

Review article

Improvement of organisms by biomimetic mineralization: A material incorporation strategy for biological modification[☆]Yueqi Zhao^a, Ruikang Tang^{a,b,*}^a Center for Biomaterials and Biopathways, Department of Chemistry, Zhejiang University, Hangzhou 310027 China^b Qiushi Academy for Advanced Studies, Zhejiang University, Hangzhou 310027 China

ARTICLE INFO

Article history:

Received 29 February 2020

Revised 19 June 2020

Accepted 25 June 2020

Available online 3 July 2020

Keywords:

Organism-material hybrid

Biomimetic mineralization

Artificial shell

Artificial organelle

Biological improvement

ABSTRACT

Biom mineralization, a bio-organism controlled mineral formation process, plays an important role in linking biological organisms and mineral materials in nature. Inspired by biom mineralization, biomimetic mineralization is used as a bridge tool to integrate biological organisms and functional materials together, which can be beneficial for the development of diversified functional organism-material hybrids. In this review, recent progresses on the techniques of biomimetic mineralization for organism-material combinations are summarized and discussed. Based upon these techniques, the preparations and applications of virus-, prokaryotes-, and eukaryotes-material hybrids have been presented and they demonstrate the great potentials in the fields of vaccine improvement, cell protection, energy production, environmental and biomedical treatments, etc. We suggest that more researches about functional organism and material combination with more biocompatible techniques should be developed to improve the design and applications of specific organism-material hybrids. These rationally designed organism-material hybrids will shed light on the production of “live materials” with more advanced functions in future.

Statement of Significance

This review summarizes the recent attempts on improving biological organisms by their integrations with functional materials, which can be achieved by biomimetic mineralization as the combination tool. The integrated materials, as the artificial shells or organelles, confer diversified functions on the enclosed organisms. The successful constructions of various virus-, prokaryotes-, and eukaryotes-material hybrids have demonstrated the great potentials of the material incorporation strategy in vaccine development, cancer treatment, biological photosynthesis and environment protection etc. The suggested challenges and perspectives indicate more inspirations for the future development of organism-material hybrids.

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1. Introduction

In nature, the biom mineralization, which is a bio-organism controlled inorganic material formation process, is a ubiquitous phe-

Abbreviations: JEV, Japanese encephalitis vaccine; CaP, calcium phosphate; rAd5, recombinant adenovirus serotype 5; EDS, Energy-dispersive X-ray spectroscopy; MOF, metal-organic framework; ZIF-8, zeolitic imidazolate framework-8; BTB, 1,3,5-benzenetri benzoate; TA, tannic acid; RBC, red blood cell; EV71, enterovirus 71; NP, nanoparticle; ROS, reactive oxygen species; LbL, layer-by-layer; PDADMAC, Poly (dimethyl diallyl ammonium chloride); PAA, polymer and polyacrylic acid; PAH, poly (allylamine hydrochloride); PSS, poly (styrene sulfonate); MDP-Na, sodium monododecyl phosphate; R, arginine; K, lysine; D, aspartic acid; TiBAlDH, titanium(IV) bis(ammonium lactato)dihydroxide; C, cysteine; TEOS, tetraethyl orthosilicate; PN, poly-(norepinephrine); PEI, poly(ethyleneimine); UV, ultraviolet; TCEP, tris(2-carboxyethyl)phosphine; MSN, mesoporous silica nanoparticle; MRI, magnetic resonance imaging; *S. cerevisiae*, *Saccharomyces cerevisiae*; HAP, hydroxyapatite; β -gal, β -galactosidase; EDTA, ethylenediaminetetraacetic acid; SOD, superoxide dismutase; CAT, catalase; AuNCs, gold nanoclusters; TPP, triphenylphosphonium; DOX, doxorubicin; ODN, GC-rich oligonucleotide; Au-ODN, gold-oligonucleotides; NIR, near-infrared; ACP, amorphous calcium phosphate; mAbs, monoclonal antibody.

ies; MPTMS, (3-Mercaptopropyl) trimethoxysilane; TMV, tobacco mosaic virus; ADE, antibody-dependent enhancement; DENV, dengue virus; OA, oncolytic adenovirus; MnCaCs, calcium and manganese carbonates; InP, indium phosphide; *E. coli*, *Escherichia coli*; FR, folate receptors; FA, folic acid; CT, computed tomography.

[☆] Part of the Special Issue on Biom mineralization: From Cells to Biomaterials, associated with the BIOMIN XV: 15th International Symposium on Biom mineralization, held at the Ludwig Maximilian University, Sept 9–13, 2019, organized by Wolfgang Schmahl and Erika Griesshaber.

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nomenon [1]. It includes the crystal nucleation, growth, polymorph and orientation evolution [2] with the precise controls in biological environments. Biomineralization brings hard inorganic matters and soft biological matters together for the construction of functionalized inorganic-organic materials [3]. Organisms regulate the mineral formation in biomineralization and in return, the resulted inorganic minerals can improve the survival and function of those living organisms [4]. For example, the vast majority of resulting mineralized tissues utilize crystalline minerals to stiffen and strengthen themselves, such as protection (shells), tools (teeth), gravity sensors (octocornia or statoliths), and skeleton (bones) etc. [5]. These biominerals exist extensively in a variety of biological organisms, such as, calcium carbonate [6] and silicon dioxide in marine organisms [7], iron oxides in snail teeth or magnetotactic bacteria [8] and calcium phosphates in vertebrates [9]. Thus, the functional biominerals actually possess both advantages of living organism and their inorganic mineral [10]. In view of the subtle characteristics from biomineralization, it is obvious that scientists are highly interested in developing biomimetic materials with superior mechanical performances and biocompatibility [11].

At present, more and more biomimetic designs show great promises for numerous applications [12]. For instance, the biological structural materials with high strength and toughness have been facilely manufactured by a new approach named “assembly-and-mineralization”, this approach can biologically fabricate highly ordered resembles of nacre in nature [13]. Similar to the wide utilization of nacre-mimetic materials, the analogue tooth enamel by bioinspired composite with both multiscale architecture and mechanical properties are prepared [14]. Except for the synthesis of nature-inspired materials, the biomimetic materials can also represent fantastic capacity in repair of dental tissues [15] and skeletal tissues [16], resistance against disease [17], drug delivery and biomedical therapy [18].

However, most artificial materials are constructed by physical and chemical synthesizing in the absence of biological controls due to the unrevealed mystery of biomineralization. Recently, biomineralization inspired designs for the integration of hard mineral and soft organism are developed [19, 20]. Numerous researches on the combination of living organism and biomimetic materials are achieved, including the enhancement of cell viability and stability in a hostile environment and improvement of their applicability for demanding biomedical, biotechnology, and bioelectronics applications [21, 22]. In traditional understanding, biomimetic mineralization is considered as the artificial preparation of materials under the controls of biomolecules and proteins. In the present issue, our biomimetic mineralization specifically focuses on the simulated processes of mineral shell formation on the living organisms, which is mediated by electrostatic and protein-specific interactions. In this review, we discuss the primary techniques of biomimetic mineralization to improve the properties and applications of living organisms. Furthermore, we introduce the applications of virus-, prokaryotes-, and eukaryotes-material hybrids in the fields of vaccine improvement, cell protection, energy production, environmental and biomedical application, etc. Finally, we summarize the achievements of organism-material hybrids, and discuss the potential improvements including various species selection, rational synthetic methods, advanced functional materials and the interactions between organism and materials, for smarter “live materials” construction in future.

