Research Progress on Construction and Biomedical Applications of Function-ion-modified Biomineralized Materials

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***Abstract*—Natural hard tissues, including bone and tooth enamel, are not simple inorganic substances, but organic-inorganic composites formed via inorganic mineral deposition regulated by biological macromolecules. Biomineralization technology imitates such biological processes. Under mild reaction conditions, mineral phases grow on organic templates, yielding repair materials whose chemical compositions and microstructures closely resemble native biological tissues. Incorporating functional ions such as magnesium, strontium, copper, zinc, and silver into biomineralized materials can endow these substrates with multiple biological properties: osteogenic capacity, pro-angiogenic effect, antibacterial activity, and immunomodulatory potential. These modified materials therefore hold great application prospects in tissue repair and regenerative medicine. Centered on function-ion-modified biomineralized materials, this paper reviews existing research from fundamental theories, fabrication strategies, performance-related mechanisms, and biomedical application perspectives. Current technical bottlenecks and prospective research directions are also discussed.**

***Keywords*—biomimetic mineralization, organic-inorganic composite biomaterials, tissue regeneration, controllable ion release, biomedical application**

I. Introduction

A. Research Background and Significance

Human hard tissues such as bone and tooth enamel are typical organic-inorganic composite biomaterials. In bone tissue, hydroxyapatite inorganic crystals do not accumulate randomly. Guided by organic macromolecules represented by collagen, these crystals arrange in an oriented fashion, constructing tissues balancing mechanical strength and fracture toughness. Clinical cases of bone defects and tissue injuries triggered by trauma, tumor lesions, and tissue degeneration keep rising, which creates strong clinical demands for regenerative repair biomaterials. Pure inorganic biomaterials generally suffer from high brittleness. Despite favorable biocompatibility, they are difficult to process into components with sophisticated geometries. Conversely, purely organic biomaterials cannot satisfy mechanical requirements for hard-tissue repair and usually exhibit limited osteogenic bioactivity. For these reasons, biomaterials that mimic both chemical constituents and microstructures of native tissues have become a hot research topic within regenerative medicine.

Functional ions play a non-negligible role in biomineralized systems. Elements including magnesium, strontium, and silicon intrinsically participate in bone mineralization and metabolic activities inside human bodies. Metal ions such as copper, zinc, and silver exert antibacterial and immunoregulatory effects. Doping these ions into biomineralized substrates maintains the structural biomimicry of natural tissues, while introducing extra biofunctions including osteogenesis, angiogenesis, and bacterial inhibition. Realizing the integration of structural bionics and biological performance, this material-design strategy provides alternative solutions for bone defect repair, soft-tissue regeneration and implant surface modification, bearing both scientific research value and clinical practical significance.

B. Domestic and Overseas Research Status

Functional-ion-doped biomaterials represent an active research branch in the field of biomaterials. Taking bioactive glasses and hydroxyapatite as two mainstream substrate systems, numerous studies have investigated how magnesium, strontium, copper, zinc, silver, and other ions reshape material microstructures and functional performances. Existing review articles have systematically summarized biological responses of cells and bone tissues induced by ion dissolution products derived from bioactive glasses, and highlighted that identical ions produce divergent biological outcomes at dissimilar concentrations [1]. Other published reviews have illustrated how ion substitution rearranges glass network frameworks, further tuning osteogenic, antibacterial, and pro-angiogenic behaviors [2]. For hydroxyapatite substrates, multiple metallic ions are adopted to offset inherent drawbacks of pure hydroxyapatite, namely insufficient mechanical

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performance and lack of antibacterial capability [3].

In recent years, multi-ion synergistic modification and mesoporous drug-loading techniques have emerged as new research focuses. Researchers introduce multiple functional ions into a single matrix or load therapeutic agents via mesoporous channels, aiming to achieve combined biological functions [4, 5]. Overall, relevant investigations have evolved from simple single-ion doping for compositional adjustment toward systematic material design integrating multi-ion synergy, structural biomimicry, and controllable ion release.

II. Fundamental Theories of Biomimetic Mineralization and Functional Ion Modification

A. Basic Principles of Native Biological Biomineralization

Biomineralization describes biological phenomena where inorganic crystals nucleate and develop specific microstructures under modulation of organic macromolecules. Representative examples cover hydroxyapatite crystals growing along collagen fibrils in bone, as well as calcium-carbonate-based skeletons of shells and corals. A core scientific question for biomimetic-mineralization research lies in how organic matrices mediate inorganic mineral formation. It is widely acknowledged that organic macromolecules enrich ambient inorganic ions and reduce energy barriers for crystal nucleation. Through molecular recognition effects, these macromolecules control crystal growth orientations and morphologies.

