Biomineralization: From Material Tactics to Biological Strategy

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Biomineralization is an important tactic by which biological organisms produce hierarchically structured minerals with marvellous functions. Biomineralization studies typically focus on the mediation function of organic matrices on inorganic minerals, which helps scientists to design and synthesize bioinspired functional materials. However, the presence of inorganic minerals may also alter the native behaviours of organic matrices and even biological organisms. This progress report discusses the latest achievements relating to biomineralization mechanisms, the manufacturing of biomimetic materials and relevant applications in biological and biomedical fields. In particular, biomineralized vaccines and algae with improved thermostability and photosynthesis, respectively, demonstrate that biomineralization is a strategy for organism evolution via the rational design of organism-material complexes. The successful modification of biological systems using materials is based on the regulatory effect of inorganic materials on organic organisms, which is another aspect of biomineralization control. Unlike previous studies, this study integrates materials and biological science to achieve a more comprehensive view of the mechanisms and applications of biomineralization.

1. Introduction

In nature, living organisms can produce hierarchically structured materials with outstanding structures and functions, including nacre, teeth, skeletons, and shells.[1] Importantly, many biologically generated organic matrices play key roles in regulating the formation processes of inorganic materials, including nucleation,[2] crystal growth,[3] phase transformation,[4] orientation and particle assembly.[5] Currently, several biomimetic strategies based on biomineralization are used to repair tooth[6] and prevent pathological diseases.[7] Many biomimetic artificial materials have been synthesized for biological applications, such as silk fibroin and artificial extracellular matrices for hepatic tissue engineering applications.[8] Furthermore, abundant biomimetic materials have been created via biomineralization-inspired processes to mimic natural biological processes.[1b,9] These approaches highlight the regulatory effects of organic matrices on mineralization, which is key to biomineralization control.[10]

Biomineralization also promotes organism evolution via the rational design of organism-material complexes.[11] Biomineralization is regarded as an effective tactic for organisms to become biologically "stealthy" and protect themselves from external damage.[12] For example, the cells of eggs and diatoms receive extra protection from their biomineralized shells.[13] The materials in organisms have important functions;[14] for example, intracellular crystals of magnetite (Fe_3S_4 or Fe_3O_4) can act as magnetic sensors, and otoliths can serve as gravity receivers.[15] Recent studies have demonstrated that people can improve organisms by using functional materials via biomimetic pathways.[16] Typical achievements in this newly emerging research area include biomineralized vaccines, which are "thermostable vaccines that do not need refrigeration", and biomineralized algae for the biological photosynthesis of hydrogen.[16d] These results represent the achievement of successful biological functional improvements using materials.[17] Furthermore, biomimetic mineralization can be attained via material-based modifications or even the evolution of organisms in laboratories, extending the current understanding and applications of biomineralization.[18]

In this progress report, the latest developments relating to the study of biomineralization and the understanding of this phenomenon are summarized and discussed. First, section 2 addresses the current understanding of the biomineralization-inspired crystallization mechanism. Then, the applications of biomimetic mineralization, including collagen mineralization, hard tissue repair and nacre-like material design, are presented in section 3. Section 4 discusses the synthetic tactics utilized for applications of biomineralization to biological organic-inorganic complexes, such as photosynthetic cell improvement, vaccine improvement, and cancer therapy. Finally, a conclusion relating to the progress in interesting and important fields is given in section 5.

In this progress report, we learn from nature that organic matrices can regulate inorganic crystallization, including the

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processes of nucleation, growth, phase transformation, orientation and assembly. To date, scientists have synthesized and biomimetically designed various advanced bioinspired materials with tuneable morphologies, well-organized structures and improved properties based upon the established biomineralization mechanisms. These achievements have great importance in biomedical applications, including collagen mineralization for hard tissue repair. Furthermore, biomineralization not only produces materials but also protects living organisms in nature. Accordingly, biomimetic mineralization represents another tactic that scientists can utilize to generate biological units with functional materials.[1g] Biomineralization studies have progressed from organically controlled material crystallization to material-based biological improvements, opening up a new avenue for related research and applications. However, although we have made great progress regarding crystallization mechanisms and their applications, many processes that remain unknown and/or controversial.[13b]

2. Approach to the Biomineralization Mechanism

Because of the optimal characteristics of biominerals, an in-depth understanding of biomineralization is of great importance for the biomimetic design and synthesis of functional materials.[16c] The classical crystallization pathway,[19] which was established based on atom/ion addition,[19e,f] has been widely applied in general crystallization studies of natural and synthetic systems. Although we have many examples of successful classical pathway models,[16e] numerous lines of evidence challenge the theory of monomer-by-monomer addition. Currently, crystallization via the addition or transformation of particles is recognized as a common phenomenon in colloidal nanocrystals[16f] and semiconductor systems. However, most investigations of the crystallization process are based on biomineralization because these crystallization routes are frequently applied by natural organisms.[18c] Biomineralization studies, even in the inorganic field,[19c] have been well documented[19d] and are currently addressing important challenges. Many aspects of crystal formation cannot be adequately explained by the traditional pathway. For example, the involvement of amorphous precursors,[20] such as amorphous calcium carbonate[21] (ACC) and amorphous calcium phosphate[22] (ACP), in biomineralization has been widely investigated. It has been suggested that the varied and complicated morphologies of natural biomineral crystals[23] can only be explained by using non-classical crystallization pathways (NCCPs), which utilize multi-ion complexes,[24] clusters,[25] and even nanoparticles[26] as biomaterialization building units instead of atoms/ions.

2.1. The NCCPs

2.1.1. Amorphous Precursors

Amorphous precursors are commonly observed in biological crystallization, especially in calcium carbonates[27] ($CaCO_3$) and calcium phosphates[22] (CaP), in which amorphous phases are first deposited and then turned into crystalline phases at mineralization fronts.[28] Scientists have successfully synthesized relatively stable amorphous phases and subjected them to in-depth examinations. Several methods of amorphous stabilization are available. For example, ACC can be obtained in finite-reservoir environments, including picoliter droplets,[29] confinement[30] and liposomes,[31] and some additives, such as magnesium ions[32] and proteins,[33] can be used to control the amorphous phase. Solvent selection is another facile strategy for stabilizing ACC via interfacial energy control.[34]

Many experiments have confirmed that the amorphous phase is critically responsible for the crystallization process. In situ transmission electron microscopy (TEM) enables

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observation of the formation and transformation of ACC in real time.[35] The multi-nucleation pathways of $CaCO_3$ can be simultaneously observed, and the direct transformation from ACC to aragonite or vaterite can be captured. By using cryogenic TEM (cryoTEM), the nucleation and growth of the amorphous precursor phase can be directly observed in biomimetic systems used for calcite[36] and apatite[37] formation. Furthermore, phase-transformation-based crystallization has been suggested to involve water loss from the amorphous phase, but the mechanism remains unclear.[38]

The crystallization of ACC occurs as follows: more metastable hydrated ACC → less metastable hydrated ACC → anhydrous ACC → biogenic anhydrous ACC → vaterite → aragonite → calcite.[39] Proto-vateritic ACC and proto-calcitic ACC have been reported to be intermediate states during this transformation.[40] Analogously, the crystallization of ACP to hydroxyapatite (HAP) proceeds via an energy-reduction process involving intermediate phases,[41] such as tricalcium phosphate and octacalcium phosphate (OCP). The involvement of an amorphous phase in mineralization has several advantages, especially in the polymorphological control of the resulting crystals. Single-crystal calcite nanowires can be readily produced from ACC by the capillary effect.[42] This pathway is similar to the formation of sea urchin larval spicule,[27] in which an amorphous $CaCO_3$ microlens array with advanced optical characteristic revealed that the amorphous precursor phase efficiently produces well-designed structures and functions.[43]

The amorphous precursor phase pathway is one of the most important crystallization pathways in biomineralization. The relevant mechanism and its role have been examined previously.[43b] Although the traditional pathway is suitable for biomineralization, the amorphous phase remains a hot research area with regard to the biomineralization mechanism because of the relative lack of phase transformation interpretations and because it is key for understanding the early biomineralization phenomena that exist in nature. Nonetheless, not all biological crystallization pathways follow the amorphous precursor route, and a more general and speculative understanding of the function of the amorphous phase in the biomineral crystallization process is needed.[28c] Indeed, the new concepts of liquid precursor phase[44] and pre-nucleation clusters (PNCs)[40a] provide a much more in-depth understanding of biomineral formation and challenge the classical crystallization theory.