2. Techniques for organism-material hybrids construction

2.1. Spontaneous mineralization

The biomimetic mineralization, which can be directly built on the biological surfaces without any modification, is referred as “spontaneous mineralization” here. In general, different kinds of

biological molecules, which are negatively charged, are distributed on the surfaces of the organisms. Thus, the oppositely charged materials, including cations [23–26], positively charged molecules [27, 28] and nanoparticles [29], can be used to directly induce mineral layer formation on organism by electrostatic interaction.

2.1.1. Ionic adsorption

A simple method of spontaneous mineralization is achieved by ionic adsorption. The positively charged ions can be condensed on the oppositely charged biological surface by electrostatic interaction, improving the nucleation of minerals. For instance, the negatively charged glutamic acids, aspartic acids, and carboxyl terminuses exist on external surface of some viruses [23–25], which demonstrates the capacity for spontaneous mineralization. The Japanese encephalitis vaccine (JEV) SA14–14–2 with negatively charged surface, as an example, has been enclosed in a mineral shell in spontaneous mineralization under calcium-rich conditions [23]. Due to the negatively charged surface of JEV viral particles, Ca^{2+} ions can be spontaneously absorbed around the virion, providing the nucleation sites to induce *in situ* mineralization of calcium phosphate (CaP). The eggshell-like coating makes the vaccine robust and endows it superior thermal stability. In addition, the biomineral coating of CaP can be produced on the recombinant adenovirus serotype 5 (rAd5) by spontaneous biomineralization in a calcium-rich medium, owing to anisotropic structures of adenovirus surface [24, 25]. The calcium-rich superficial surfaces provide the nucleation sites and further build the mineral shell in a controlled titration of dibasic sodium phosphate solution (Fig. 1). The biodegradable core-shell structure of vaccine-biomaterial hybrids can mask their surface with controllable thickness and preserve their original activity. However, many viruses cannot be mineralized and remain in their bare state in biological fluids, in which the calcium concentration is insufficient. By coincidence, a suitable mineralization environment can be present in the avian intestinal tract, especially the jejunum and ileum, with high calcium content [26]. In this discovery, the influenza viruses can be self-mineralized in simulated avian intestinal fluid and clearly manifest different infectious properties.

The spontaneous mineralization by ionic adsorption on vaccines is feasible because of their highly charged surfaces and versatility [30]. However, it is difficult to fabricate the consecutive and structured coating on the surface of most organisms, due to their insufficient ion receptors or electronic charges [31].

2.1.2. Self-assembly

Self-assembly, which is a phenomenon that the molecular units or nanoparticles are spontaneously organized into sequential structures by non-covalent interactions, is an important tactic to modify organism under mild conditions. This spontaneous mineralization can be achieved by self-assembly. It is required that the molecular units and nanoparticles carry the positive charges, which facilitate mineralization on biological surface. Among the choices of self-assembly, metal-organic frameworks (MOFs) is a class of porous materials, which can be integrated with organisms under mild physiological conditions [32]. Maddigan et al. demonstrated that the surface charge and chemical properties of a protein impacted the growth of MOFs, the negative charged surface and electrostatic potential of a protein can induce biomimetic mineralization [33]. Therefore, the efficient encapsulation on negatively charged carbohydrates by the spontaneous crystallization of MOFs can be realized [34], and this strategy has great potential in biological development including cell coating. For example, Liang et al. found that the MOFs can self-assemble on surfaces of the living organisms *Saccharomyces cerevisiae* and the bacterium *Micrococcus luteus* in the solution, which contains excesses precursors [27]. The representative MOF material, zeolitic imidazolate framework-8

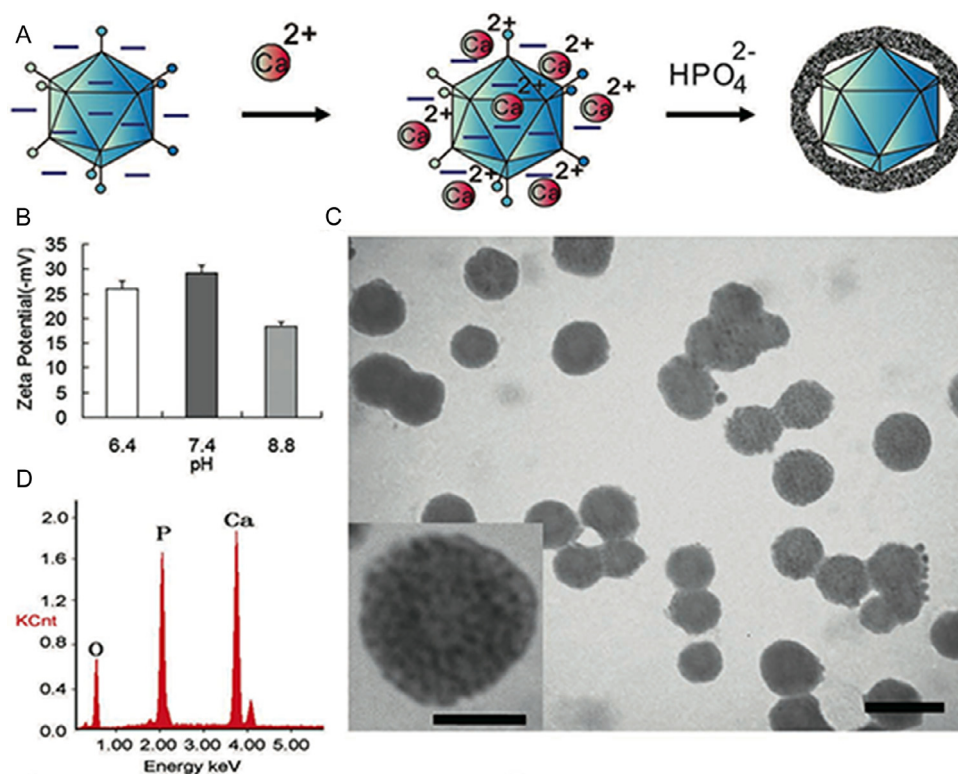


Fig. 1. (A) Schematic presentation of direct mineralization on Ad5 virus with core-shell structure by ionic adsorption. (B) The zeta potential of Ad5 in different pH conditions. (C) TEM image of Ad5 modified by CaP without stain treatment. (scale bar: 100 nm); Insert in high magnification (scale bar: 50 nm). (D) Energy-dispersive X-ray spectroscopy (EDS) analysis of Ad5 with CaP shell. Reproduced with permission [24]. Copyright 2012 John Wiley and Sons.