The Polymer-Induced Liquid-Precursor (PILP) hypothesis proposed by Gower and co-workers indicates that biomineralization does not always follow classical one-step crystallization pathways. Amorphous precursor phases form in advance and transform into well-ordered crystalline structures in subsequent procedures [6]. Chinese scholars have published review papers sorting out theoretical advances of classical and non-classical nucleation theories, alongside applications of biomimetic mineralization in bone tissue engineering and enamel restoration [7]. The amorphous-precursor-oriented theoretical framework supplies theoretical support for fabricating complex organic-inorganic composites under mild experimental conditions [8].

B. Biological Functions and Differences of Typical Biologically Active Ions

Various functional ions undertake distinct physiological tasks in vivo. Material designers need to fully understand the biochemical characteristics of each ion before practical application. Magnesium, strontium, and silicon belong to osteogenic ions: they participate in bone metabolism and facilitate osteoblast differentiation. Copper ions simultaneously drive angiogenesis, promote osteogenic differentiation, and suppress bacterial proliferation. Zinc, silver, and cerium ions mainly contribute to antibacterial and immunomodulatory effects. Specifically, zinc assists bone regeneration; silver serves as a broad-spectrum antibacterial agent; cerium combines antibacterial and anti-inflammatory capacities.

Notably, biological behaviors of functional ions exhibit obvious dose-dependence. Excessively high ion concentrations trigger cytotoxic responses instead of producing beneficial effects [1, 2]. Functional discrepancies among these ions remind researchers to select ion species and determine doping dosages according to practical repair requirements of target tissues.

C. Theoretical Basis for Regulating Mineral Crystal Growth via Functional Ion Modification

Functional ions incorporate into mineral crystals through lattice-site substitution. For hydroxyapatite matrices, magnesium, strontium, and zinc partially replace calcium sites within crystal lattices; silicate and carbonate groups substitute phosphate or hydroxide sites. Such substitution events alter lattice parameters, crystallinity, and surface morphologies of crystals, hence modifying material degradation rates and biological activities [9]. For bioactive glass systems, ion substitution rearranges glass network architectures and chemical bonding states, which further governs in-vitro hydroxyapatite deposition kinetics and ion-release profiles [2]. In essence, functional ion modification tunes macroscopic physicochemical properties and biological performances of biomineralized materials by adjusting chemical compositions and crystal structures.

D. Regulatory Mechanisms and Influencing Factors for Controllable Ion Release

Only when released at appropriate rates and maintained at effective local concentrations can doped functional ions exert expected biological effects, which raises demands for controllable ion release. Multiple factors, including material composition, crystal configuration, pore dimension, and surface decoration, jointly determine ion-dissolution speeds. Mesoporous materials feature large specific surface areas and tunable pore channels, which makes them suitable carriers for ions and therapeutic drugs. Ion-release kinetics can be adjusted by optimizing pore geometries and surface modification protocols [5, 10]. Moreover, physiological microenvironments inside organisms (pH value, endogenous enzymes, and so forth) also interfere with ion-dissolution behaviors. Ideal material design targets sustainable ion output at therapeutic concentrations throughout tissue-repair processes. This strategy avoids acute cytotoxicity caused by burst ion release and excessively high local ion concentration.

III. Construction Strategies and Preparation Technologies for Function-Ion-Modified Biomineralized Materials

A. Fabrication of Biomineralized Materials Modified with Single Functional Ion

Single-ion modification represents the most fundamental material-construction route. Researchers introduce one specific functional ion into material substrates to realize a single biological function. For

bioactive glass preparation, single-ion lattice substitution can be achieved by adding strontium-, zinc-, copper-, or silver-containing raw materials into basic glass formulations [2]. For calcium-phosphate-based materials such as hydroxyapatite, wet precipitation, hydrothermal treatment, and high-temperature sintering are frequently adopted to incorporate metal ions into crystal lattices. Crystal structures and ion-release performances are adjusted by changing doping proportions [3, 9]. This preparation approach possesses clear underlying mechanisms and simple operating procedures. Nevertheless, it merely delivers one type of biofunction and hardly meets complicated multi-functional clinical repair requirements.