2.1.2. Liquid Precursor Phase

The liquid-like character of the amorphous precursor phase in biomineralization has been discussed for a long time, and a biomimetically produced polymer-induced liquid phase (PILP) was first reported in 2000.[44] However, this liquid-phase mineral precursor must be stabilized by high-molecular organics, similar to biomineralization processes involving a high content of organic components.[45] Theoretically, computer simulations suggest a liquid-liquid coexistence area in the aqueous $CaCO_3$ solution.[46] Thus, through liquid-liquid separation, the formation of a dense liquid phase in supersaturated $CaCO_3$ solution can be predicted. A liquid precursor phase is also discussed in the framework of spinodal decomposition.[47] The behaviour of a liquid amorphous phase can be described by classical colloid chemistry:[33] electrostatic and depletion stabilization and de-emulsification by depletion destabilization. Subsequently, the coalescence of nanoscale droplets leads to the formation of the precursor amorphous phase. However, investigating the physicochemical characteristics of liquid-like precursor phases, including PILP, is difficult because of their unstable structures and short lifetimes.

2.1.3. PNCs

A few studies have investigated the early stage of nucleation. Stable solute species have been observed in solution crystallization systems of $CaCO_3$[40a] and CaP[37] and are called PNCs. In the $CaCO_3$ system, the existence of PNCs has been confirmed by incorporating potentiometric titrations and analytical ultracentrifugation.[40a] The notion of ACC polyamorphism suggests that the nucleation can proceed from PNCs[48] and subsequently lead to less or more stable ACC.[40a] Thus, PNCs actually exhibit distinct proto-crystalline structures.[40b] Since there is no phase boundary between PNCs and the solution, PNC aggregation becomes spontaneous, requiring no driving force.[49] Most non-aggregated nanoscopic entities are solutes and represent PNCs. However, some aggregates with interfacial surfaces must be considered as nanophases rather than PNCs.[50] Whether the ACC polyamorphism depends upon the presence of PNCs remains unknown.

In the CaP system, the role of small clusters as building units in ACP has been reported.[37] Chemical analysis revealed that these clusters are $Ca_9(PO_4)_6$ and have a mean diameter of 0.87 ± 0.2 nm. In biomimetic mineralization studies, a composition of $Ca_9(PO_4)_6$ during the early nucleation stage has been observed under Langmuir monolayers. However, another recent report suggests that PNCs of CaP are ion-association complexes containing a single calcium ion and three coordinated hydrogen phosphate ions (i.e., $[Ca(HPO_4)_3]^{4-}$). These small clusters are too highly thermodynamically unstable to be nucleated via aggregation.[24] Currently, PNC studies are challenging the well-established understanding of crystallization. It should be noted that studies of PNCs frequently rely on the quenching technique; thus, some important information is still missed.[24,37,40a] Intense debates regarding which species can be treated as PNCs and their lifetimes are still ongoing.

2.1.4. The Aggregation-Based Pathway

Aggregation-based crystal growth is now considered to be an important pathway for biomineralization.[51] The final crystal structure diffracts as a single crystal, suggesting that the main building units align during growth.[52] When coalescence and alignment occur simultaneously, this process is usually called oriented attachment (OA).[51b,52b,c] OA is one of the most essential mechanisms of controlling crystal growth in the nanoscale regime. Evidence for OA was first reported by Penn and Banfield in 1998.[53] High-resolution TEM (HR-TEM) investigations indicate that OA causes the oriented arrangement of

nanoparticles. The driving force of OA is the reduction of the surface energy by the fusion of high-energy facets,[54] which is easy to achieve through effective collisions in a crystallographic manner or particle rotation.[26,55] The OA of calcite nanocrystals has been demonstrated in an aqueous system at room temperature.[56] Single-crystalline calcite rod formation can be enhanced by improving the particle collision frequency.[57]

Recent in situ liquid-cell TEM reveals that the OA of nanoparticles is accompanied by a sudden jump to contact only after obtaining a perfect lattice match by continuous interaction and rotation.[26] This process is driven by a strong short-range force that works within 1 nm. Here, coulomb interactions are most likely the origin of this force. The recent advancements in in situ TEM, our understanding of the alignment process and attachment mechanism has been further improved.[58] However, the inherent complexity of OA makes studying the detailed growth mechanism difficult.[55,59]

Molecular calculations have demonstrated that the thermodynamic driving force for OA is derived from the interatomic/coulombic interactions of the attaching nanoparticles and the surface energy of the attaching surface.[60] OA growth orientations can be predicted based on energy calculations, and the result can provide clues regarding how OA produces crystals with lower symmetry.[59c] As a new and important strategy, OA is significant for guiding the design of materials with desired features.[61] The use of nanoparticles as building blocks in the OA growth strategy is an effective way to obtain novel materials with collective properties if the attachment process can be performed in a controlled manner, as can sometimes be achieved using additives.[61d,e] Although some work has been performed from the perspective of energy[61b] or the driving force,[61c] a detailed mechanistic understanding of OA remains lacking. For example, the function and evolution of organic additives in inorganic crystal formation by particle attachment remain largely unknown.[61f] Moreover, experimental and theoretical blueprints that can quantitatively describe attachment-driven crystallization have not yet been well established, and a real-time, in situ investigation is key to an in-depth understanding of OA.

The achievement of crystalline alignment between building units and large dimensions may be difficult.[62] Significant evidence indicates that particular polymorphs are involved in the course of crystal growth, eliminating the possibility of the co-alignment of building blocks.[36,63] Furthermore, random attachment (RA) has also been observed in the course of crystal growth.[64] Recent work from Zhejiang University reveals that RA during aggregation-based growth initially produces a non-oriented growth front.[65] The chaotic surface layer further drives the subsequent evolution of the orientation by surface stress and leads to single-crystal formation via grain boundary migration (**Figure 1**). Measuring the orientation rate relative to external stress could corroborate this mechanism, and a predictive relationship has been established. These findings advance our understanding of the aggregation-based growth of natural minerals, especially biominerals, through the aggregation of amorphous precursors or the near-OA of nanocrystals and suggest a strategy for the synthesis of materials that take advantage of stress-induced co-alignment.[65a]

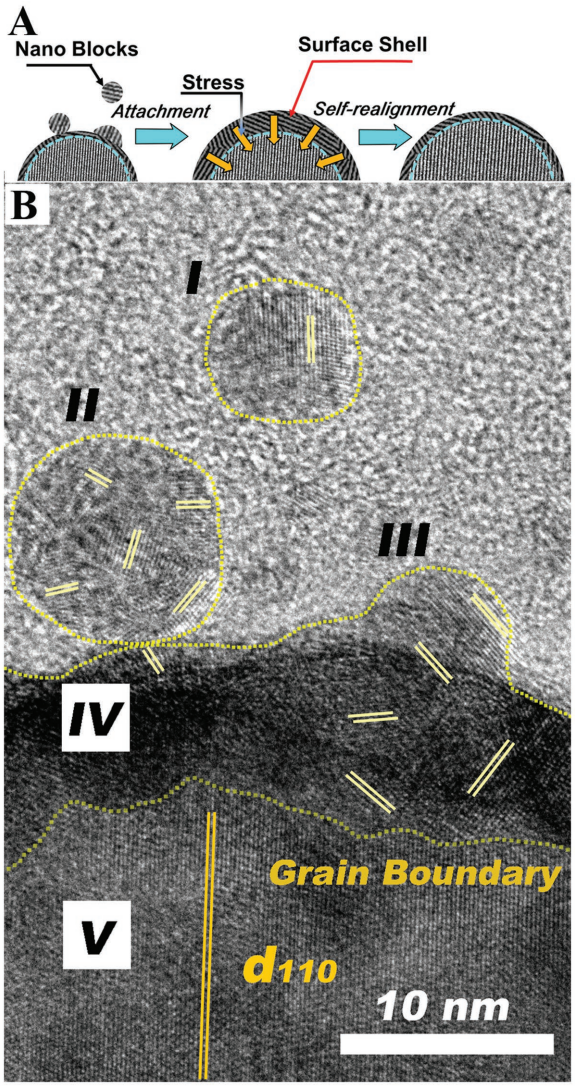

Figure 1. A) Schematic of stress-driven, aggregation-based growth by RA. B) Attachment of nanocrystals onto the vaterite surface at early stages. Reproduced with permission.[65a] Copyright 2016, Wiley-VCH.

2.1.5. Mesocrystal Formation

The concept of mesocrystals is considered to be one of non-classical crystallization[66] and is extensively used to obtain that form by oriented assembly, especially in biominerals and bioinspired materials. Mesocrystals are built from hundreds or thousands of nanocrystals with an organic stabilizing shell and an internal crystalline structure, analogous to the single crystal.[67] Mesocrystals can be transformed into single crystals through block fusion. As a result, they are frequently misinterpreted as single crystals. Mesocrystals can only be distinguished from single crystals based on their substructures, including atomic-scale lattice structures and nanoscale secondary structures.[66]

Mesocrystals have been documented in several biominerals, including nacres,[67] corals,[68] sea urchin spines,[69] and fish otoliths.[70] A remarkable example of a calcite biomineral is from red coral: The skeleton of the red coral *Corallium rubrum*

contains multiple levels of crystallographic hierarchy. Vielzeuf et al. reported the existence of submicrometre mesocrystals at the lowest hierarchical level that are separated by thin organic layers;[68] these calcite crystallites aligned along the same crystallographic direction. A recent study revealed that calcite single nanocrystals with a brick-like structure constitute the framework of the spine.[69] Surprisingly, ACC can also be used biologically to isolate calcite bricks, such as amorphous layers on aragonite in nacre.[71] These 2-nm-thick amorphous layers can be used to protect the organism.[69] Briefly, biominerals consisting of mesocrystals have better mechanical performance and optical properties reflecting the precise and exquisite control of the mineralization process.

