide) are synthesized via chemoenzymatic, solution-based, ring-opening polymerization, introducing catechol group into the side chain of the polypeptide backbone. For instance, in chemoenzymatic approach, L-tyrosine and L-lysine residues are initially linked into polypeptides, and L-tyrosine is subsequently converted into DOPA catalyzed by tyrosinase, which enhances the polymerization degree of the copolymer and increases the yield, thus improving the synthesis efficiency of the peptide-based materials. Notably, as a scaffold surface-coating material, these materials are broadly applied in the medical field.[52–54] From the end of the twentieth century, the solution-based synthesis

**Table 2** The Fundamental Interaction Mechanisms of Mussel-Inspired Chemistry Including the Interaction Types, Classifications, the Essence, the Factors Influencing the Strength and the Existence or Application

| Types | Classification | Essence | Strength Influencing Factors | Existence/Application | Ref. |
|---|---|---|---|---|---|
| Non-covalent interactions | Hydrogen bonding | Weak interaction | DOPA; hydroxyl groups | Surface modification | [144–147] |
| | Hydrophobic interactions | Attractive force driven by entropy | Aromatic moieties; hydrophobic residues | Mfps; synthesized mussel-inspired materials | [148–150] |
| | Cation–π interactions | Electrostatic force | Aromatic moieties; hydroxyl groups; cation species ($NH_3R^+$, $NH_4^+$, $K^+$) | Paired catechol and amine moieties | [151–155] |
| | π–π interactions | Non-covalent interaction | Hydroxyl groups | π-electron-rich aromatic heterocycles | [156–159] |
| Covalent bonding | Metal coordination | Chemical interaction | — | DOPA–$Fe^{2+}$ complex; DOPA–$Ca^{2+}$ complex | [93,160] |
| | Boronate–catechol complexation | Covalent bonding | DOPA oxidation; pH | Regulation of mussel-inspired adhesion | [161] |
| | Schiff base reaction/ Michael addition | Nucleophilic addition reaction/ electron transfer | — | Amine- and thiol- molecules; cross-linked catechol and polyethyleneimine | [162,163] |
| | Coupling reaction | — | — | Catechol groups; dopamine | [164] |


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method was invented to prepare DOPA-containing poly amino acids,[55,56] including various PDA and polypeptide polymers. The synthetic polymers are water-soluble, cross-linked by tyrosinase, presenting high adhesion properties similar to mussels. Moreover, Wang et al[57] synthesized DOPA- and lysine-containing polypeptides by ring-opening polymerization in which ring monomers are connected to each other to form linear polymers, and introduced iron ions into the system to optimize the bond strength and water resistance, suggesting high functional tunability.

## Catechol – Polysaccharide Polymer

Polysaccharide is a kind of natural polymer consisting of aldose or ketose connected by glycosidic bonds, and widely exists in natural animals and plants, which is safe, non-toxic, easy to extract and water-soluble.[58] The -OH and $NH_2$ functional groups in the polysaccharide act as the active center to dominate the crosslinking reaction. The catechol was grafted to those groups to generate a cross-linked three-dimensional network, facilitating large-scale biomaterial formation and application.[59]

### Self-Polymerization of Dopamine and Its Derivatives

PDA is mainly extracted from mussel adhesion protein and displays strong wet adhesion to the matrix.[60] It can be traced back to 2007 when Messersmith et al found that the self-polymerization of dopamine was able to create a thin and surface-adherent PDA film on the surface of various inorganic and organic materials.[42] Since then, many other researchers have followed this strategy to modify polysaccharides in various fields including tissue engineering and wound healing, to name only a few, which endows the polysaccharides with diverse promising functions, such as excellent adhesion, oxidation resistance, antibacterial ability, high reactivity, chelation, corrosion resistance, biocompatibility, and so forth.[61,62]

### Grafting Dopamine to Polysaccharides

In addition to self-polymerization, a myriad of polysaccharides enable dopamine graft through covalent bonds based on existing functional groups, including -$NH_2$, -COOH, -OH, and -SH. These groups were grafted with catechol to generate a three-dimensional cross-linked network. Notably, there are mainly three methods to graft specific groups to prepare catechol polysaccharides, including chemical, electrochemical, and enzymatic methods, among which electrochemical methods are the most commonly applied.[63] Taking chitosan as an example, the methods of integrating catechol to the main chain of chitosan are classified according to the following three strategies: (1) Using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and N-hydroxy succinimide (NHS) to chemically build amide bonds. Hu et al[64] employed quaternary ammonium chitosan grafted with tyrosine as raw material, which was grafted with EDC and NHS, and then introduced tyrosine to enhance the mechanical properties. This strategy endows chitosan with high adaptation to complicated vascular structures, indicating great potential as a promising scaffold material. (2) Direct oxidative coupling of catechol to amino groups in chitosan. Zhang et al[65] applied $NaIO_4$ to oxidize catechol to quinone and reduced the byproduct production via the Michael addition reaction or Schiff base reaction accompanied by the cross-linking agent decrease. (3) Incorporating the amino group with an aldehyde group at one end to produce chitosan-catechol. It is arduous to chemically link the primary amine with polyethylene glycol catechol as the classic reaction between the primary amine and carboxyl group is main to form amide bonds. To overcome this challenge, Hong et al[66] chose to produce secondary amines through aldehyde chemistry, which is termed as reductive amination reaction.