B. Fabrication of Composite Biomineralized Materials via Multi-Ion Synergistic Modification

Multi-ion synergistic modification introduces more than one functional ion into identical material matrices to realize combined biological functions. Ye and colleagues constructed hydroxyapatite nanorod arrays on implant surfaces by combining micro-arc oxidation and hydrothermal post-treatment. During hydrothermal reactions, strontium, magnesium, zinc, silicate, and carbonate ions were co-introduced to mimic ionic microenvironments of native bone matrix from both compositional and structural perspectives [4]. Cell assays and animal-model evaluations demonstrated that such modified coatings manipulated macrophage polarization and steered immune responses toward bone-repair-favorable directions. These coatings improved bone-implant osseointegration and alleviated implant aseptic loosening induced by wear particles. Compared with single-ion-doped counterparts, multi-ion-modified materials better reconstruct ionic microenvironments of native tissues and achieve dual bionics of composition and structure. Meanwhile, material-design complexity increases correspondingly [3].

C. Preparation Systems for Organic-Inorganic Composite Biomineralized Materials

Organic-inorganic composite characteristics constitute a prominent feature of biomineralized materials. Guided by organic templates, inorganic minerals deposit in-situ. The resulting composites combine flexibility originating from organic phases as well as mechanical strength and bioactivity inherited from inorganic phases. Biomimetic mineralization enables in-situ deposition of calcium carbonate and calcium phosphate onto organic substrates such as polymers and collagen, forming tight interfacial bonding between organic and inorganic domains [6, 7]. Under mild conditions, biomimetic mineralization techniques can also immobilize bioactive molecules.

Luo *et al*. [11] investigated enzyme immobilization inside calcium-carbonate-based nanocarriers using Catalase (CAT) as the research object. Urease catalyzed urea hydrolysis to continuously generate carbonate ions. Calcium carbonate was deposited around enzyme molecules under physiological-like ambient conditions. Nanocarrier formation and enzyme immobilization proceeded simultaneously to synthesize CAT@$CaCO_3$ nanocomposites. Experimental measurements revealed that the average particle size of nanocarriers reached 187 nm, enzyme loading capacity was 322 mg/g, and enzyme-activity retention rate stood at 84 %. After immobilization, pH tolerance, thermal stability, and anti-proteolytic degradation performance of catalase were significantly enhanced. 76 % of initial enzyme activity remained after 5-day room-temperature storage, and 80 % catalytic activity was preserved after ten cyclic catalytic runs. These experimental data prove that biomimetic mineralization accomplishes high-efficiency biomacromolecule immobilization under mild conditions, offering feasible routes for fabricating organic-inorganic functional nanocarriers. Besides, bioactive-glass-polymer hybrid materials keep developing. Compound bioactive glasses with polymer matrices preserve biological activity while improving material moldability and mechanical properties [12].

D. Performance Comparison and Trade-offs of Different Preparation Techniques

Each construction strategy has its own strengths and limitations. Wet precipitation and sol-gel methods feature simple operations and mild reaction conditions, yet precise control over crystallinity and crystal morphology remains challenging. Hydrothermal synthesis generates highly crystalline products with controllable morphologies, but high-temperature and high-pressure reaction conditions consume substantial energy. Electrospinning fabricates oriented fibrous scaffolds, whereas the whole manufacturing workflow is relatively cumbersome.

TABLE I. ADVANTAGES AND DISADVANTAGES OF DIFFERENT MATERIAL CONSTRUCTION STRATEGIES

Construction strategy	Advantages	Disadvantages
Single-ion doping (wet precipitation / sol-gel)	Simple manufacturing process, mild conditions, relatively well-understood mechanisms	Single biological function, limited control over crystallinity and morphology
Hydrothermal treatment	High crystallinity, controllable crystal morphology	Requirement for high temperature and high pressure, high energy consumption
Multi-ion synergistic doping	Diversified biological functions, high degree of structural biomimicry	Complicated design, difficult interpretation of synergistic mechanisms
Mesoporous structure for ion / drug loading	High loading capacity, tunable release behaviors	Hard-to-balance ion release and cytotoxic risks
Organic-inorganic composite / electrospinning	Biomimetic microstructure, capability for complex-scaffold fabrication	Relatively complicated preparation workflow

Multi-ion modification and mesoporous drug-loading integrate multiple biological functions at the cost of elevated fabrication difficulty and production expenses [3, 13]. Advantages and drawbacks of mainstream construction approaches are summarized in Table I.