Mesocrystal formation strategies have been applied to bioinspired mineralization processes. For example, silicatein fibres are used for the synthesis of mesocrystalline calcite spicules with extreme bending strength.[72] **Figure 2**A shows a representative synthetic calcite spicule with a high organic content of 10 –16 wt%. Surprisingly, mesocrystalline calcite spicules can undergo very large plastic deformation without any sign of brittle fracture (Figure 2B). This remarkable bending strength is attributed to the "sintering" effect of the initial granular structural units based on a combination of atomic force microscopy (AFM) and scanning electron microscopy (SEM). A mature synthetic spicule is an efficient wave-guiding material for visible light because of its uniform circular cross section (Figure 2C). Microscopy images of the wave-guiding capacity show that the light-guiding occurs throughout the deformation process without considerable loss of intensity. The reconstructed X-ray diffraction (XRD) pattern of a mature synthetic spicule reflects the twin crystal structure (Figure 2D). The small coherent scattering domains are 5 to 7 nm, consistent with those determined from the HR-TEM images (Figure 2E). The small calcite crystals are embedded in amorphous protein matrices, forming mesocrystals with high protein contents.

Another synthetic mesocrystal, a calcite nanocrystal with a fibrous structure formed in water/tetrahydrofuran, has been shown to evolve into a calcite mesocrystal via aggregation.[73] The ACC particles form first and subsequently aggregate via a bridging mechanism. The calcite nanocrystals are produced via a solid-state transformation, and they exhibit very little angular spread. This finding facilitates explaining how biological organisms produce large-scale single-crystal-like materials. Moreover, vaterite hexagonal mesocrystals that are similar to nacreous layers have been successfully prepared (Figure 2F,G).[74] The preparation of fluorapatite-gelatin nanocomposites indicates that foreign components can be incorporated without distortion of the mesocrystalline structure.[75]

Although mesocrystals have been studied for decades, the concept is sometimes misinterpreted, and thus, a re-evaluation of the existing literature on mesocrystals is urgently needed. Detailed analyses of calcite/polymer mesocrystals have been reported. Kim et al. critically examine the concept of mesocrystals and demonstrate that the applied methods (e.g., SEM and TEM) have confirmed that mesocrystal structure may be unsafe and insufficient.[62] Furthermore, no evidence exists regarding the formation of the calcite-polymer composites by assembled crystalline precursors. Furthermore, they reveal the existence of a sector-like mosaic microstructure in synthetic mesocrystals. Therefore, the only way to estimate whether a crystalline material is mesocrystalline is by determining the crystalline hierarchical structure, not the formation mechanism.[66a,76]

The essence of biomineralization is that the crystallization process produces inorganic minerals with remarkable properties. A major feature of both biomineralization and other crystallization processes is the regulatory effects of organics, which facilitate achieving controllable crystallization. The crystallization pathways by which biomineralization occur are diverse. Although the classical crystallization mechanism of atom/ion-mediated growth is important for the formation of the biomineral phase,[13b] here, we highlight the importance of NCCPs in biomineralization studies. Non-classical crystallization is characterized by the possible involvement of an amorphous precursor, liquid precursor phase, PNCs or so-called mesoscopic transformation and, thus, presents an alternative strategy for biomineralization and materials science. During the past few decades, the scope of the crystallization process has been the subject of considerable effort, and impressive progress has been achieved. However, we do not understand how the structure evolves as a function of

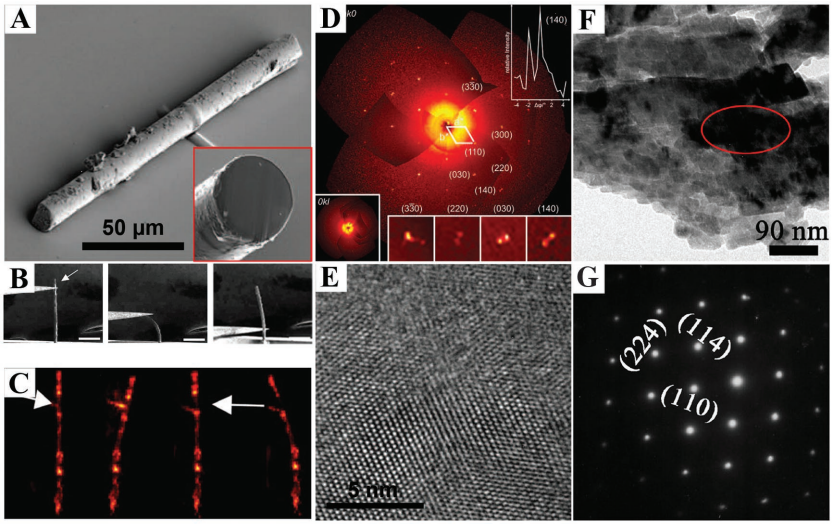

Figure 2. A) SEM image of a synthetic spicule. B) Time series of SEM images illustrating the fracture properties of spicules. C) Microscopy images of the wave-guiding capacity of the synthetic spicule during deformation. D) Reconstructed XRD pattern of the (hk0) plane of a mature synthetic spicule (10 months). (Inset) Reconstructed diffraction pattern of the (0kl) plane (bottom left) and rocking curve of the (104) reflection illustrating a split peak with peak widths (full width at half maximum) of ≈ 0.6 to 0.7°, respectively (top right), and the enhancement of the intensity distribution of some selected reflections (bottom right) shows the splitting of the diffraction peaks. E) HR-TEM image of a cross section of a mature spicule. Reproduced with permission.[72a] Copyright 2014, American Association for the Advancement of Science. F, G) Typical TEM image and selected-area electron diffraction (SAED) pattern of synthetic hexagonal prismatic vaterite mesocrystals. Reproduced with permission.[74] Copyright 2016, American Chemical Society.

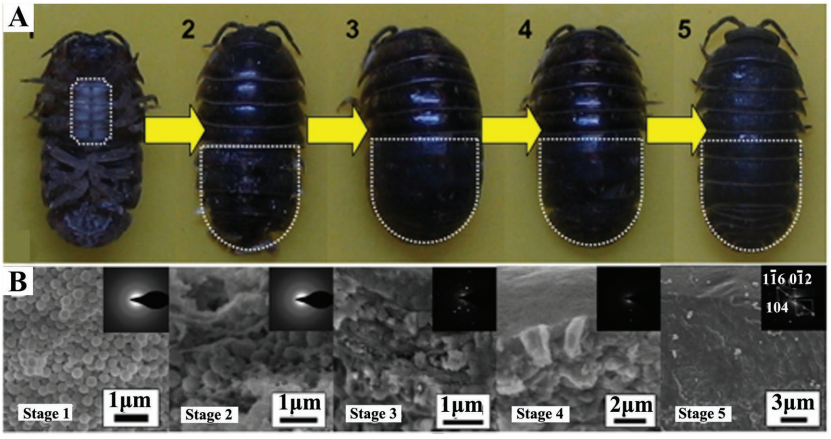

Figure 3. A) Photos of *Armadillidium vulgare* at different moult states. B) SEM observation and SAED patterns of the cross sections of the exocuticle layer shown in A. Reproduced with permission.[79] Copyright 2009, National Academy of Science.

interparticle separation; to exploit the crystallization process, identifying the crystal systems involved using a combination of techniques is important to elucidate the comprehensive morphological and structural features of crystallization pathways.[20] In summary, a detailed mechanistic understanding of biomineralization remains lacking, and in the future, this progress may help materials scientists explore the biomimetic principles of crystallization.