## Catechol-Adhesion Protein Polymer

The coupling location of polymers such as polyethylene glycol, polyethyleneimine, polyacrylamide (PAM), and polystyrene are mainly in the side chain or the end of the skeleton, which are linked to catechol-contained polymers to create new materials with superior stability, selectivity, and reactivity. For example, Or Berger et al[67] introduced peptide units as side chains on brush polymer, rather than being linearly arrayed in natural proteins. Intriguingly, it demonstrated obviously high adhesion after modification even over natural proteins. Lu et al[13,68] prepared a mussel-like, super stretched, self-healing hydrogel that held a two-dimensional space of nano clay inside. DOPA was intercalated into the clay to facilitate PDA production during polymerization, which was oxidized in a narrow space that would reduce the oxidation rate, thus maintaining long-term adhesion performance. Subsequently, acrylamide, initiator, and cross-linking

agents were added to PDA clay, which remarkably enhance the toughness and tensile properties of the hydrogel, improving the following adhesion and drug delivery.

## The Applications of Mussel Biomimetic Materials in MSDs

Induced by injuries, tumors, and many other pathological factors, MSDs remain a great challenge in clinical practice. Nowadays, the application of biomaterials especially adhesives has provided a potential strategy for MSDs as a result of its biocompatibility, degradability, and particularly strong adhesion ability.[69] However, the biofunction of regular materials such as the invasive inert materials that only serve as a support for broken bones is usually limited, which cannot meet demands in specific application scenarios, such as immunomodulation and antibiosis, to name only a few. Moreover, the direct extraction of relatively pure adhesives from living organisms is also a challenge. Thus, this section mainly focuses on physical/chemical modification of mussel-based biomimetic materials and their applications in MSDs as shown in Figure 3, including osteochondral defects, osteosarcoma, osteoarthritis, ligament rupture, and osteoporosis. The research stages and treatment outcomes of these biomimetic mussel materials are included in Table 3.

### Osteochondral Defect Treatment

Osteochondral defects, involving the fracture of both articular cartilage and subchondral bone, are a tremendous challenge to repair due to the complex hierarchical architecture of the osteochondral tissue.[70] Nevertheless, it is proved that mussel-based biomimetic materials could play a significant role as surface coatings, adhesives, hydrogels, etc., in osteochondral regeneration.[71–73] Gan et al[74] intercalated ODMA into GelMA hydrogel to enhance toughness and resilience, which was verified to serve as a growth-factor-free support for cartilage regeneration. Given that the applied materials slack specific flexibility to improve adaptation to the human body environment, subtle advancements are needed to improve shape alteration and duration. More encouragingly, Han et al[75] designed a mussel-inspired PDA-CS-PAM hydrogel through PDA integrating strategy, which enhanced the tissue repairing potential of various materials even