IV. Performance-Regulation and Action Mechanisms of Function-Ion-Modified Biomineralized Materials

A. Mechanisms for Physicochemical-Performance Modulation

Introducing functional ions changes multiple physicochemical indices of materials. Lattice-site substitution modifies lattice parameters and crystallinity, which directly determines material degradation rates. Doped ions also adjust mechanical strength, thermal stability, and surface physicochemical features. For hydroxyapatite substrates, appropriate ion-doping dosages raise material density and mechanical properties. Nevertheless, excessive doping triggers severe lattice distortion and reduces mechanical strength [3]. For bioactive glass systems, ion substitution rearranges internal glass-network structures and modulates material biological activity [2]. Accurate regulation of physicochemical performances relies on rational selection of ion species and precise control over doping content.

B. Mechanisms for Biological-Function Regulation

Functional ions exert biological effects mainly after dissolving and diffusing into cellular microenvironments. Magnesium and strontium activate intracellular signaling pathways to promote osteoblast differentiation and bone formation. Copper stimulates proliferation of vascular endothelial cells and facilitates angiogenesis. Silver and zinc damage bacterial structures or interfere with microbial metabolic pathways to realize antibacterial effects.

Recent research advances indicate that functional ions can reshape phenotypes of immune-related cells such as macrophages, indirectly modulating tissue-repair outcomes, namely immuno-osteogenic effects [1, 4]. Research perspectives have expanded from direct ion-cell interactions to immune-microenvironment regulation, supplying more material-design ideas.

C. Dose-effect Relationships among Ion Species, Doping Content and Release Modes

Biological outcomes of functional ions are tightly associated with ion concentration and release patterns. For one specific ion, concentrations below effective thresholds produce negligible biological effects; favorable tissue-repair behaviors appear within optimal concentration windows; cytotoxic damage occurs once concentrations exceed safety limits, reflecting obvious dose-effect relationships. Taking copper ions as an example: proper copper concentrations promote angiogenesis and osteogenesis, while over-high copper dosages induce cytotoxicity [1, 2]. During material development, researchers need to strike a balance among ion-release rate, effective therapeutic concentration, and cytotoxic risks. Adjusting doping ratios, optimizing ion-release kinetics, or adopting mesoporous carriers can maintain ion concentrations within safe and effective ranges [5].

D. Analysis of Synergistic and Antagonistic Mechanisms in Multi-Ion Systems

When multiple ions coexist in one substrate, synergistic promotion or antagonistic offset phenomena may emerge. Reasonable ion combinations realize functional complementation. For instance, matching osteogenic ions with pro-angiogenic ions satisfies dual requirements of new-bone formation and vascular ingrowth during bone-repair procedures [4]. However, multi-ion systems may also generate antagonistic consequences originating from ion-site competition or superimposed cytotoxicity. Further investigations focusing on ion-ion interactions are required to optimize ion combinations and proportional distributions [3].

V. Biomedical Research on Function-Ion-Modified Biomineralized Materials

A. Applications in Bone-Tissue Repair and Regeneration

Bone-defect repair constitutes the most widely-explored application scenario for function-ion-modified biomineralized materials. Benefiting from favorable bioactivity and bone-binding capacity, bioactive glasses and hydroxyapatite have already been extensively applied for bone-repair purposes [1, 12]. Incorporating strontium, magnesium, copper, and other ions enhances osteogenic induction performance and bone-implant integration effects.

Ren and coworkers synthesized Strontium-doped Hydroxyapatite (Sr-HA) microspheres via hydrothermal methods. Osteoporotic rat models were adopted to compare biological influences of Sr-HA and pure hydroxyapatite on Bone Marrow mesenchymal Stem Cells (BMSCs) [14]. Experimental results demonstrated that Sr-HA exhibited a stronger capacity for driving BMSC osteogenic differentiation, and more neo-bone tissue formed in vivo. Follow-up mechanistic studies revealed that such biological effects were associated with activation of the CaSR-JAK2/STAT3 signaling pathway. This research confirms that strontium doping improves osteogenic performance under harsh repair conditions such as osteoporosis. Apart from material matrices themselves, combining ion-modification technology with scaffold structural design and growth-factor delivery transforms ion-functionalized materials from simple bone fillers into tissue-engineering scaffolds that actively guide tissue-regeneration processes [15].

B. Soft-Tissue Repair and Wound Regeneration Applications

Apart from hard-tissue restoration, these modified materials show application potential in soft-tissue repair and wound healing. Tendon-bone interfaces represent gradient transitional regions between soft tissues and hard tissues. Conventional repair strategies hardly reconstruct native gradient structures. Researchers fabricate biomimetic scaffolds with bilayer oriented-random architectures for ordered tendon-bone interface regeneration, and electrospinning acts as the primary manufacturing technique for such scaffolds [16].