2.2. In Vitro and In Vivo Models of Biomineralization

Biomineralization proteins are widely involved in the formation of hard tissues, such as osteopontin[77] and ovalbumin.[33] Dentin matrix protein (DMP) is a biomineralization-inspired protein and acts as an accelerator of HAP formation.[78] Recent achievements suggest that this protein can promote the reorganization of the internal structure of ACP, which affects its transformation to HAP.[78] How living organisms adjust the transition of the precursor phase was the subject of little research until a study of the shell moult of crustaceans. Tao et al. suggested that the cooperation of magnesium ions and an aspartic acid-rich compound serves as a crystallization switch in biomineralization (**Figure 3**). The modification function of crystallization kinetics can be understood using an aspartic acid-enhanced magnesium de-solvation model.[79]

Biomineralization frequently occurs via metastable amorphous precursor phases, which crystallize into the final stable biominerals. Although extensive attempts have been made to elucidate this transition, it remains elusive. The process by which ACP transforms into HAP in the cells and bones of zebrafish fin rays has been mapped (**Figure 4**A–D).[28] The amorphous phase is considered to provide reserve nutrition to the subsequent phase transformation and be released from the intracellular vesicle. The mechanism by which ACP is transformed into HAP at the mineralization front is unknown. The presence of ACC in 2-nm-thick layers in natural nacre has been demonstrated.[71] Hydrated ACC phases also exist in fresh nacre.[80] In vivo, the first direct observation of ACC precursors for nacre formation was achieved using synchrotron spectromicroscopy.[80] Similarly, biomineral calcite is also formed from hydrated and dehydrated ACC in sea urchin spicules (Figure 4F).[69,81] The spicules evolve over time from amorphous to crystalline forms. The biominerals appear as a sequence of three mineral phases as follows: hydrated ACC → dehydrated ACC → calcite. This order corresponds to the sequence of decreasing energy (Figure 4E).[39]

Type I collagen is the major organic component of bone extracellular matrix (ECM). The involvement of collagen in bone and tooth biomineralization is widely supported by evidence. Nudelman et al. showed that collagen acts in synergy with inhibitors of HAP nucleation to regulate mineralization.[82a] The collagen matrix not only has a significant effect on the atomic-scale structural features but also regulates the size and three-dimensional structure of HAP at a large length scale.[83] Finally, the hierarchy of the HAP assembly within collagen

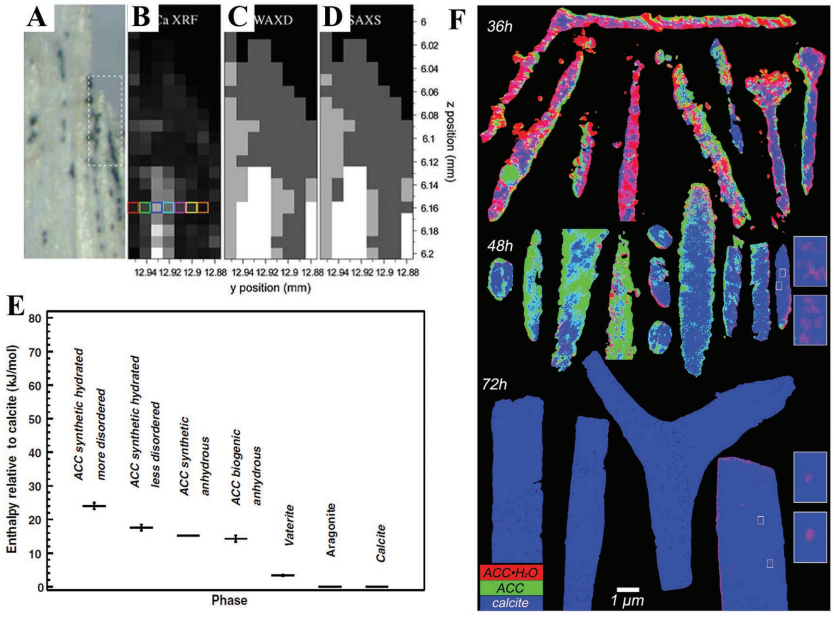

Figure 4. A–D) Calcium X-ray fluorescence, XRD, and small-angle X-ray scattering (SAXS) acquired with a 10-μm beam from zebrafish tissue. Reproduced with permission.[28] Copyright 2010, National Academy of Science. E) Relative stabilities of different $CaCO_3$ phases. Reproduced with permission.[39] Copyright 2010, National Academy of Science. F) Red, green and blue maps of spicules extracted 36, 48, and 72 h after fertilization. Reproduced with permission.[81] Copyright 2012, National Academy of Science.

fibrils is critical to the characteristics of the collagen matrix in nanomechanics and cytocompatibility, the details of which are discussed in section 3.1.

Organic-inorganic interactions in bone represent a key issue in biomineralization studies.[1d,e] The function of citrate in bone has been widely studied by in vitro and in vivo models.[84] Jiang et al. from Zhejiang University investigated the HAP-citrate interfacial structure at the atomic level using AFM and found that a layer of citrate on HAP can improve the adhesion force of HAP crystal surfaces.[84a] Subsequently, solid-state nuclear magnetic resonance (ssNMR) revealed that the HAP surface is covered with strongly bound citrate, which implies this compound's key role in stabilizing the HAP in bone.[85] Davies et al. proposed an OCP-citrate structural model based on NMR data on bone and OCP-citrate.[86] They also determined that the bisphosphonate structure can affect binding to bone by interacting with HAP and that the binding ability is related to the number of hydroxyl groups and the location of the ester group.[87] Similarly, extrafibrillar organic–mineral interfaces with osteocalcin and osteopontin in bone contribute to the fracture toughness,[88] and other organic molecules[89] may also be implicated in biomineralization. For example, poly(adenosine diphosphate ribose) is involved in the calcification of the bone matrix and was used to refine an in vitro model of developing bone.[90]

3. Applications of Biomineralization

Inspired by the natural generation of biominerals, scientists have identified methods of designing and developing various biomimetic functional materials.[1a,91] Recently, scientists have successfully designed and fabricated "bioinspired materials".[92] An organic matrix is typically used as a template or scaffold to deposit and mineralize the inorganic materials.[93]

3.1. Collagen Mineralization

Collagen, which is one of the most abundant proteins in nature,[15] constitutes most tissues in vertebrates.[94] Type I collagen has a triple-helix structure[95] and can orientate the growth of biominerals.[1b,96] In a mineralized system, collagen can be used as a potentially biomimetic material for various engineering applications, including repairing calcified tissues, such as bone and cartilage.[97]

The mineralized fibrils include apatite crystals and collagen fibrils,[98] and the apatite is embedded within the collagen fibrils and oriented along its longitudinal axis.[83,99] The process of mineralizing collagen is elusive;[82,100] thus, investigations are being performed to solve three problems relating to the mineralization process: (1) the morphology and features of the collagen fibrils and apatite, (2) the inception and evolution of the confined mineralization, and (3) the mechanism of amorphous precursor phase permeation into collagen fibrils.[101]

Recently, biomineralization-inspired collagen fibrils have been reported using bone ECM from vertebrate calcifying tissues.[102] CryoTEM has revealed that the driving force between the positively charged sites and negatively charged CaP-polyaspartic acid composites plays a key role in controlling the entry of ACP into the collagen fibrils.[82,103] Collagen can also adjust the mineralization of carbonated HAP, as observed in bone.[104] Collagen fibrils and minerals are two major components of bone and are used as models to research fundamental issues relating to biomineralization. These models represent a starting point for bone tissue engineering and the design of new implantable materials.[105]

The biomineralization of collagenous mineralized tissues is a precisely cell-controlled process. The biominerals in vertebrates include collagenous mineralized tissue characterized by a matrix that allows organic fibrils and inorganics to associate into well-organized nanocomposites. Thus, organic fibrils and inorganic materials play key roles in the process of collagen mineralization. In the mechanism underlying the mineralization process, the precursor amorphous phases easily infiltrate into the fibril, and the charged amino acids in collagen form nucleation sites that control the transformation of ACP into apatite. This is important for the further development of biomimetic materials and scaffolds for tissue engineering. However, investigating the collagen mineralization in detail using in vivo models has proven to be very challenging because of the complexity of biological systems.[82a]

3.2. Hard Tissue Repair

3.2.1. Bone Repair

Bone is a hierarchical composite material that consists of collagen and minerals.[7c,8,106] Previous studies have suggested that the crystalline relationship between collagen and minerals in the formation of bone[107] is as follows: The calcium and phosphate ions are transferred to minerals within the collagen.[108] Two primary models have been proposed for bone mineralization: Nanocrystals nucleate from solution in the presence of collagen, and matrix vesicles assemble ions from the ECM.[1a,7b,109] Rodriguez et al. demonstrated that osteoblasts concentrate calcium and phosphate ions to form ACP, which then permeates into the collagen fibrils and crystallizes into HAP.[110]

Bone defects originate from trauma and other diseases.[111] Ideal bone-fixation materials have certain characteristics, including good osteoconductivity, biocompatibility, resorbability, and adequate mechanical strength.[112] Frequently used bone repair materials include metal materials, ceramic implants, polymeric scaffold materials, and composite hydrogels.[113] Metals, including stainless steel and titanium, have appropriate biocompatibility and strength, but conventional metals are not suited for bone repair because of their nonbiodegradability and brittleness.[114] Ceramic implants principally consist of CaP because it is important in native bone tissues to induce bone bonding and healing;[115] however, the poor fracture toughness and tensile strength of CaP restrict their biological applications.[116] Polymeric scaffold materials are used for tissue guidance and carrying growth factors to expedite bone repair.[117] However, most polymers have weak osteoconductive ability.[118] Adding polymer matrices to inorganic materials can improve their mechanical properties and osteoconductive ability.[119] Biomaterials with bone introduction and regeneration abilities can efficiently integrate with natural

bone tissues.[120] Tough hydrogels are promising materials for bone substitutes,[121] but they exhibit low sliding friction on soft supporting tissues.[15,122] Recently, Nonoyama et al. developed a novel double-network hydrogel that, combined with HAP, has excellent mechanical properties and the biological ability to induce the regeneration of cartilage tissue in vivo.[117a] Min et al. designed an injectable dual-therapy nanolayered implant coating that can completely and rapidly repair bone tissues.[123] Hu et al. prepared absorbable bacterial cellulose composites to realize the repair of bone defects.[124]