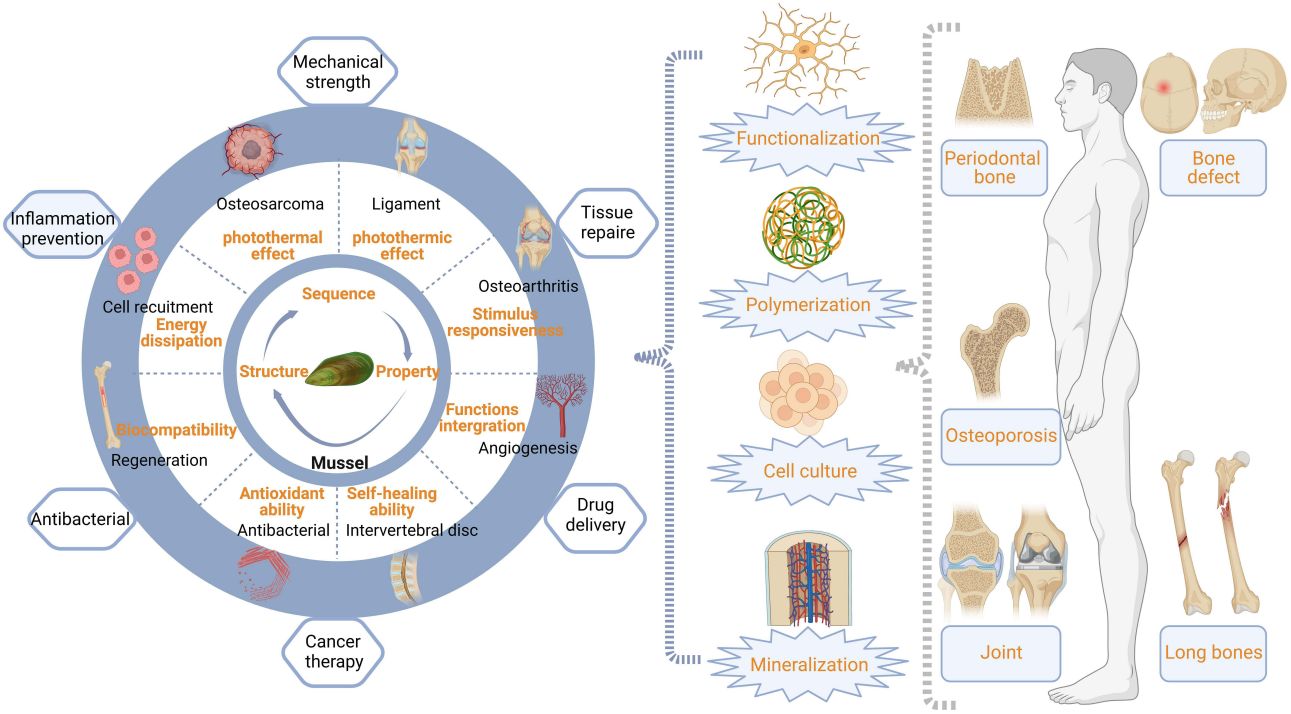


**Figure 3** Schematic illustration of bioinspired adhesive formulations based on biomimetic strategies. (Created with BioRender.com).

**Table 3** Diverse Applications of Mussel Biomimetic Materials Used in MSDs Along with Research Stages and Outcomes

| Disease Type | Materials | Research Stages | Outcomes | Ref. |
|---|---|---|---|---|
| Osteochondral defects | PDA−CS−PAM hydrogel | In vivo | Cartilage regeneration | [75] |
| | ODMA–GelMA hydrogel | In vivo | Cartilage regeneration | [74] |
| | Bilayer hydrogel | In vivo and in vitro | Cartilage and subchondral bone regeneration | [77] |
| | PGS-PCL-PDA membrane | In vivo | Craniofacial bone regeneration | [79] |
| | tHA−BFP/QK nanoparticles | In vivo | Periodontal bone regeneration | [86] |
| | tHA/PCL composite nanofibers | In vivo | Osteogenesis | [87] |
| | AD/CS/RSF/EXO hydrogel | In vivo | Superficial cartilage regeneration | [165] |
| Osteosarcoma | 3D Ca-P/PDA nanolayer scaffold | In vivo and in vitro | Cancer therapy; bone regeneration | [92] |
| | pZIF-8/ pHA-G scaffold | In vivo | Anti-tumor therapy; bone regeneration | [96] |
| Osteoarthritis | CM-SIN GelMA hydrogel | In vivo | Cartilage matrix degradation retarded | [103] |
| | GelMA@DMA-MPC | In vivo | Osteoarthritis inhibited | [104] |
| Ligament rupture | APA/PDA-PET | In vivo and in vitro | Osseointegration for ligament reconstruction | [117] |
| | CMWAs | In vivo and in vitro | Anterior cruciate ligament reconstruction | [118] |
| Osteoporosis | PEM-1 | In vivo | Osteoporosis prevention | [122] |

**Abbreviations**: PDA−CS−PAM, polydopamine-chondroitin sulfate-polyacrylamide; ODMA, oligomers of dopamine methacrylate; GelMA, Gelatin methacryloyl; PGS, poly (glycerol sebacate); PCL, polycaprolactone; tHA, PDA-templated nanohydroxyapatite; BFP-1, bone-forming peptide-1; QK, growth factor-mimicking peptide; AD, alginate-dopamine; CS, chondroitin sulfate; RSF, regenerated silk fibroin; EXO, exosomes; pZIF-8, PDA- hybridized nanosized zeolitic imidazolate framework-8; pHA-G scaffold, PDA-decorated hydroxyapatite nanoparticles on the surfaces of the 3D-printed gelatin-based scaffold; CM-SIN, sinomenium encapsulated by chitosan microspheres; DMA-MPC, a self-adhesive polymer synthesized through free radical copolymerization; APA/PDA-PET, apatite/PDA hybridized-polyethylene terephthalate; CMWAs, Citrate-based mussel-inspired whitlockite composite adhesives; PEM-1, YPRKDETGAERT peptide.

that were cell-repellent. The PDA and CS self-assembled into a cartilage-specific PDA−CS complex, which was incorporated into the hydrogel and then covalently cross-linked to the PAM network, imparting the hydrogel with high toughness and resilience. In addition, the photo-crosslinked hydrogel scaffold designed by Ju et al[76] can accelerate cartilage regeneration via recruiting endogenous TGF-β1 and inducing the differentiation of mesenchymal stem cells into chondrocytes, which provided a potential system for clinical cartilage tissue repair.