(ZIF-8), can be coated on yeast cells and bacterium in an aqueous solution containing 2-methylimidazole and zinc acetate. It is possible because the metal cations can gather onto the cell surfaces to increase the supersaturation for the nucleation of frameworks. Thus, while the structure of frameworks forms, the coatings on cells are fabricated. ZIF-8 as an exoskeletal shell, maintain the cell viability for a variety of basic functional biological units [27]. With the difference of *in situ* growing assembly, the spontaneous wrapping on cell surface can occur by the coordination bond. The MOF $[Zr_6O_4(OH)_4(BTB)_2(OH)_6(H_2O)_6]$; BTB = 1,3,5-benzenetribenzoate] with low toxicity and high stability has been selected for cell wrapping. A MOF monolayer construction can be self-assembled by zirconium clusters and BTB linkers (Fig. 2(A)). Following the teichoic acid on cell wall bond with these clusters of pre-synthesized MOF monolayer, the spontaneous wrapping could assemble on bacterial surface (Fig. 2(B)–(D)). The MOF monolayer with efficient catalytic performance enhances the tolerance and elongates the lifetime in oxidative environment [28]. In the meantime, the positively charged nanoclusters can assemble on biological surface to generate the mineral coating. For example, the alumina nanoclusters with positive charges can concentrate on external surface of oppositely charged human enterovirus 71 (EV71) by electrostatic interaction to *in situ* encapsulation of an alumina gel-like nanocoating [35]. The combination of nanoalumina and EV71 can simultaneously enhance thermostability and immunogenicity of the engineered viral particles. The great challenge of nanoparticles on cells may be the material internalization by phagocytosis or macropinocytosis based on membrane extension. Modifying the nanoparticles (NPs) with suitable molecular units is a feasible method to avoid such a problem [29]. Using the ZIF-8 nanoparticle as a model, the cellular internalization can be suppressed by tannic acid-mediated interparticle binding, owing to strong multivalent metal-phenolic complexation (Fig. 2(E)). This

approach can be extended on other kinds of MOFs (e.g. MIL-100, UiO-66- NH_2 , MET-3-Fe types, and *vide infra*), mesoporous silica nanoparticles (MSNs), iron oxide (Fe_3O_4) NPs and NP combinations (Fig. 2(F)) [29].

Self-assembly is performed on a wide range of materials including ion-organic complexes and nanoparticles, demonstrating an extremely rapid and controlled technique for producing structurally functional diverse coating on organisms. This research is in its infancy and needs extensions to more applications on different organisms, and the biomaterials are required to prove the versatility of this technique and the synergistic effects between materials and organisms. In the foreseeable future, the diverse application of biomimetic mineralization on living cells by self-assembly will present many dramatic possibilities for cell biology and biotechnology.

2.2. Mineralization enhancement

Although the spontaneous biomimetic mineralization is convenient for the integration of organisms and materials, the surfaces of most living organisms have insufficient density of ion receptors or electronic charges to induce the mineralization spontaneously. For these cases, the pre-treatments over the bio-surface should be required to promote the mineralization processes. Accordingly, another technique - mineralization enhancement, is established for modification of biological surface, which can provide organisms sufficient nucleation sites to ensure their mineralization abilities.

2.2.1. Layer-by-layer treatment

Layer-by-layer (LbL) assembly is a common technique for the enhancement of mineralization on living organisms. It can repeatedly deposit multilayer polymeric molecules with opposite charges by intermolecular interactions. Consequently, the outmost

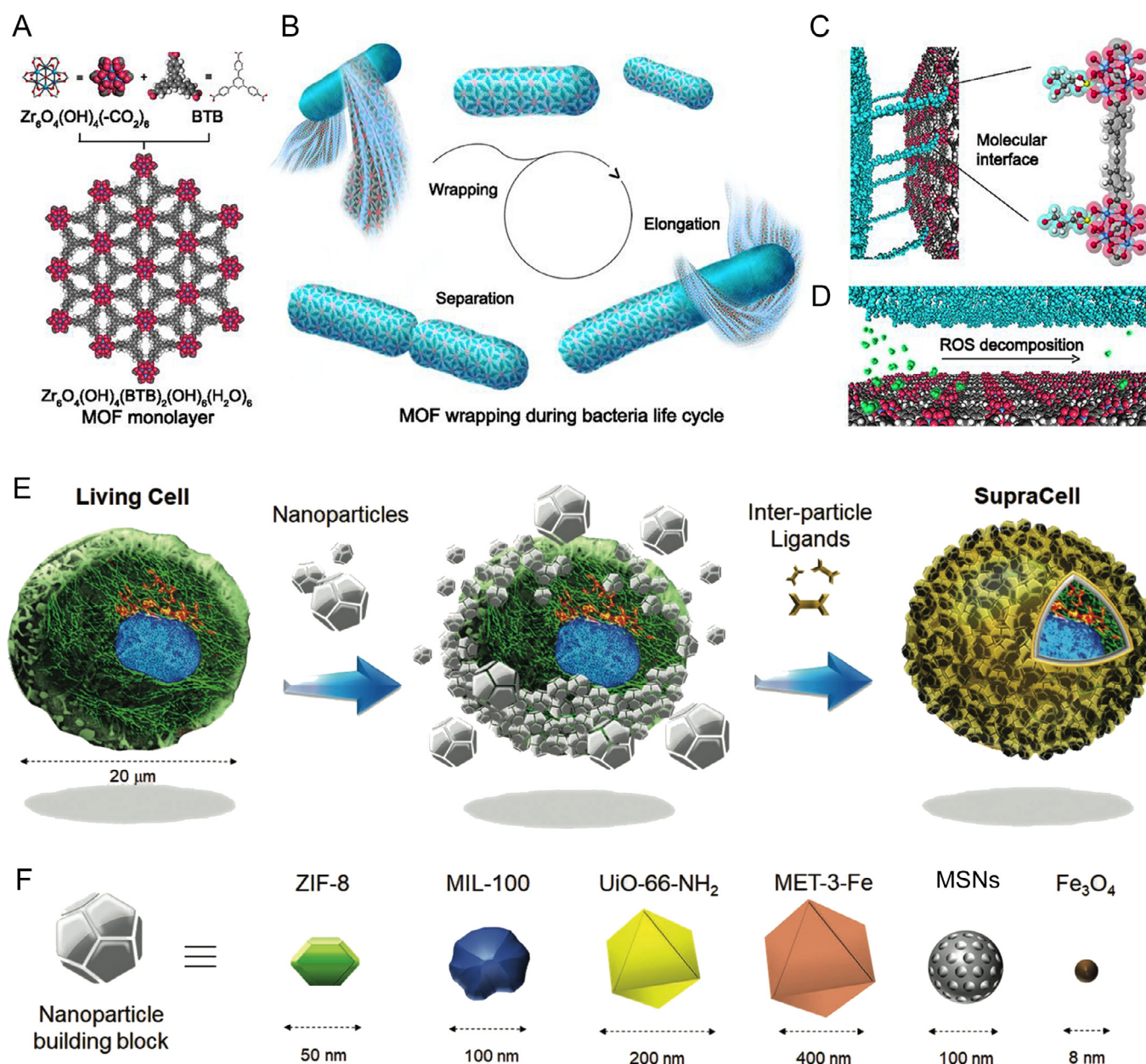


Fig. 2. (A) Design of MOF monolayer comprises 6-connected $Zr_6O_4(OH)_4(-CO_2)_6$ cluster and trigonal BTB linker. (B) Monolayer of MOF spontaneously wraps around the cells, which allows for elongation and separation of cells. (C) Molecular interface on the cell walls illustrates form between the inorganic clusters of MOF and the phosphate moieties of teichoic acid with the multivalent coordination bonds. (D) Decomposition of reactive oxygen species (ROS) by the MOF monolayer encapsulation on cell surface. Reproduced with permission [28]. Copyright 2018 National Academy of Science. (E) Schematic representation incorporation of NPs into the living cells by tannic acid-mediated inter-particle binding. (F) Various kinds of NPs to build blocks including MOFs (ZIF-8, MIL-100, UiO-66-NH₂, MET-3-Fe), mesoporous silica nanoparticles (MSNs), and iron oxide (Fe₃O₄) NPs. Reproduced with permission [29]. Copyright 2019 John Wiley and Sons.

surface has higher density of charges compared to the original biological surface. Then, the highly versatile multilayer on bio-surface can facilitate the production of integrated mineral layer on the cell surfaces. Due to the facility of this technique, it has been widely utilized as a promising alternative strategy with tunable structures, functions, and physicochemical properties of cell surfaces [36].