The bone structure consists of ordered mineral-collagen composites with several levels of hierarchy. Recently, the biomimetic synthesis of artificial bone has attracted substantial research interest. Thus, developing biocompatibility materials that are able to induce bone regeneration, bone repair and be used directly as a replacement for bone is necessary. Great achievements have been made in bone repair, and the bone structure is reasonably well defined. However, its mineralization process remains unknown, and the mechanism underlying the initiation of bone biomineralization is controversial.[106c]

3.2.2. Tooth Repair

Dental caries are both a universal disease and a primary health problem.[125] Recently, a diverse range of novel biomimetic strategies have been developed to reconstruct subsurface enamel lesions using remineralization.[125c,d] In these studies, proteins or peptides that exert control effects on the nucleation, growth and features of HAP are added into the enamel mineralization systems to achieve an artificial enamel-like structure.[126]

Casein phosphopeptide (CPP) containing phosphoryl residues combines with calcium and phosphate ions to prevent the ACP from transforming into HAP crystals, resulting in amorphous nanocomplex CPP-ACP in a metastable solution.[127] CPP-ACP serves as a supersaturation calcium and phosphate reservoir on the enamel surface and promotes the mineralization of enamel subsurface lesions.[128] Amelogenin can stabilize the ACP and alter the aggregation to produce oriented rod-like HAP crystals.[129] Kim et al. reported that amelogenin can promote the formation of a well-organized enamel-like structure when it is added to mineralization medium containing fluoride,[129b] and an amelogenin-containing chitosan hydrogel has also been developed for enamel regeneration that can promote the assembly of enamel-like layers on mature enamel.[130] Some peptides/oligopeptides play roles similar to those of biomineralization proteins and accelerate enamel repair.[131] Similar to amelogenin, poly(amido amine) dendrimers are used to repair the etched enamel surface and trigger aggregation-based HAP crystal growth and the formation of well-arranged HAP crystals.[132] Moreover, other available polysaccharides, such as agarose and gelatin, have been utilized to generate HAP crystals and promote enamel repair.[133] In addition to peptides, amino acids, such as glutamic acid (Glu), can induce the aggregation of HAP and control the resulting hierarchical structure.[134] Li et al. from Zhejiang University observed a biomimetic cooperative effect of Glu and HAP particles that can lead to the formation of a large-scale enamel-like organized assembly.[135] Bioactive glass materials have been extensively used as tooth and bone graft materials, and some can be used for clinical treatment.[136] Polyacrylic acid (PAA) can be added to bioactive glass to repair demineralized enamel via stable ACP precursors.[137] Fluoride is also used to repair etched enamel and promote the formation of new enamel.[138] Yan et al. remineralized an etched enamel surface by forming organized needle-like fluorapatite crystals in the presence of 1 ppm of fluoride.[139]

It is well established that dental caries occur via a dynamic disease process caused by an imbalance between demineralization and remineralization. Biomimetic mineralization simulates the natural process of mineralization, and the biomimetic synthesis of repaired layers under physiological conditions represents an alternative pathway. Although significant achievements have been achieved in tooth repair using biomimetic mineralization approaches, producing a repaired layer with a hierarchically organized structure and high strength requires the development of a new technique.[140] Currently, biomimetic mineralization approaches are used to synthesize repaired layers, although such layers have only been produced in the laboratory scale. A cost-effective, industrial-scale synthesis with direct technological applications remains elusive.

3.3. Nacre-Like Material Design

Nacre contains 95 wt% $CaCO_3$ nanocrystals and 5 wt% organic polymers and displays high mechanical properties, including toughness and strength.[141] Mellow nacre has a "brick-and-mortar" structure in which the inorganic layers are linked by the organic matrix. Through a series of structural designs and toughness mechanisms at near-macroscopic scales, the toughness and strength of nacre can be adjusted to be similar to those of artificial materials. Therefore, the design and development of bioinspired structural materials is important.[142] Because of its "brick-and-mortar" structure and excellent mechanical binding characteristics, natural nacre is a highly attractive model.[142a] Its mesoscale sandwiched structure serves as a template to control the mineralization of $CaCO_3$ and provides mechanical support to improve the shear strength.[142b]

Mimicking the structural characteristics of nacre is a promising method of developing new materials with superior mechanical performance. In the past decade, a variety of tactics have been applied to create nacre-like materials with hierarchical "brick-and-mortar" structures,[143] such as hot pressing,[143a] spraying methods,[143b] layer-by-layer (LBL) assembly,[143c] vacuum-assisted filtration,[143d] and ice-templating.[143e] Among these methods, ice-templating has proven to be a potent strategy for producing nacre-like structures with well-organized and excellent mechanical properties.[144] For example, Bai et al. designed a bidirectional freezing technique to develop bioinspired nacre-like hydroxyapatite/polymethylmethacrylate composites that display excellent elastic modulus and fracture toughness. This technique has been demonstrated to have potential for other applications.[143e] Mao et al. developed an assembly and-mineralization process to fabricate nacre-like materials using a mesoscale tactic in which the nanostructure and microstructure are controlled simultaneously. Through a freezing-induced assembly process, a chitosan matrix with predesigned laminated structure has been

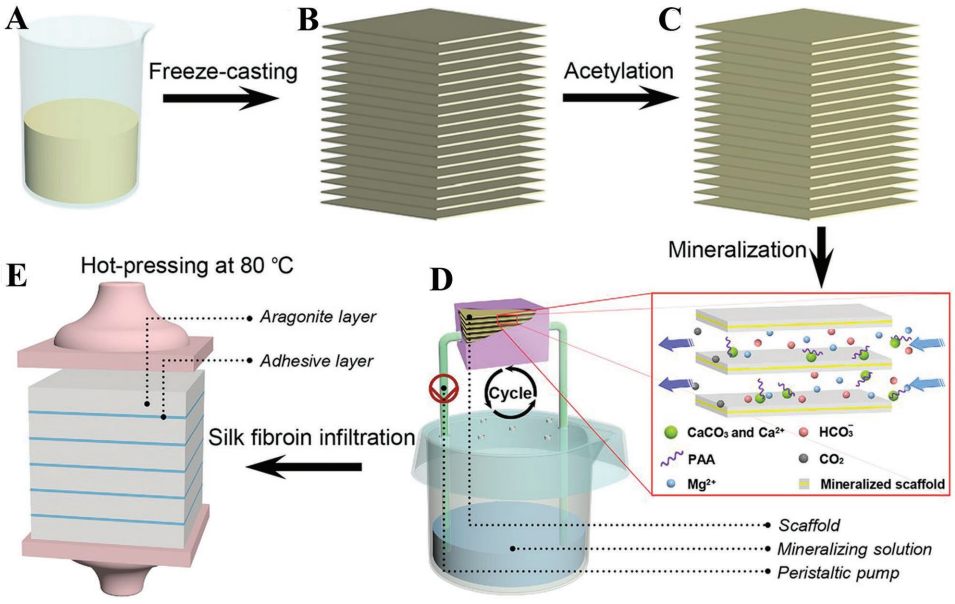

Figure 5. Fabrication scheme for synthetic nacre. A) Starting solution: chitosan/acetic acid solution. B) Freeze-casted laminated chitosan matrix. C) Matrix after acetylation in which chitosan is converted to β-chitin. D) Mineralization of the matrix. E) Laminated synthetic nacre obtained after silk fibroin infiltration and hot pressing. Reproduced with permission.[144b] Copyright 2016, American Association for the Advancement of Science.

fabricated (**Figure 5**A–E). This matrix is subsequently acetylated (Figure 5C) and transformed to β-chitin to avoid unnecessary swelling or dissolution. The matrix is mineralized in a peristaltic pump-driven circulatory system via the decomposition of $Ca(HCO_3)_2$ in the presence of PAA and magnesium ions.[144b] These organic-inorganic materials, which are prepared by a predesigned matrix-directed mineralization approach, are quite comparable to natural nacre and accelerate the progress being made in developing nacre-like nanocomposites. Additionally, they have a profound significance for exploring future structural materials, although the relevant techniques still have some limits. For example, controlling the structural features over multiple large-scales in materials with high ceramic contents, especially for practical applications, remains difficult.[143e,144]