Compared with homogenized single-layer hydrogels that only partially restore the osteochondral tissue's original function, researchers from Lu's team[77] developed a mussel-inspired bilayer hydrogel that was efficient in osteochondral defect repair. A one-pot method was ingeniously employed to simultaneously generate upper and lower layers.[78] The upper layer acted as a cartilage repair layer, while the lower one served as a subchondral bone regeneration layer. Notably, traditional 2D or 3D structures were rarely responsible for osteochondral microenvironment reconstruction, thus scientists have already invented a 4D membrane for to enhance bone repair via both structure and microenvironment adjustment. Based on the adhesion of mussels, Liu et al[79] optimized the microstructure of PDA-anchored grafts, and successfully prepared porous elastomer scaffolds by mixing the thermoplastic PGS with an appropriate amount of PCL to obtain 3D printed additives with desirable mechanical strength and degradation rate (Figure 4). Additionally, the immunomodulatory effect of PDA coatings is significantly enhanced by the proper design of channels and intrinsic pores in the microstructures. This 4D-PDA membrane, taking PDA as an ideal polymer membrane surface modifier, has been widely used to improve the interfacial environment between the implant and host owing to its excellent biocompatibility, mild synthesis conditions, and effective drug delivery capability.[72]

In recent years, mussel-based biomimetic strategies have been applied to treat periodontal bone defects caused by periodontitis, occlusal trauma, and congenital malformations.[80–82] Diverse biomaterials, including nanoparticles[83,84] and nanohydrogels,[85] have been developed to treat periodontal bone defects. For instance, Xiang et al[86] designed a multifunctional nanohydroxyapatite assisted by tHA and modified the surface with BFP-1 and vascular endothelial QK via a single step of catechol chemistry, which was confirmed to regulate periodontal ligament stem cell activity. Moreover, Gao et al[87] applied a similar strategy to prepare tHA/PCL with the purpose of cytocompatibility and osteogenesis enhancement, and their results indicated that the degradation rate and pore size would dominate the clinical