Biomimetic mineralized materials serve as immobilization carriers for bioactive molecules such as enzymes. These carriers retain enzyme bioactivity while improving enzyme environmental stability for biomedical and biocatalytic applications. Research work conducted by Luo *et al*. [11] (Section III.C) provides a typical case. In stomatological research, Ren *et al.* [17] constructed amino-modified Mesoporous Bioactive Glass (aMBG) carriers loaded with Polyacrylate-stabilized Amorphous Calcium Phosphate (PAA-ACP) to treat enamel white-spot lesions. Artificially-induced enamel-white-spot samples were used for remineralization evaluation, with Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) groups set as experimental controls. PAA-ACP@aMBG groups achieved significantly higher surface microhardness and color-recovery ratios compared with negative controls, and also achieved deeper remineralization depth than other experimental groups. These findings verify that mesoporous bioactive glasses work as ion-release carriers, promoting deep-layer enamel remineralization through sustained calcium-phosphorus component release.

C. Antibacterial Biomedical Coatings and Implant-Surface Modification

Post-surgical implant infection remains a challenging clinical complication. Constructing antibacterial coatings on implant surfaces effectively lowers infection probabilities. Silver, copper, and zinc ions have intrinsic antibacterial properties. Incorporating these ions into bioactive-glass or hydroxyapatite coatings endows implants with antibacterial functions without sacrificing osseointegration performance [2, 3].

Wu *et al.* [18] fabricated Copper-containing Mesoporous Bioactive Glass (Cu-MBG) scaffolds, which possessed hundreds-micrometer-scale macropores and well-ordered mesopores with an average diameter of approximately 5 nm. Scaffold substrates and corresponding ion-extracted solutions both up-regulated hypoxia-inducible factor and vascular-endothelial-growth-factor expression in human bone-marrow stromal cells, increased osteogenic-related gene expression, and maintained long-term antibacterial potency. In short, copper-doped mesoporous scaffolds integrate pro-angiogenic, osteogenic-stimulating, and antibacterial functions within a single material system. Furthermore, multi-ion-doped hydroxyapatite coatings mentioned above modulate immune responses, suppress inflammation and bone resorption triggered by wear particles, and reduce risks of implant aseptic loosening [4]. Collectively, realizing simultaneous antibacterial and osteogenic effects represents a critical developmental direction for implant-surface modification.

D. Existing Bottlenecks for Clinical Biomedical Translation

Despite promising application prospects, multiple obstacles still block clinical transformation of such biomaterials. First of all, molecular-level mechanisms behind ion-mediated biological behaviors remain incompletely clarified. Especially for multi-ion synergistic effects and immunomodulatory performances, most available studies merely report experimental phenomena without thorough mechanistic interpretation [3]. Secondly, precise balancing among ion-release rates, effective therapeutic concentrations, and cytotoxic risks is difficult to accomplish, and systematic dose-effect-relationship frameworks have not been well-established [5]. Thirdly, most existing experimental data originate from in-vitro cell tests and animal-model assessments. Long-term in-vivo material performances and clinical-transformation-relevant data are still insufficient [1].

VI. Conclusions and Future Perspectives

Function-ion-modified biomineralized materials introduce diverse functional ions into mineralized matrices. While preserving structural-biomimicry advantages, these materials gain multiple biofunctions including osteogenesis, angiogenesis, antibacterial capacity, and immune regulation. Satisfactory application prospects have been demonstrated in bone-defect repair, soft-tissue regeneration, and implant-surface modification. This paper sorts out research advances covering fundamental theories, material-construction routes, performance-action mechanisms, and biomedical-application cases. Relevant investigations have evolved from simple single-ion doping toward systematic material design combining multi-ion synergy, structural bionics and controllable ion release.

Nevertheless, unsolved scientific challenges still exist. Biological mechanisms of functional ions are not fully interpreted; multi-ion matching rules and comprehensive dose-effect relationships await further exploration; long-term in-vivo performances and clinical-transformation datasets are inadequate. Follow-up research should deepen mechanistic understanding of ion-triggered biological responses, systematically optimize multi-ion matching schemes and ion-release behaviors. These efforts will push forward clinical-practice transformation of biomineralized materials within regenerative-medicine domains.

Conflict of Interest

The author declares no conflict of interest.

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