4. Biological Strategy for Organism Modification

Biomineralization is a complex organic-inorganic precipitation system.[12a,145] The designed functional shells can defend and enhance these organisms,[146] such as by improving biological systems and vaccines and recycling greenhouse gases.[14a,147] In this section, we highlight the control of nucleation sites and several biological applications relating to organism improvement, namely, endowing organisms with functional materials for protection, storage, biological stealth, improvement, and biocatalysis.[11a,148]

4.1. Biomimetic Systems

Certain biological systems can protect their species under unfavourable conditions by safeguarding genetic information with a solid shell; such species include diatoms, molluscs, fungi and radiolarians.[149] However, most organisms cannot self-biomineralize because they lack relevant molecules for mineralization.[150] The artificial mineralization of materials onto non-biomineralizing organisms may strengthen the mineralization capability and generate material shells through biomimetic mineralization strategies.[151]

4.1.1. Enhancement of Nucleation by Polyelectrolytes

The enhancement of nucleation using polyelectrolytes is intended to improve yeast mineralization capability and could potentially become a universal strategy for organism improvement.[152] LBL assembly is typically applied to form thin films by depositing alternative layers based on electrostatic interactions on the cell surface[17a,153] and is an effective strategy for cell-surface modification.[154] In LBL assembly, polyelectrolytes with relevant structural features are used to connect the oppositely charged polymers, maintain the surface mobility of cells,[155] adjust cell agglomeration,[155c,156] and ensure material shell generation.[157] Eukaryotic cells, such as *Saccharomyces cerevisiae (S. cerevisiae)* cells, can enter a resting state when they are encapsulated by a material shell. The formation of a CaP shell on *S. cerevisiae* cells confirmed that LBL assembly can efficiently adjust in situ mineralization on living cells.[158]

4.1.2. Particle Assembly

Unlike LBL assembly, particle assembly is the one-step adsorption of a charged polymer or polyelectrolyte on the surface of a virus of cell. Many viral particles have a highly negatively charged surface and can immediately absorb and concentrate cations, leading to the in situ generation of a material shell.[159] The direct deposition of a mineral shell on viral particles is

difficult to realize when the surface charge density is relatively low. To address this issue, a charged capping agent can be introduced onto the surface of the organism via electrostatic adsorption and used as a precursor building block to induce in situ mineral shell deposition.[160] For example, cationic polymers, such as branched polyethyleneimine molecules, can absorb onto the surface of viral particles and facilitate the efficient formation of silica nanoclusters.[161] By combining the surface assembly character of the capping agent and its ability to direct mineral deposition, the self-formation of an artificial shell on a living organism can be achieved under mild conditions.[162] The abundance of charged groups can effectively initiate the formation of the mineral shell, leading to the preservation of bioactivity.[163] Although many artificial molecules have been exploited to modify organisms' surfaces,[164] only a few have been utilized to construct material shells for organisms.[165]

4.1.3. Genetic Engineering

Organisms can undergo self-biomineralization under the control of special functional proteins.[166] Carboxyl-rich peptides have been suggested to influence mineral nucleation during biomineralization. Therefore, anionic polypeptides or proteins that expose repetitive patterns of carboxyl-rich groups play a vital role in the direction of mineral aggregation. Since proteins and peptides originate from the genetic code, genetic engineering is a potential strategy to essentially modify organisms and imbue them with biomineralization abilities[167] that are perpetual and inheritable.[168]

In nature, many biological systems lack biomineralization-related proteins. To achieve self-biomineralization, carboxyl-rich proteins can be genetically engineered to create the possibility to improve their biomineralization abilities.[169] Wang et al. from Zhejiang University rationally designed a engineered virus by inserting genes carrying the selected biomineralization peptides to achieve self-biomineralization. Acidic phosphate-chelating peptides (N6p) and calcium-chelating peptides (NWp and W6p) are displayed on the virion surface and spontaneously trigger the formation of CaP mineralization (**Figure 6**) because the carboxylate groups of the peptides can efficiently concentrate the inorganic cations and create local supersaturation to initiate biomineralization.[166c] Since acidic proteins play a vital role in biomineralization processes, self-biomineralization can be developed into a universal approach for improving living organisms using genetic engineering.

4.2. Biological System Improvement

During the process of biological evolution over approximately 50 million years, organisms started to grow tough minerals, including $CaCO_3$, CaP, and silica.[170] These organisms use delicate structures, such as shells, to protect themselves against hostile conditions.[171] Inspired by the formation of natural shells, cell-surface modifications have been achieved via complex approaches, which can be developed into a platform for functional single-cell studies in cell biology.[172] Silicification-induced cell aggregation has been studied as a route for the introduction of chemical functions into cells[173] and has attracted extensive attention in the past few years.[147] Many cells, including algae, yeast and red blood cells (RBCs), are widely used for surface functionalization.[17a,158]

In nature, green algae cannot generate hydrogen, but Xiong et al. at Zhejiang University demonstrated that

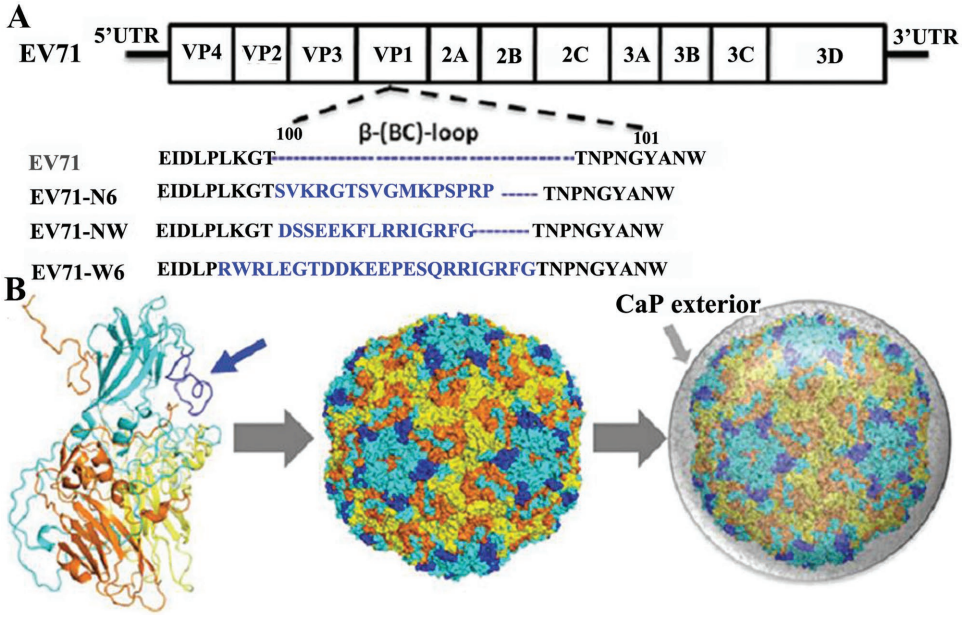

Figure 6. Characterization of engineered EV71. A) EV71 genome and the insertion site of the β-(BC)-loop of VP1. B) Homology modelling of the mutant viral protein. The EV71 capsid proteins VP1, VP2, and VP3 are shown in cyan, yellow, and orange, respectively. Reproduced with permission.[159b] Copyright 2013, National Academy of Science.

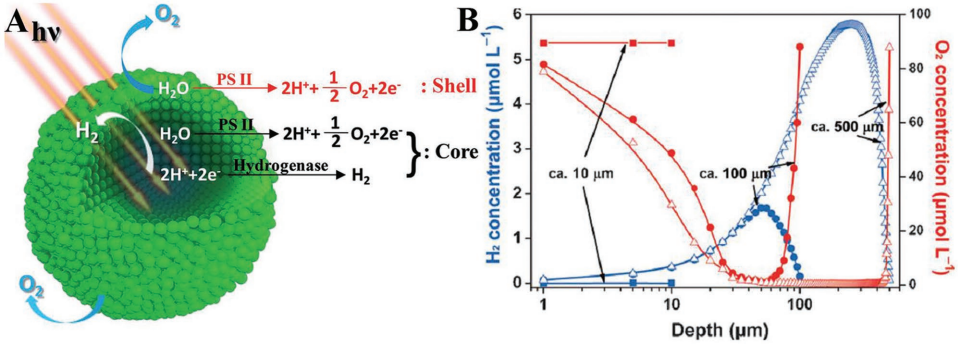

Figure 7. A) Spatial–functional differentiation in aggregated Chlorella cells. B) H_2 (blue) and O_2 (red) microprofiles of aggregated Chlorella with different sizes. Reproduced with permission.[174] Copyright 2015, Wiley-VCH.

silicification-induced green algae can exhibit continual photobiological hydrogen production. The novel core-shell structure creates an equilibrium between photosynthetic electrons and hydrogenase activity and lead to the generation of hydrogen: In this system, the core cells obtain the ability to produce hydrogen, and the shell cells reserve the function of native algae and isolate the core cells (**Figure 7**A). The respiration reaction of the core cells consumes oxygen to produce a hypoxic environment within the enclosure and can, thus, activate hydrogenase. This dynamic anaerobic condition leads to a balance between hydrogenase activity and photosystem II (PSII) that ensures sustainable photobiological hydrogen production. It also follows that mineralization treatment can lead to the spatial-functional differentiation of the aggregated algae cells based on their core-shell structures[174] (Figure 7B). This discovery reflects a feasible and effective approach for the solar-induced splitting of water into hydrogen and oxygen to exploit green energy alternatives by designing cell-material complexes.