In general, the multilayers of LbL assembly are formed via multiple intermolecular interactions, including electrostatic interaction, Van der Waals forces, covalent bonding, hydrogen bonding, hydrophilic and hydrophobic interactions, charge-transfer interactions, host-guest interactions, biologically specific interaction, *etc.* [37]. Among these forces for preparing multilayers, the electrostatic interaction is the most widespread used for biomimetic

mineralization, owing to the electric charges on cell surfaces. LbL assembly is established based on electrostatic interactions by using the oppositely charged polyelectrolytes depositing alternating layers, which allows scientists to obtain multilayer films with well-controlled composition, structure, as well as thickness. As the first polycationic layer directly contacting on cell membrane, it may lead to the perforation of mammalian cell membrane during electrostatic LbL assembly, due to the cytotoxicity of most polycations [31]. Nevertheless, natural cationic polyelectrolytes have revealed good biocompatibility without significant cytotoxicity. The yeast cells are firstly coated with an artificial shell (calcium mineral layer) by LbL, which concentrate ions on the cell surface via alternatively assemble oppositely charged polyelectrolytes to promote biomimetic mineralization. For example, Wang et al. used

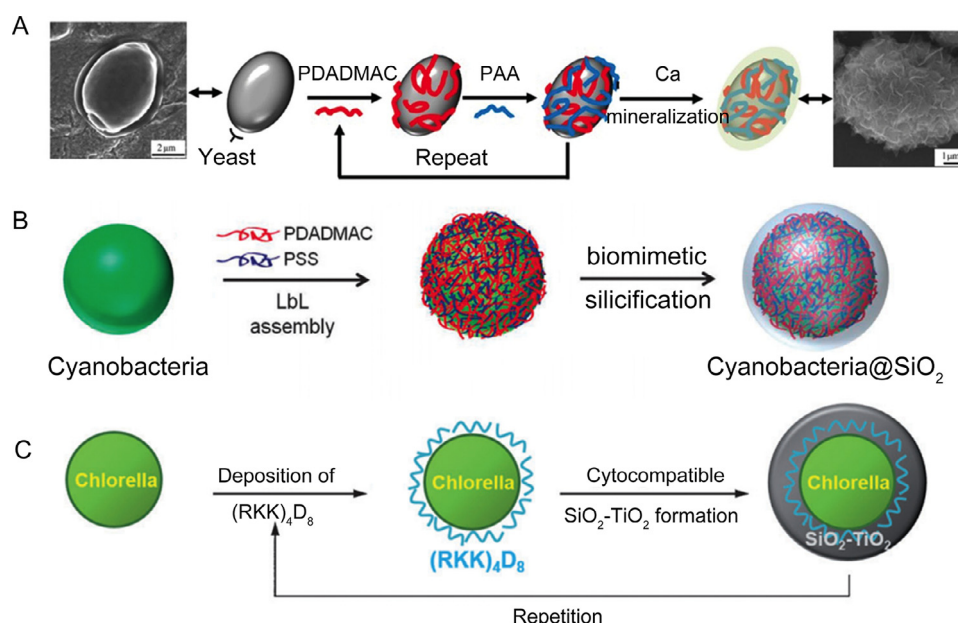


Fig. 3. LbL self-assembly technique used on cells. (A) The formation of biomimetic CaP shell on yeast cell after alternatively depositing PDADMAC and PAA. Reproduced with permission [61]. Copyright 2016 John Wiley and Sons. (B) Procedure for silica coating on individual cyanobacteria by LbL deposition of PDADMAC and PSS. Reproduced with permission [39]. Copyright 2013 Royal Society of Chemistry. (C) Scheme for encapsulation of individual Chlorella cells within the SiO₂-TiO₂ composite shell by depositing (RKK)₄D₈ peptide. Reproduced with permission [42]. Copyright 2013 John Wiley and Sons.

poly (dimethyl diallyl ammonium chloride) (PDADMAC) as the electropositive polymer and polyacrylic acid (PAA) molecules as the negatively charged polymer for study [31]. The PDADMAC molecules can absorb on negative charged yeast cell surface to fabricate the electropositive outside layer, and then, the PAA polymers give the negative charged outermost layer. The mineralization ability of yeast cell can be produced significantly by depositing alternating two polymers, which bind Ca²⁺ ions and *in situ* calcification via the heterogeneous nucleation (Fig. 3(A)). The artificial biosilica shell can also be constructed by LbL [38–40]. Some organisms can hardly induce spontaneous silicification, such as native cyanobacteria, which lacks silicification related proteins (silaffins or silicateins) on their surface. To realize *in situ* silicification on native cyanobacteria, a multilayer structure of (PDADMAC/PSS)₆-PDADMAC is firstly generated on the cell surface, the outmost PDADMAC, which acts as a catalytic template, can promote the formation of the biosilica shell (Fig. 3(B)). The silicification modification not only retains photosynthetic activity of cyanobacterial cells, but also significantly reduces their photoinhibitory effect [39]. Various kinds of coating can be easily put in between these multilayers, including metal nanoparticles, nanoparticles, carbon nanotubes, and magnetic nanorods, etc. [41]. The charged nanoparticles can substitute the polyelectrolyte layers by adsorption onto the cell surface, reinforcing the membranes and making the cell resistant to external impacts. The deposition in one step of polyelectrolyte-stabilized nanoparticles coacervates with polycations onto cells, which is simpler than traditional polyelectrolyte layer-by-layer method. The cationic peptide can be adsorbed electrostatically onto the negatively charged cell membranes and induce the deposition of biomimetic mineralization [42]. A peptide, (RKK)₄D₈ (R: arginine; K: lysine; D: aspartic acid), has been designed to realize the formation of bioinspired mineral shells (Fig. 3(C)). The cationic R and K residues render positive charges the D moiety eliminates the cytotoxicity. The biomimetic mineralization shell of SiO₂-TiO₂ composites with (RKK)₄D₈, which improves the cellular thermo-tolerance, has been encapsulated on individual Chlorella cells from both titanium(IV) bis(ammonium lactato)dihydroxide (TiBALDH) and silicic acid [42].

The organism-material hybrid construction based on LbL-induced biomimetic mineralization has made remarkable achievements. Undoubtedly, there are still challenges including the superior performances, optimization of process parameters, designing of highly flexible multilayer materials. Moreover, it is of critical importance to simplify the process of this technique, which can provide organisms a mild condition to survival. It can be more feasible to obtain subtle structures and physiochemical properties for the requirements of new applications.

2.2.2. Bridge molecule treatment

Considering the complex procedure of LbL technology, there are some relatively simple modifications that can provide a viable solution for the biomimetic mineralization enhancement of living organisms without multilayer alternative deposition. The electric charge of cell surface can be modified after one-step modification by using peptides [43], nanoparticles [44], polymers and polyelectrolytes [45], which provide a potential interface with promoted biomimetic mineralization ability.