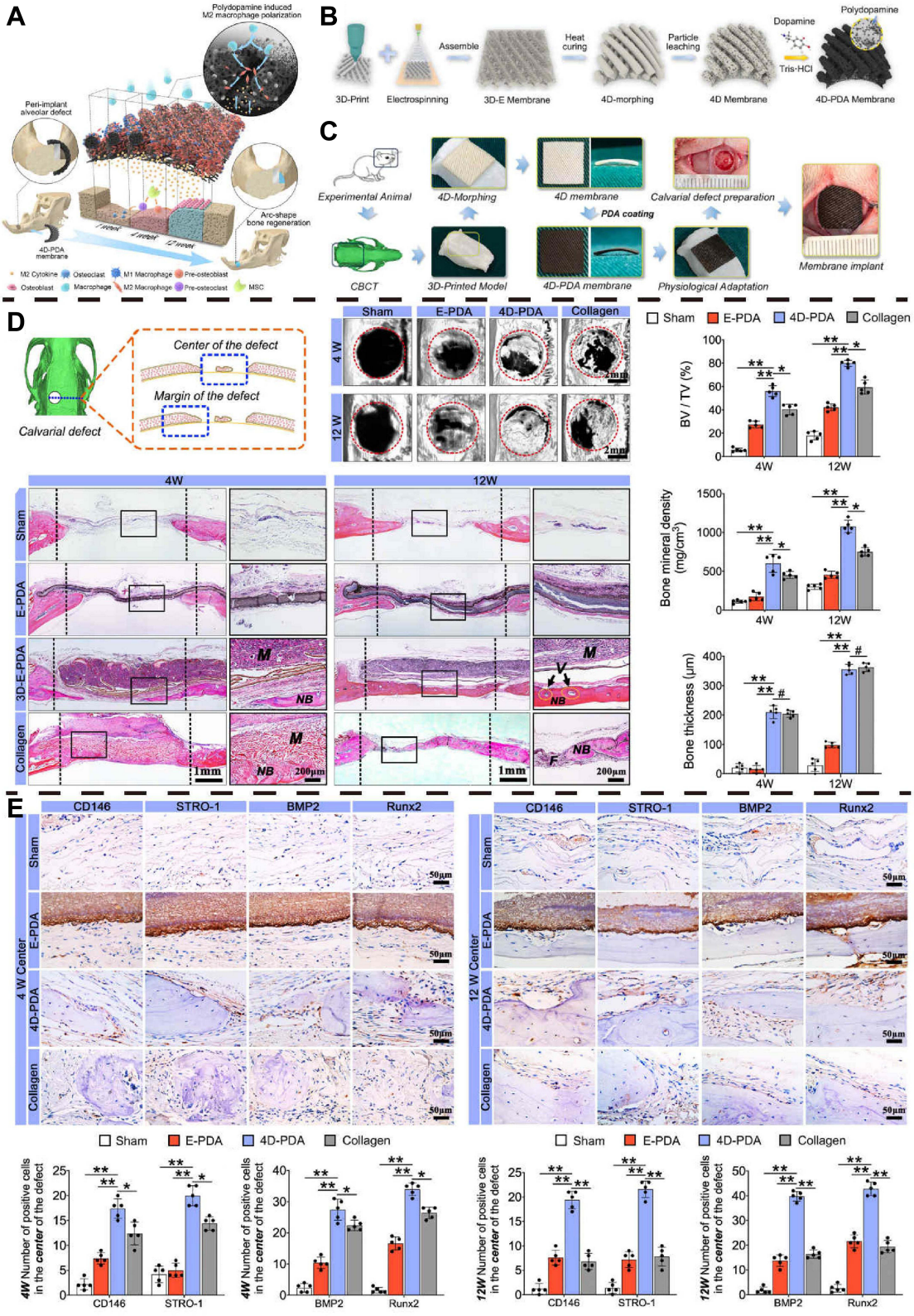


**Figure 4** 4D-PDA membrane enhances bone regeneration by recruiting BMSCs and accelerating osteogenesis. (**A**) The schematic diagram illustrates that M2 macrophages mediated by the elastic membrane of 4D stratified channel are enriched in the early and persistent period above the bone defect, which contributes to the formation of bone regeneration with specific shape. (**B**) Schematic illustration of 4D membrane fabrication process. (**C**) Schematic illustration of the application process of 4D-PDA membrane in rat calvarial bone defects. (**D**) H&E staining of the regenerated bone and the quantitative analysis at 4 and 12 weeks after implantation. (**E**) Immunohistochemistry staining of CD146, STRO-1, Runx2, and BMP2 in the defect areas and the semi-quantification of positive cells in the staining at 4 and 12 weeks. Reprinted from *Biomaterials*, Volume 276, Liu X, Chen W, Shao B, et al, Mussel patterned with 4D biodegrading elastomer durably recruits regenerative macrophages to promote regeneration of craniofacial bone, Pages No. 120998, Copyright (2021), with permission from Elsevier.[79] #p>0.05, *p<0.05 and **p<0.01.

application of the materials. Generally speaking, from 2D, 3D to 4D structures, mussel-based biomimetic materials present the advantages of toughness, resilience, and superior biocompatibility, suggesting a superior therapeutic effect on bone defects.

## Osteosarcoma Treatment

Osteosarcoma (OS), frequently resulting in tumor-induced bone loss, is a prevailing disease that engenders extreme pain to patients.[88,89] Currently, surgical resection, radiotherapy, and chemotherapy, as well as specific combinations of these treatments, are widely employed to eradicate osteosarcoma.[89,90] However, healthy bone tissues are usually removed during the operation, which may lead to nonunion and fracture of the bone after surgery. Therefore, it is necessary to develop a bioactive implant to fill the defect, replace the removed bone tissue, and improve bone function recovery.[91] To address these issues, Ma et al[92] produced a 3D-printed bioceramic scaffold with a uniform self-assembled Ca-P/PDA nanolayer, which effectively induced tumor cell death and inhibited tumor growth. Notably, in previous works,[93–95] a series of 3D scaffolds with bone regeneration and tumor inhibition capability was achieved by using photothermal agents, such as magnesium powder, Cu-TCPP nanosheets, or MoS2 nanosheets. In striking contrast, Jiang et al[96] fabricated a mussel-inspired 3D-printed implant that released anticancer drugs and growth factors for enhanced anticancer treatment and osteogenesis over others through a PDA-assisted layer-by-layer assembly strategy. pZIF-8 (a nanoMOF), induced by mussels and pHA nanoparticles, was alternately assembled on the surface of 3D-printed gelatin scaffolds, manifesting that the mussel-biomimetic nanoMOF acted as a valid drug carrier and nano-building block in surface modification. Therefore, mussel nanostructures via 3D printing display promising potential in tumor therapy and bone regeneration, especially for tumor-induced bone tissue defects.