Mammalian cells, including RBCs, HeLa cells, NIH 3T3 fibroblasts and Jurkat cells, do not process a functional shell but instead have a weak membrane composed of a liquid bilayer that is fluidic and susceptible to environmental changes. Mammalian cells are separately coated with silica via silicification-induced function. This silica coat efficiently defends HeLa cells from proteolytic attack by trypsin and other toxic compounds. Choi, et al. individually encapsulated HeLa cells in suspension with silica by a cytocompatible silicification process, and the viability of the SiO_2-coated HeLa cells was measured to be 76.8% within the first four hours. However, the encapsulated silica shell ultimately caused cell death after 12 h. This finding led to the attractive hypothesis that cancer cells could be inhibited via a shellization-based strategy[162] (**Figure 8**). This bioinspired cytocompatible tactic has also been implemented in Jurkat cells and NIH 3T3 fibroblasts.

4.3. Vaccine Improvement

Vaccines are sensitive to temperature changes; thus, continuous refrigeration facilities are required to maintain their potency.[175] However, some areas lack dependable refrigeration equipment to store and deliver vaccines, and thus, a significant portion are wasted. Consequently, the thermal instability of vaccines is an enormous barrier to vaccination programmes and viral-based therapies.[158b,176] New progress in genetics has created the possibility to enhance and stabilize vaccines. The viral capsid can be reasonably genetically engineered to improve physicochemical traits. Many strategies have been employed to stabilize vaccines, including silk, minerals, and sugars.[175b] Among the biogenic stabilizers utilized, CaP are of interest because of their good biocompatibility and are now utilized as a transferring agent and adjuvant to stabilize vaccines.[175b] CaP shells can be introduced onto viral surfaces when the calcium ion concentration is high.[177]

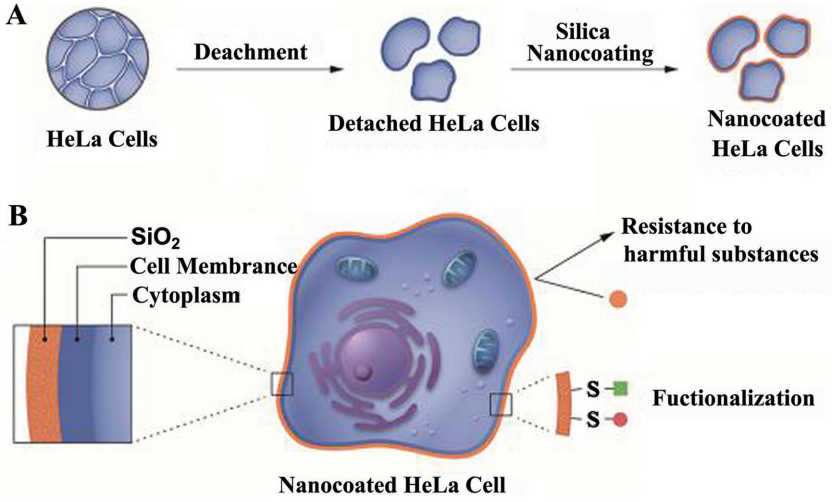

Figure 8. A) Schematic of the silica coating of HeLa cells via silicification. B) The silica coat protects the HeLa cells against enzymatic attack and provides an opportunity for post-functionalization and the control of cell division. Reproduced with permission.[162] Copyright 2014, Wiley-VCH.

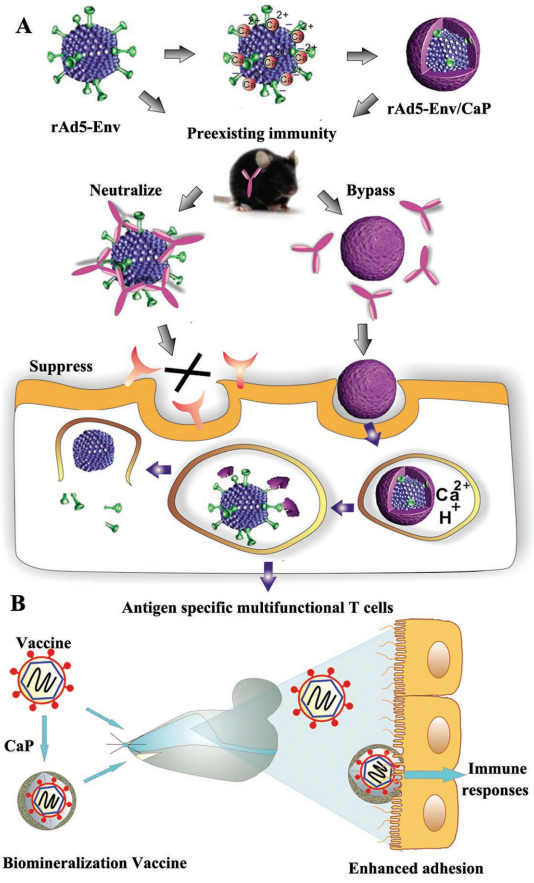

Figure 9. A) Schematic description of vaccine engineering with a dual-functional mineral shell. Reproduced with permission.[167] Copyright 2016, Wiley-VCH. B) Schematic description of a biomineralized vaccine nanohybrid for intranasal immunization. Reproduced with permission.[178] Copyright 2016, Elsevier.

A natural virus cannot induce biomineralization spontaneously during its natural life cycle. To imbue a virus with the ability to self-biomineralize, scientists have attempted to employ nucleating peptides on the virus layer to increase its ability to initiate CaP mineralization. CaP-nucleating peptides can be exhibited on the virus layer after genetic modification to increase the CaP mineralization capacity.[178] Wang et al. at Zhejiang University designed a biomineralization-inspired engineering strategy to subtly modulate the vaccine surface through a material coating.[17b] Specifically, the recombinant adenovirus serotype 5 (rAd5) vector expressing simian immunodeficiency virus (SIV) envelope protein (rAd5-Env) can be biomineralized in situ to obtain vaccine-material core-shell structure hybrids that can be used to cover the surfaces of vaccines and conserve their incipient activity (**Figure 9**). Wang et al. also proposed increasing the utilization of nasal vaccinations through biomineralization-based tactics.[167] Vaccine hybrids can be acquired by masking the viral surface with a CaP shell, thereby altering the physiochemical traits of the incipient vaccine and leading to mucosal adherence to the nasal tissues. These strategies are expected to lead to a material-based concept for vaccine enhancement and applications.[178]

In summary, biomineralization-inspired viral engineering, which was originally proposed in the late 1990s, has evolved into an interdisciplinary strategy to synthesize ordered composite materials.[175c,d] Despite these recent advances, generalized methods for viral biomineralization are still required to ensure the efficiency of rationally designed hybrid devices. In contrast, biomineralization at inorganic-virus interfaces can shield viral proteins and expose functional groups, altering the interplay between viruses and biological systems, which remains poorly understood and could potentially provide new strategies for virus applications. Thus, developing versatile biomineralization techniques and elucidating the material/biological potential of biomineralized viruses will benefit the multifunctional applications of viral nanocomposites.

4.4. Cancer Therapy

Cancer is the cause of massive mortality and morbidity worldwide.[179] Currently, traditional cancer treatments are limited to surgery, chemotherapy and radiotherapy; additionally, anti-cancer drugs are always accompanied by serious side effects.[180] Recent progress in nanotechnology has contributed enormously to the development of cancer therapies, although the cytotoxicity and biosecurity of nanoparticles remain controversial, which limits their biomedical applications.[181]

In nature, mineral accumulation is significant biological processes. However, calcium ions can also be deposited anomalously in soft tissues, causing pathological diseases, such as kidney stones and vascular calcification.[182] These abnormal biomineralization processes generally occur in damaged or defective tissue surfaces in the presence of normal calcium/phosphorus metabolism, and the pathologically calcified minerals can ulcerate calcified lesions and accelerate cell death.[183] Zhao et al. at Zhejiang University suggested that the specific introduction of "biomimetic pathological mineralization" onto tumour cells/tissues could be an alternative treatment strategy for cancer and is designated cancer cell-targeting calcification (CCTC) (**Figure 10**A). Some categories of cancer cells characterized by folate receptor overexpression can selectively assimilate folate and concentrate calcium ions to trigger cell calcification (Figure 10B). Meanwhile, scientists investigated a complete calcification-based tumour therapy. In the calcification treatment, the nuclei of tumour cells become agglutinated and abnormal, indicating that the CaP mineral coat promotes cell death[184] (Figure 10C,D). It should be noted that both folate and calcium are essential ingredients in human metabolism and exhibit drug-free features, which is a primary advantage of CCTC. Most cancer deaths are caused by the formation of secondary metastases rather than by the primary cancer, and after CCTC treatment, the survival rate of mice improved significantly (to ≈ 90%) because of the effective suppression of metastasis under a similar total growth inhibition (TGI) level, demonstrating another key advantage of CCTC over chemotherapy. In this work, a biomineralization-inspired, drug-free strategy for cancer therapy that involves CCTC was developed. This strategy may lead to a replaceable cancer therapy