The modification enables incorporation of various materials and cells, and sustains their stable attachment to cells in the complex biological environment. Several kinds of positively charged peptides have been designed to alter the negatively charged cell surface by electrostatic adsorption. For instance, a peptide sequence, R₄C₁₂R₄ (R: arginine; C: cysteine), can mimic the serine residue in the active site of silicatein-α and catalyze the silicification on yeast cell surface in the hydrolysis of tetraethyl orthosilicate (TEOS) [43]. In addition, there are various polymers (e.g. polydopamine [46], polyglycerols [47], polypyrrole [48], etc.) to be previously used in cell surface engineering, which can make a uniform, conformal contact with cell membrane. The polymer layers firstly form in cell surface, and then integrate polyelectrolytes to achieve biomimetic mineralization. For example, the cyto-compatible poly-(norepinephrine) (PN) can modify individual yeast cell surface by gentle shaking, and graft poly(ethyleneimine) (PEI) via nucleophilic 1,4- conjugate addition of hydroquinone and amine group [45]. A biomimetic silica layer is accomplished onto the outer layer of yeast cell with PEI as a catalytic template. The double-layered shell

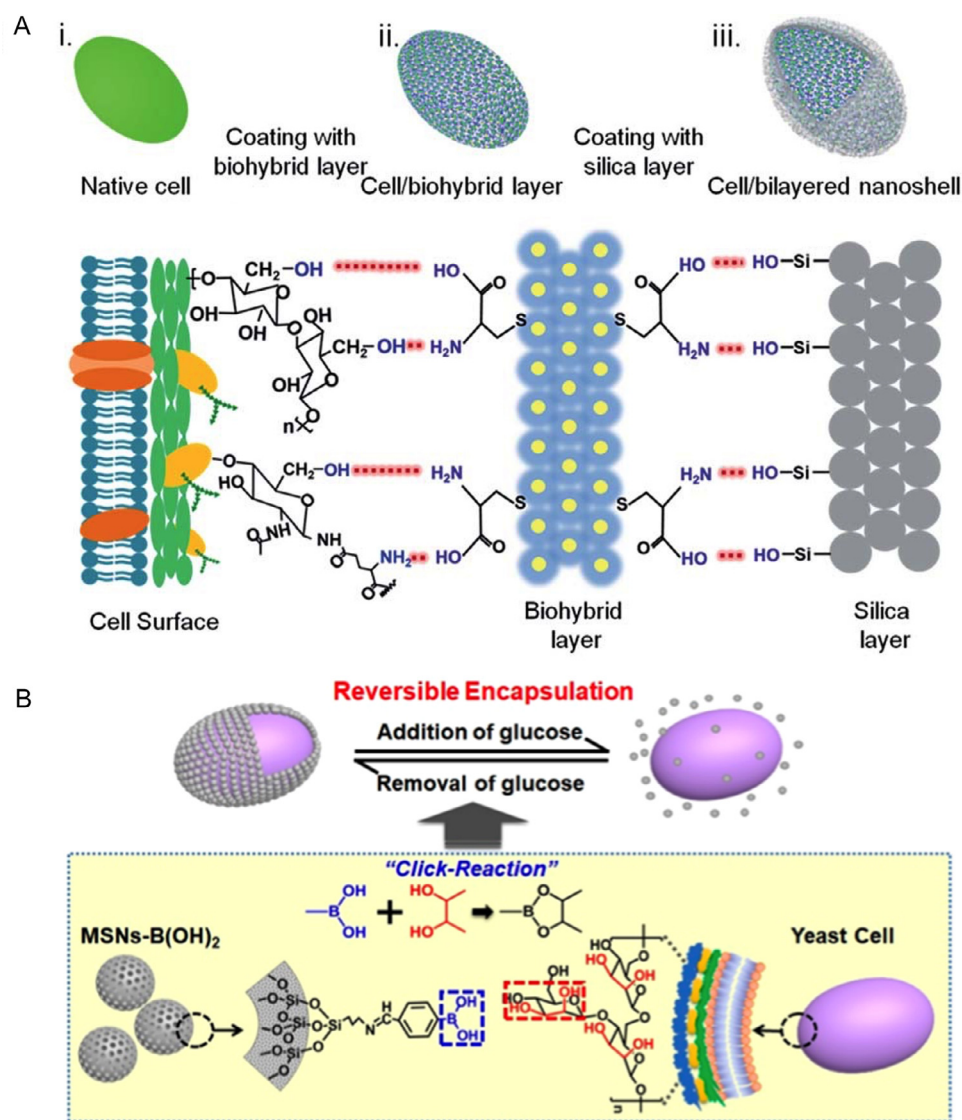


Fig. 4. (A) Bilayered nanoshell formation on a single yeast cell. (i) The native yeast cell; (ii) modification of a biohybrid layer, which is composed of amino-covered gold nanoparticle groups and carboxyl groups (yellow dots: gold nanoparticles; blue layers: L-cysteine molecules); (iii) formation of the bilayered nanoshell with the amorphous silica layer. Reproduced with permission [44]. Copyright 2018 Royal Society of Chemistry. (B) Schematic of MSN-B(OH)₂ encapsulation on yeast cells through a boronic acid vicinal-diol-based click reaction. Reproduced with permission [50]. Copyright 2019 American Chemical Society.

has been shown to be effective in the prevention of enzymatic attack, desiccation, and ultraviolet-C (UV-C) irradiation. The medium layer of double-layered shell can be a biohybrid layer, providing high biocompatibility without affecting viability and morphology of cells. The composition of biohybrid layer is created by L-cysteine functionalized gold nanoparticles by hydrogen bonds. Due to the massive hydroxyl groups of polysaccharides on the yeast cell surface, these nanoparticles cannot enter the cell [44] (Fig. 4(A)). After the modification of the biohybrid layer, as a bridge, the biomimetic silica nanoshell is formed in suspension of amorphous silica with hydrogen bonds as well. In comparison with the above-mentioned multi-step LbL techniques, these modifications require the relatively simple steps, which are beneficial to the efficiency enhancement of biomimetic mineralization materials and living organisms as well as widen the chemical tools for single-cell engineering.

Another of the main modifications for organism-material hybrids construction is realized by linking functional groups on the cell surface via covalent bond. Although the construction by amide coupling has been developed, the cross-linking of carboxylate and amine groups is inefficient and nonspecific be-

tween biomimetic materials and cell surface. There are several reported approaches for cell surface chemical engineering, such as the temperate reduction of disulfides in cell membrane proteins with tris(2-carboxyethyl)phosphine (TCEP) and subsequent thiol-maleimide conjugation [49]. The facile and universal method can be used for diverse cell types without any adverse effects to their functions. Multifunctional nanoparticles (e.g. mesoporous silica nanoparticles (MSNs)), as a model in shellization studies, can be adhered to cell surface after chemical reduction, which could apply to track the target cells and simultaneously deliver adjuvant drugs. The MSNs are accomplished by the Schiff-base-forming reaction, modified with B(OH)₂ covalent linking to cis-diols of alcohols [50] (Fig. 4(B)). The hydroxyl groups of polysaccharides can rapidly graft on the yeast cell surface via the phenylboronic acid-based click reactions. It is necessary to point out that the encapsulated cells present a higher viability to native ones in a lot of hostile conditions, including longtime exposure in water, elevated temperature, UV light, lyticase, and osmotic pressure. Moreover, the MSN-B(OH)₂ shells are regulated phenylboronic acid ester formation and cleavage with glucose and pH, which can be converted

in demands [50]. The weak interaction treatment is used to fabricate dynamic nanostructures with high selectivity and tunability, however, the stability is feeble if the interaction is too weak. Consequently, the strong interactions are often required for generating stable organism-material hybrids, such as covalent bonding. However, extremely strong interactions give rise to the lack of reversible dynamics and influence the viability of living organisms. Therefore, the interactions between materials and cell surfaces require precise strength of chemical conjugation. In the future, the flexible and stable method should be used for multifunctional cell applications, such as cancer immunotherapy, hematopoietic stem cell transplantation and production of artificial tissue.