## Osteoarthritis Treatment

Osteoarthritis (OA) is a common joint disease accompanied by pain and disability that arouses tremendous psychological and physiological stress in patients while posing a great burden on socioeconomic costs.[97] Currently, tissue engineering, with the potential to overcome the defects of existing clinical treatment methods (disintegration of cartilage), has been well studied with great clinical potential.[98] Moreover, mussel-based biomimetic materials are tailored to provide instructive cues for OA, which is an indispensable in tissue engineering.[99] Mussels, containing a large amount of 12% glycosaminoglycans, are a high source of a rare, potent form of omega-3 fatty acids (called eicosatetraenoic acid (ETA)), indicating the intense anti-inflammatory properties through inhibiting the enzyme-related pathways (cyclooxygenase and lipoxygenase-based paths) from producing inflammatory factors.[100] Interestingly, antioxidants in green-lipped mussels were proven to mediate the free radicals, which were the typical indicators in inflamed joints.[101,102] Therefore, a variety of injectable materials have been developed to fill the joint cavity, capable of inflammatory factor elimination especially in the liquid form. For instance, Chen's[103] study demonstrated that GelMA hydrogel implantation combined with CM-SIN injection was a promising strategy for inducing autophagy and ameliorating osteoarthritis cartilage degradation. Furthermore, inspired by catecholamines, Han et al[104] developed an injectable hydrogel microsphere for OA treatment by utilizing the lubrication characteristics of mussel cartilage through hydration lubrication of zwitterionic phosphobile base groups in the copolymer to synergistically reduce the coefficient of friction (Figure 5), which could also improve drug (diclofenac sodium) unloading via adjusting the proportion of dense coating on the surface of the microspheres.

In addition, Bai et al[105] designed a mussel-inspired peptide bound to the Ti-based implant, remarkably increasing the bone-implant contact area and improving osteogenesis. Besides, Xiao et al[106] presented a surface engineering strategy to create functional surfaces by introducing dibenzylcyclooctyne (DBCO)-modified bioactive molecules on diverse surfaces. Similarly, Mou et al[107] applied an analogous strategy to build a surface with DBCO-modified antimicrobial peptide (DBCO-AMP), indicating great potential for thrombosis and infection treatments. Collectively, no matter it is an injection system, an implant, or a surface coating, mussel-based materials exhibited promising potential osteoarthritis treatment by offering omega-3, unsaturated fatty acids and other anti-inflammatory substances.