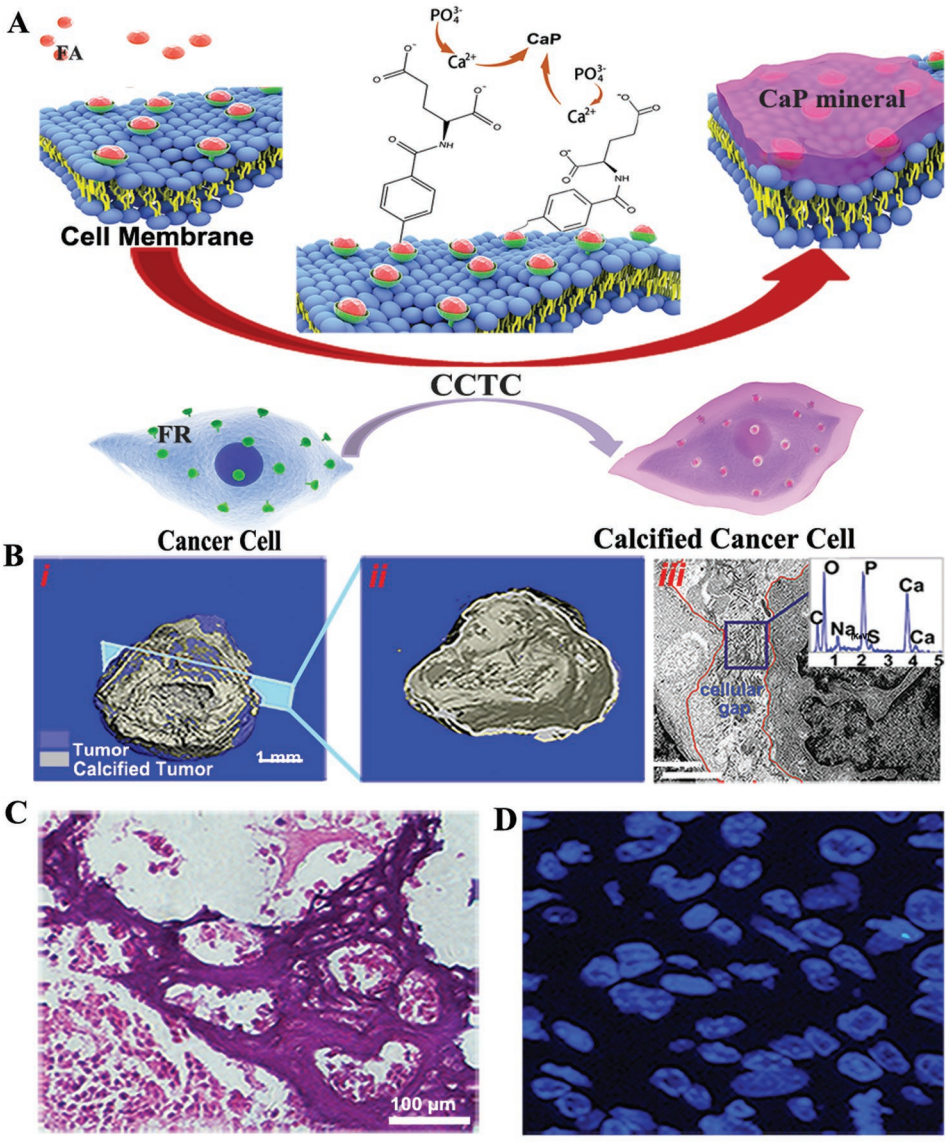

Figure 10. CCTC is a drug-free tumour therapy strategy. A) Schematic of CCTC. B) In vivo CCTC treatment effects on tumours. (i, ii) Micro computed tomography (μCT) detection of tumours; (iii) TEM images and (inset) energy-dispersive X-ray spectroscopy (EDX) of calcified matter in tumour cellular gaps. C) Haematoxylin and eosin (H&E) staining of a tumour section. D) Confocal laser scanning microscopy (CLSM) images of a tumour slice stained with Hoechst 33342. Reproduced with permission.[184] Copyright 2016, Wiley-VCH.

characterized by the selective calcification-based substitution of sclerosis for tumour disease. Compared with traditional chemotherapy, this approach can effectively suppress tumour growth and secondary metastases without destroying normal cells and, thereby, improve the survival rate. The proof-of-concept of disease replacement may be designed as a vital medical treatment to reduce disease risk. However, the concentration of calcium ions required exceeds physiological levels. Thus, identifying a new material to accumulate calcium ions in bodily tissues to facilitate calcium mineral nucleation and induce in vivo calcification is not simple.

In this progress report, transformative medicine approaches aiming to transform irreversible diseases into curable ones, such as transforming cancer to sclerosis, are described. In a sense, by applying CCTC, the tumour is calcified into a sclerotic tissue, implying that the cancer may be substituted by a sclerosis associated with low mortality. CCTC anti-cancer therapy is mediated by folate, which is selectively highly expressed on the cell membrane in most cancers. Additionally, many other ligands could be chosen based on antigen-antibody and ligand-receptor interactions that are highly expressed and rich in cancer cell membranes. Furthermore, the growth of solid tumours has been proven to depend on their capacity to obtain sufficient blood supply. One potential strategy is the targeted calcification of the established tumour vasculature based on its unique structure and protein-expression profile. This strategy represents another avenue that could lead to exciting therapeutic opportunities.

5. Conclusions

Biomineralization is a widespread phenomenon that leads to the formation of well-organized biominerals. The pathway and mechanism of this process are the main subjects of this biomineralization study. Biomineralization can control crystal formation at all levels, including the crystal composition, structure, nucleation, growth and morphology. The resulting biominerals may be shaped by direct interactions between the forming crystals, ions and biological organic compounds, which are introduced in nucleation sites and act as structural frameworks, nucleation templates, and growth inhibitors.[185] Great progress has been made in the field of organic-inorganic systems, but the integration of biomimetic inorganic materials and organic molecules remains largely unexplored.

Although non-classical crystal growth frequently occurs in biomineralization, understanding the detailed mechanisms and their application requires additional work. The amorphous phase has been proven to be a precursor phase for most biominerals;[69,80,81] however, the molecular mechanisms of phase stabilization and the subsequent phase transition remain largely unexplored. Both the OA and RA pathways have been recognized,[53,65] but the factors that regulate these processes, such as surface energy, solvation energy and phase stability, are poorly understood. In situ measurements are critical for revealing these mechanisms and problems.[26,35] Electron microscopy, scanning probe approaches and X-ray spectroscopy are powerful tools for such in situ studies.[186] Elucidating the underlying mechanisms could further guide the fields of material science and the design of numerous functional materials.[27] Many important nanomaterials can be synthesized, and their assembly can be controlled to form hierarchical structures[72,74] through biomineralization strategies.

Biomineralization is an evolutionary course that has yielded complex organisms capable of producing hierarchical structures from organic-inorganic material templates.[187] The combination of minerals with biological systems is an interesting research topic but remains largely unexplored. Previous studies of biomineralization focused on the regulatory effects of organic constituents on inorganic crystallization. Conversely, current attempts at material-based biological improvement aim to regulate the influence of inorganic species on biological organisms in biomineralization studies.[188] To mimic the biological mineralization process, many biocompatible and biodegradable polymeride materials have been developed to simulate functional matrices in living organisms. These materials can be used to control mineralization at the molecular level. Recently, scientists have become highly interested in designing promising biominerals that have many applications, including hard tissue repair, biomimetic materials, biological system improvement, cancer therapy, and vaccine improvement. We have made considerable progress in understanding the mechanisms of self-assembly. For example, Mao et al. successfully fabricated bulk synthetic nacre that highly resembles both the chemical composition and hierarchical structure of natural nacre. However, in other fields, mimicking such natural materials and developing biomimetic materials with desirable properties remain highly challenging.[144]

Optimizing organisms using functional biominerals constitutes an important and interesting subject. The genetic engineering-induced self-biomineralization of organisms is a potential tactic for optimizing shell function. The genetic engineering of a virus to obtain biomineralization has been successfully achieved, but similar modifications of other organisms remain lacking. Furthermore, if the artificially modified organisms, such as biomineralized viruses, are returned to nature, they may act like a new species. Hence, the manufacturing process and biological safety of natural systems should be carefully evaluated after all genetic modifications.

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