2.3. Genetic engineering

In nature, the biomineralization ability of living organisms is regulated by biomineralization-related proteins, which is derived from the gen code controls. In other words, the genetic engineering could manipulate and tune the biomineralization in organisms, particularly if it lacks the special functional proteins. Obviously, this technology could keep the mineralization capacity in genetic inheritance. Relative to the above-mentioned techniques, which could not pass it integrally on to the next generation, the genetic engineering changed it once and for all. Therefore, the integration of biomineralization-relevant gene and living organisms could realize an inheritable biomineralization via gene expression.

The genetic engineering could enhance both intracellular molecular-level and extracellular biomineralization. For instance, in low-iron conditions, the iron-responsive transcriptional activator Aft1 would translocate into the nucleus, which regulates the intracellular iron level of yeast cells. The high-affinity iron transporter on cell surface would be generated by one of the genes upregulating of Aft1 encodes, and produce abundant iron accumulation by individual protein macromolecules to achieve intracellular ferritin biomineralization processes [51]. In mammalian cells, the metal biomineralization processes could be occurred by genetically control under specific localized environmental conditions. The multifunctional orthogonal compartments in eukaryotic cells would be regulated via expressing N- or C-terminally modified encapsulins, which encapsulated series of cargo proteins and enabled size-constrained metal biomineralization [52]. Magnetogenetics, a effective method for remote-controlled operation of cellular functions in tissues and organisms, has been emerged [53]. It can be manipulated cellular activities in living cells by using external magnetic fields, utilizing genetically encoded probes. The genetically encoded protein crystal with ferritin subunits maintains their ability to mineralize iron, which could generate magnetic forces and attract by a permanent magnet [54]. While this system does not yet enable *in vivo*, a genetic construct magnetic cells to be trapped with magnetic fields and imaged with magnetic resonance imaging (MRI) *in vitro* and *in vivo*. The combination of a fusion protein and decameric ferroxidase from *Rhodospirillum Rubrum* with the iron-binding peptide M6A, which was previously shown to promote and stabilize the nucleation of magnetic iron species *in vitro*, could engineer bacterial cells to accumulate iron in “ultraparamagnetic” macromolecular complexes at room temperature [55] (Fig. 5(A)). The genetic encoding provides to facilitate magnetic capture and inherited advantage during cell proliferation. The genetic engineering also could endow the capacity of extracellular biomineralization. As the example, two types of nucleating peptides (N6p, NWp and W6p) had been selected on the virion surface to strengthen its ability to initiate mineralization of CaP (Fig. 5(B)). The nucleating peptides were cloned into the attenuated EV71 strain A12 by using standard DNA recombination technology, without impacting the primary structure of the EV71 virion. W6p, an acidic protein, which is the most useful peptides to enhance spontaneous biomin-

eralization capacity in calcium-enriched culture medium, and can trigger the formation of CaP *in vitro* by binding calcium ions [56]. The calcium phosphate shell on vaccine was provided with stable heritability and pH-sensitivity, improving the thermostability and immunogenicity.

Genetic engineering is a progressive technique, which could be combined with biomineralization to produce inheritable and multifunctional changes on organisms. It could be used as a protective shell on vaccine or extracellular, enhancing their stability. In eukaryotic cells, the versatile reaction chambers could also be achieved by genetically encoded encapsulins [52]. Moreover, this approach could reinforce therapeutic efficacy of mammalian cells with metabolic pathways for genetically modification. Therefore, genetically controlled biomineralization has profound implications for cell engineering and emerging cell therapies. This technique still face several challenges, including complicated process, difficult characterization, epigenetics and gene mutations [57], etc., which need more in-depth understandings.

2.4. Intracellular mineralization

The mineralization processes occur not only extracellularly, but also intracellularly. The inorganic minerals can be composed inside biological organisms, these biosynthetic pathways called “intracellular mineralization”.

A typical synthesis, for example, biogenic CaCO₃ nanoparticles can also be generated inside *Saccharomyces cerevisiae* (*S. cerevisiae*) cells [58]. At first, the yeast cells are reactivated in maltose solution, which can internally produce carbon dioxide by respiration. Subsequently, Ca²⁺ and OH⁻ enter inside the yeast cells by adding Ca(OH)₂ saturated solution. Under normal growth conditions, CO₂ inside the yeast cells converts into CO₃²⁻. Finally, the CaCO₃ nanoparticles are fabricated in the yeast cells by the endogenous reaction of Ca²⁺ and CO₃²⁻ (Fig. 6). Due to the interaction between CaCO₃ and biomolecules, these biogenic CaCO₃ nanoparticle can be stabilized by the cellular biomolecules [58]. The hydroxyapatite (HAP) can also be generated inside yeast cells by endogenous mineralization [59, 60]. The Ca²⁺ ions firstly pass through the cell membranes and enter into the interior of the yeast cells by incubating in CaCl₂ solution. Then, the collected and washed cells are added into a Na₃PO₄ aqueous solution, which provides PO₄³⁻ into the yeast cells. The HAP nanoparticles are formed through the endogenous reaction between Ca²⁺ and PO₄³⁻ to achieve the intracellular mineralization [59, 60].

In general, the cations and anions successively enter into the interior of cells, and the intracellular mineralization can form by the endogenous reaction. This biosynthesis can avoid several problems such as non-compatibility in biological organisms and environmental pollution. The endogenous mineral synthesis can functionalize cells to develop drug carriers [58, 59] and environmental scavenges [58]. Expanding the material library available with rational design through intracellular mineralization will break down limitations and exploit more innovative and useful applications.

3. Materials for organism improvement

3.1. Artificial shell

The biological organisms are weak in many *in vitro* conditions due to many external stresses. Inspired by eggshell, the construction of artificial shell with biomimetic mineralization on the organisms can confer several functions [61], such as cell protection [28, 29, 31, 39, 42, 62–64], facile degradability [27, 50, 65], efficient biocatalysts [28, 66, 67], etc.