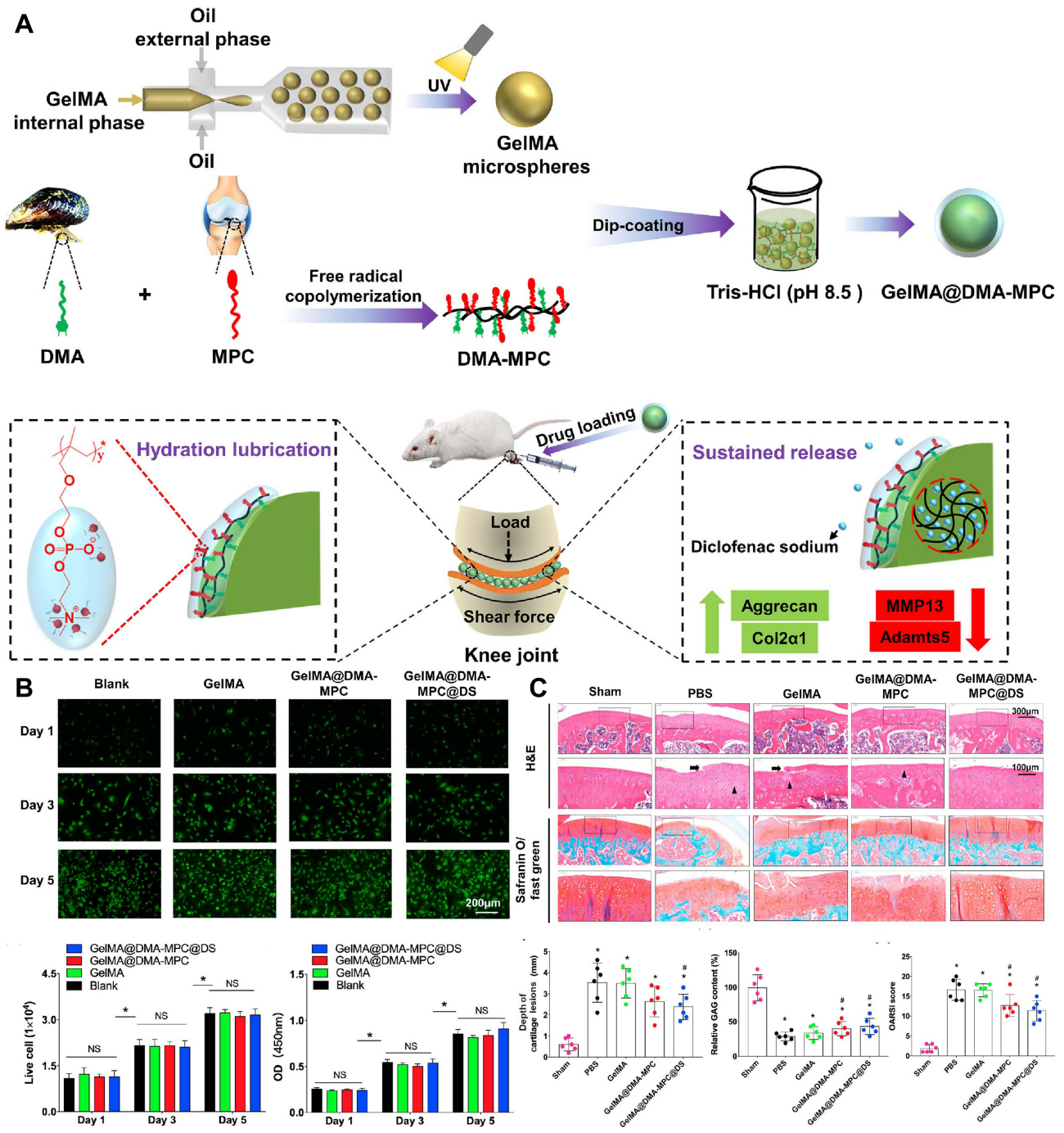


**Figure 5** Mussel biomimetic material applied in osteoarthritis. (**A**) Schematic illustration of preparation process and application of GelMA@DMA-MPC. (**B**) In vitro cell viability and cell cytotoxicity of three different GelMA microspheres. (**C**) The results from H&E staining and Safranin O-fast green staining verified that functionalized GelMA microspheres can delay the progression of osteoarthritis in vivo. Reproduced with permission from: Han, Y., et al. Biomimetic injectable hydrogel microspheres with enhanced lubrication and controllable drug release for the treatment of osteoarthritis. Bioact Mater. 2021;6(10):3596–3607. doi: 10.1016/j.bioactmat.2021.03.022.[104] Copyright 2021, Elsevier. https://creativecommons.org/licenses/by-nc-nd/4.0/. #Represent P < 0.05 by comparing with the control and blank groups, respectively.
**Abbreviation**: NS, no significance.

## Ligament Rupture Treatment

Ligament rupture mainly occurs in sports or an accident, requiring reconstruction of the injured ligament.[108–110] To avoid complications resulting from autologous or allogeneic tendon transplantation, artificial ligament transplantation is an appropriate selection for human ligament reconstruction,[111–113] which allows the patient to quickly recover and restore to

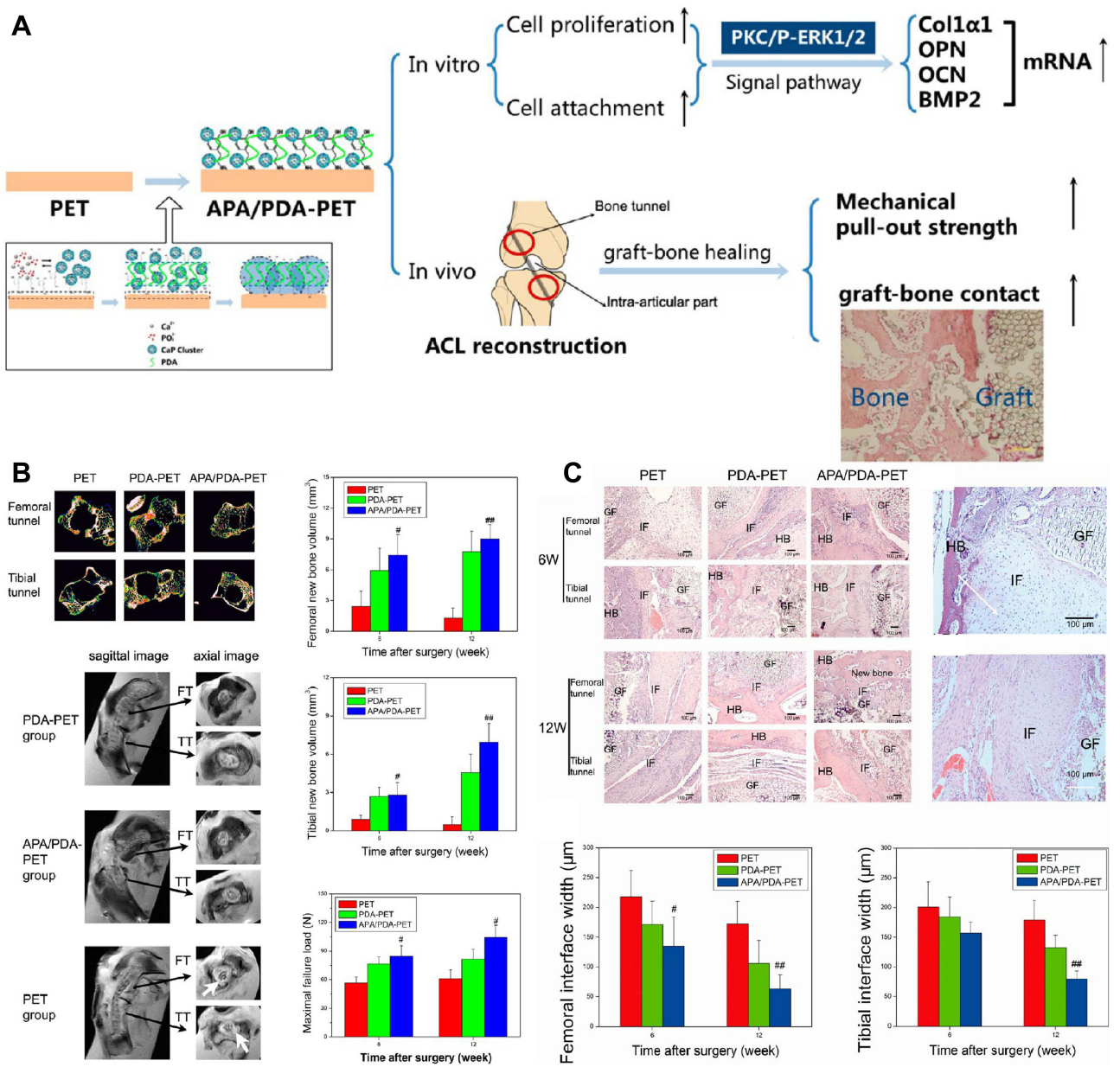


**Figure 6** Mussel-based biomimetic material applied in ligament rupture. (**A**) Schematic illustration for mussel-inspired APA/PDA–PET grafts in vitro and in vivo experimental results. (**B**) The micro-CT images of the bone tunnels and the quantitative analysis in vivo promote the osseointegration of APA/PDA–PET Grafts. (**C**) The histological results of HE staining and Masson trichrome staining with quantitative analysis verified the results. Reprinted with permission from: Li H, Chen S, Chen J, et al. Mussel-inspired artificial grafts for functional ligament reconstruction. ACS Appl Mater Interfaces. 2015;7(27):14708–14719. doi:10.1021/acsami.5b05109.[117] Copyright 2015, American Chemical Society. < 0.01), #p < 0.05.

normal moving status due to the excellent strength and toughness of artificial ligaments.[114] Compared to natural ligaments, the bionic structure was challenged to induce the anterior cruciate ligament on the original interface.[115,116] Inspired by mussels, Li et al[117] successfully prepared biomimetic calcium phosphate APA/PDA-PET grafts with an active interface (Figure 6). Based on the synergistic effect of polyamines and apatite, the in vivo osseointegration during ligament reconstruction would be significantly improved, upon osteogenesis stimulation. However, direct graft-bone contact was not effective in reducing stress concentration at the interface compared to natural tendon-bone implantation. Fortunately, Yuan et al[118] developed the CMWAs to enable the osteotendon interface reconstruction in the anterior cruciate ligament (ACL). In summary, mussel-based biomaterials could be well adjusted to fit the bone and joint interface by providing a superior adhesion to achieve joint ligament reconstruction.

## Osteoporosis Treatment

Osteoporosis is a global bone tissue disease that poses a heavy financial burden on the world's health system, and the number of affected patients is expected to double in the next 20 years.[119–121] Especially in older women, the risk and prevalence of the disease are significantly higher due to quicker bone tissue degradation, which may increase bone fragility and fracture.[120] Facing this problem, PME-1 extracted from mussel byssus protein has been applied to promote the proliferation and differentiation of osteoblasts, indicating preventing effect against osteoporosis.[122] In the future, unraveling the structure and function of this protein may help doctors and scientists become more potential candidates.

# Conclusions and Outlook

Within the framework of this paper, we discussed the classification and adhesion mechanism of Mfp. To deepen the understanding of mussel-based biomimetic strategies in MSDs, we first introduced the different molecular structures related to mussel components, such as polysaccharides and peptides, and then discussed the existing synthesis methods. Finally, the specific applications, and the advantages and disadvantages of mussel biomimetic strategies in different diseases were included. It is believed that biomimetic adhesion materials have made outstanding achievements in scientific research and clinical applications, especially in the field of MSD treatment.[123–125] Despite remarkable success in this area, there are still several challenges that need to be addressed. First, compared with natural methods, biomimetic approaches are not able to effectively regulate the oxidation reaction of DOPA or catechol in an alkaline environment. Second, considering the Mfp and other excellent adhesion properties of the material for multivariate equipping, the modification of free groups on the membrane surface can make biomaterials acquire new functions to make up for the deficiency of existing materials, research and development of the new type of high adhesion polymers is a future development trend of the bionic adhesion material. In this emerging area, it is obvious that geometric properties of mussel-based materials play a significant role in regulating their properties. Powered by the advantages of hierarchical architectures, advanced processing techniques such as 3D/4D printing offer great opportunities to organize mussel-based biomimetic materials to multiscale hierarchical structures, possibly extending their biomedical applications.

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# Disclosure

The authors declare no conflicts of interest in this work.

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