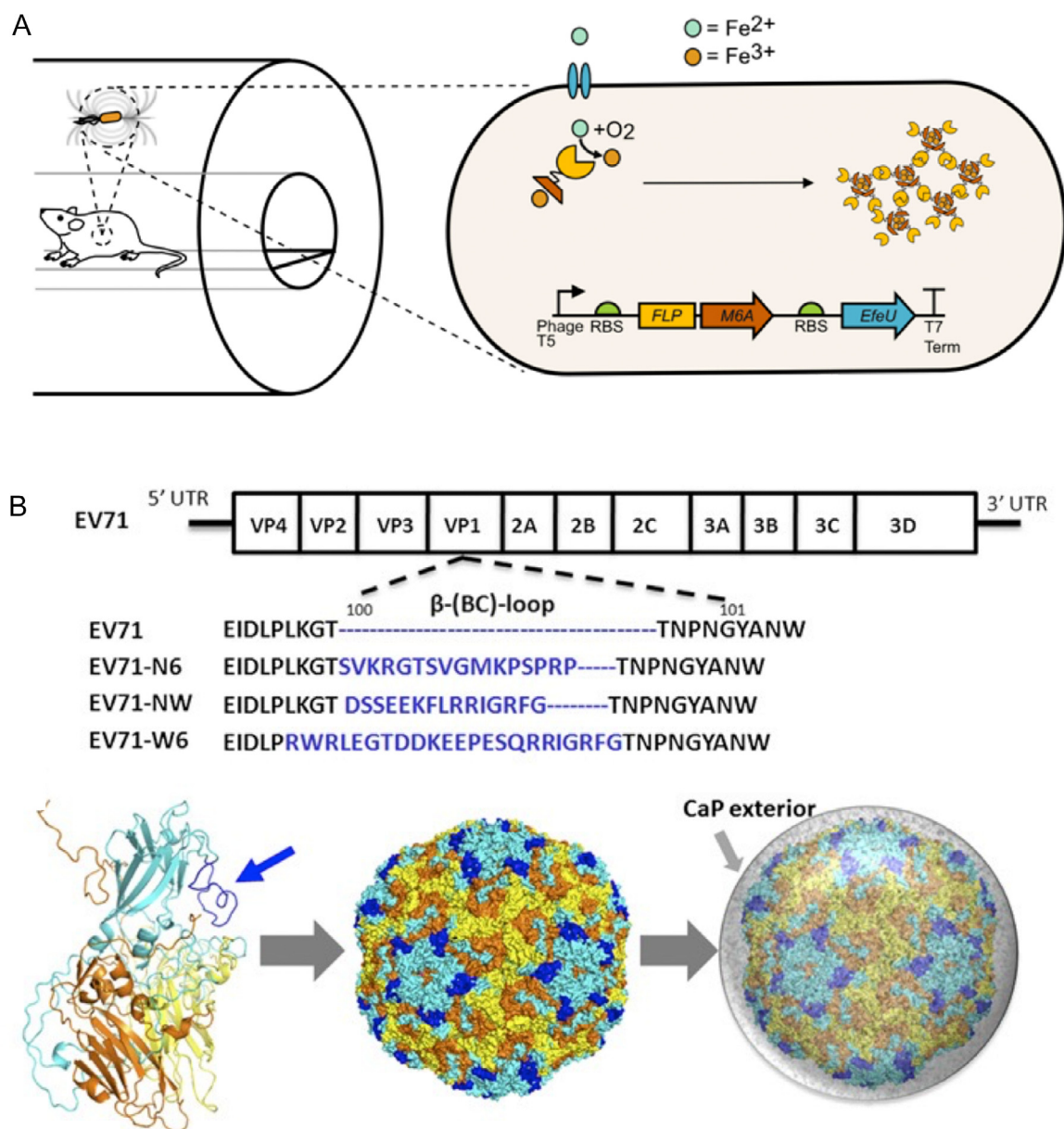


Fig. 5. (A) Scheme of ultraparamagnetic gene circuit. Paramagnetic cells produce magnetic fields and experience force while placed inside a strong magnetic field (e.g. in MRI scanner). The gene circuit is driven using an IPTG-inducible T5 phage promoter, increasing the intracellular iron content available to FLPM6A, which forms macromolecular assemblies with oxidized iron. Reproduced with permission [55]. Copyright 2018 John Wiley and Sons. (B) Scheme of engineered EV71 carrying nucleating peptides. EV71 genome and the insertion site of the β -(BC)-loop of VP1. It might induce in situ biomineralization to form a CaP mineral exterior for the engineered vaccine. Reproduced with permission [56]. Copyright 2013 National Academy of Science.

3.1.1. Cell protection

The artificial shells on the organisms can be served as “biomimetic” to promote their durability in hostile environments. For example, *S. cerevisiae* cells, a typical yeast cells, are firstly individually encapsulated with a biocompatible CaP mineral shell [31]. The CaP layers on cell surface could be performed as a protection shell to resist the hostile environment (e.g. in lytic enzyme condition). Moreover, due to the slow diffusion and transport of oxygen and some nutrients through the mineral coating, the encapsulated cells were dormant and their lifetime would be extended (Fig. 7). This tactic could be used for prolong the lifetime of cell storage and provide another pathway to reactivate therapeutic cells in human body [31]. Thus, the organism-material hybrids are potential to immensely improve the cell viability in hostile conditions and extend the lifetime of cell preservation.

The light and high temperature are the harmful external stresses. The photosynthetic microorganisms have been given an intensive attention in the research fields of biology, energy, and environment [68]. However, the efficiency of photosynthesis is extremely sensitive to environmental stresses, such as high sunlight stress, UV radiation and hyperthermy, which limits their industrial applications [69]. The biomimetic mineralization may be efficient tactics to protect the algae and cyanobacteria against harsh environment and enhance adaption in practical applications by generating the exquisite inorganic shells [70]. The photoinhibition under high light stresses is one of the primary reasons that influence photosynthetic efficiency. An artificial biosilica shell with good biocompatibility has been fabricated onto the unicellular cyanobacterium, which can reduce light transmission and alleviate the effects of photosynthetic activity under intense light conditions [39].

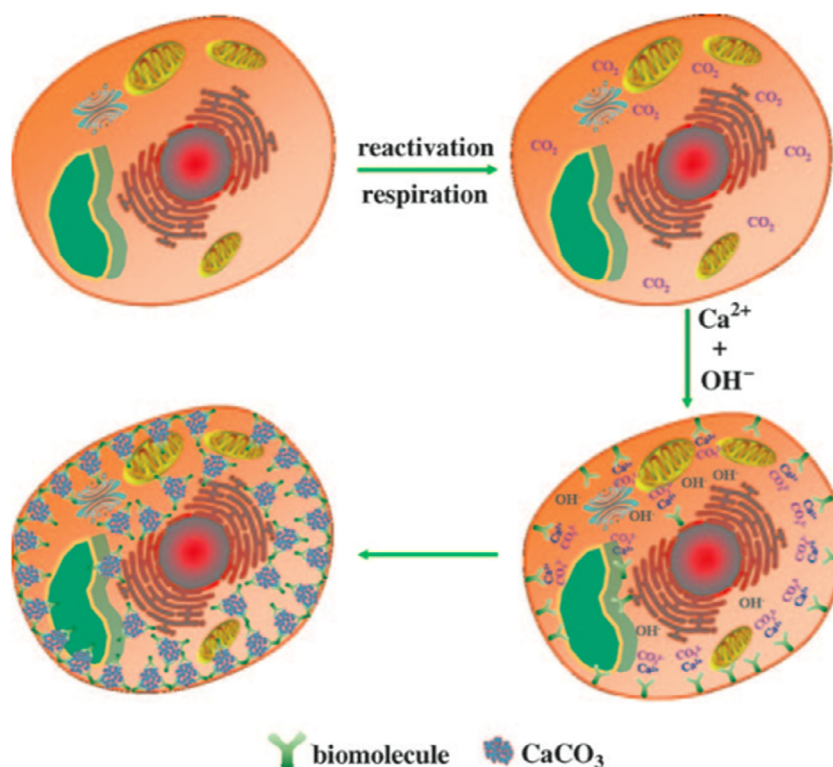


Fig. 6. Mechanism of the formation of intracellular mineralization, which demonstrates the production of CaCO_3 nanoparticle by endogenous reaction. Reproduced with permission [58]. Copyright 2011 John Wiley and Sons.

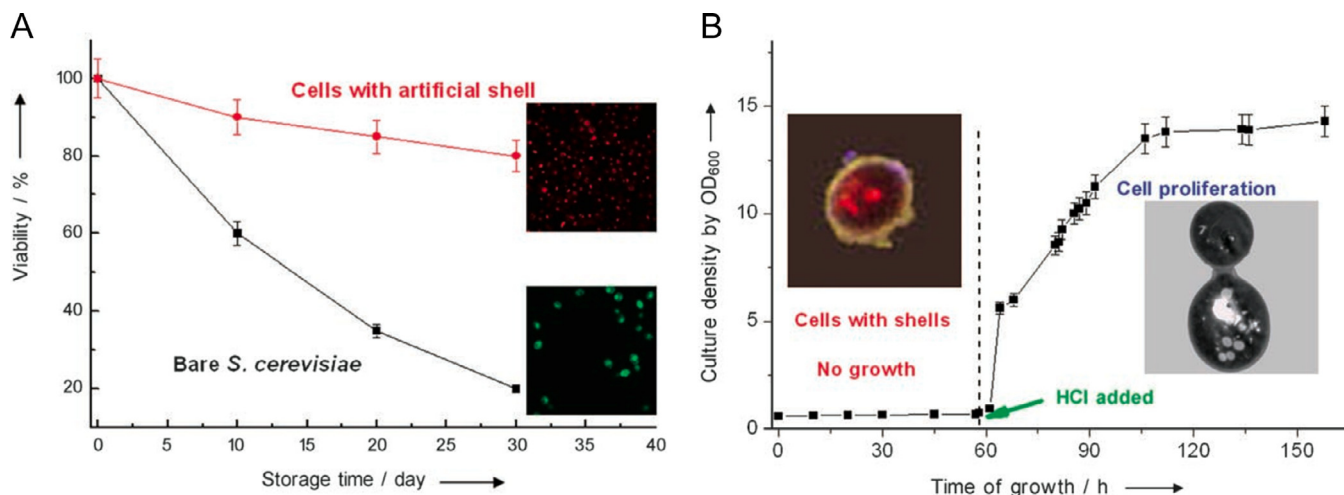


Fig. 7. (A) The curves of cell viability between bare *S. cerevisiae* and coated ones in pure water against time. (B) The curves of culture density by OD₆₀₀. 1 mM HCl was added at $t = 60$ h to induce the dissolution of the mineral shell. Reproduced with permission [31]. Copyright 2008 John Wiley and Sons.

A nanoporous bio-interface of nanosized gold and L-cysteine is further manufactured between mesoporous silica layer and a single cyanobacterium, which can not only provide high stability under high light stress, but also can effectively protect cyanobacterium against abrupt acid-base changes and strong UV radiation. Moreover, this biohybrid-coating can facilitate reactants diffusion and energy transmission, which is more biocompatible than the silica-coating [71]. The biomimetic shell can also resist the significant injury of UV radiation to the photosynthetic microalgae [72]. CeO_2 nanoparticles, a UV filter material with good biocompatible, can be adsorbed on *Chlorella* cells surface by electrostatic interaction. The outmost CeO_2 shells could not only efficiently percolate the UV radiation before it reaching the inside cells, but also scavenge

reactive oxygen species (ROS) through the surface redox reaction to guarantee the normal photosynthetic system in harsh UV radiation [62]. The SiO_2 - TiO_2 shells could be encapsulated on *Chlorella* cell surface after the peptide modification. The encapsulation process was highly cytocompatible and led the *Chlorella* cell to approximately three-times enhancement of the cellular thermo-tolerance [42].

In addition, bacteria have many the practical applications, such as degradation of organic pollutants, industrial production, however, their weaknesses and unnegligible infectivity limit their applications. They are fragile and easily inactivated in hostile environments *in vitro*, rapidly cleared by the host immune system *in vivo* [73]. Therefore, it is significantly important to improve cyto-

protection ability and shielding infectivity for the application of bacteria. The biomimetic materials also could be coated on bacteria surface to enhance their viability under harsh environments. For example, the MOF monolayer can encapsulate bacteria, which strengthens tolerance of the anaerobes against oxidative stress, owing to the catalytic performance of the MOF shell. Meanwhile, the MOF encapsulation permits the transportation of small molecules necessary for cell growth to maintain the cell life [28]. Moreover, the bacteria can also be enclosed with sophisticated mesoporous silica shell, which has selective permeability and self-protection in harsh conditions (e.g. hydrolases and toxic nanoparticles). At the meanwhile, this artificial layer can shield the bacterial surface antigen to evade the host immune clearance both *in vitro* and *in vivo* [63].

Different from the above cells, the animal cells lack robust cell walls or exoskeletons. Their bilayer lipid membranes, which are fragile and highly susceptible to environmental changes, make them even weaker than yeast cells [64]. The development of cyto-compatible approaches for improving animal cells with biomimetic materials would be available for long-term protection and storage of cells. The TiO_2 and SiO_2 coating had been used in microorganisms, which demonstrated their stronger resistance to external stressors by bio-inspired silicification method [63]. This approach could be used for mammalian cells (HeLa cells, NIH 3T3 fibroblasts, and Jurkat cells) endowed the mechanical rigidity and enhanced resistance by the physical impermeability to proteolytic attack of trypsin. Owing to the non-degradable silica encapsulation, it is only available for a short-term, which might led the death of mammalian cells after long time period [64].

However, sometimes the bio-armor may become unfriendly to the human society. For example, the viruses can wildly exist on the Earth, from the atmosphere to the deep biosphere, and viral pathogens infect a broad range of evolutionarily divergent groups of organisms [74]. In nature, the virus exists in not only the native state, but also the mineralized state. For example, some bacteria phages in hot springs, they are encapsulated with a mineralized state inside archaea cells or fossils [75]. The spontaneous biomineralization is served as the survival tactics for viruses to resist the hostile environment. It is known that the avian influenza viruses directly transmit to human is limited, but they can widely spread via the birds. Zhou et al. found that the viruses can be self-mineralized in simulated avian intestinal fluid, which are more robust with enhanced infectivity and thermostability [26], which may explain the unexpected infections of bird flu viruses among human. Potentially, the incorporation of viruses and biomimetic minerals provides in-depth understandings of virus infection and its control. In general, the biomimetic mineralization can be formed on cell surface to encapsulate individual living cells with good bioactivity under physiologically mild conditions. Meanwhile, the modifications on various kinds of living organisms by biomimetic materials have great effects to enhance the mechanical strength, stability and survivability in common. We believe that the rational design of organism-material hybrids will break down limitations and exploit more innovative and useful applications.

3.1.2. Biodegradability

The biomimetic encapsulation is designed for a facile degradability to control the cell division, such as the coatings by MOFs [27, 65], the encapsulation by specific reactions [50]. It is particularly important for cell-based devices that require both long-term storages of cells and command exposure to the cells.

As mentioned above, the biodegradable coating also could be composed with MOF and β -galactosidase (β -gal), which could form the exoskeleton on the coated cells and generated nutrients in an oligotrophic environment (Fig. 8(A) and (B)). When recovered to optimal growth conditions, the biocomposite MOF shell can

be easily removed by the addition of EDTA, meanwhile, the cells could regained full growth immediately and remain healthy after this process [65]. The reversible coating on cells is also achieved by specific reaction, for example, a phenylboronic acid based click reaction for cell encapsulation [50]. Due to the glucose and pH responsiveness of the boronate ester bond, the cell encapsulation could reversible by addition or removal of glucose. Upon addition of glucose at pH 7.0, the borate-ester linkage between MSN-B(OH)_2 and cis-diol groups is disrupted by the click reaction equilibrium. During the removal of glucose, the pH decreased to 6.0, the connection between MSN-B(OH)_2 and cell surface polysaccharides can re-form. Following glucose addition and dilution, the daughter cells of MSN-B(OH)_2 encapsulation can be generated by redistribution or extra addition of MSNs (Fig. 8(C) and (D)) [50].

The improvement of organism-material hybrids should be fabricated in a gentle condition, with subtle structure, high stability and controllable degradability. The biodegradable encapsulation for living organisms can prevent undesirable permanent shell coverage and cell hibernation. These designs on demand show the new potential for facile cellular manipulation and engineering selective adaptability in living cells.

3.1.3. Biocatalysts

Another important field of functionalized organism-material hybrids is the development of biocatalysts [76]. For example, catalytic functions of biomimetic materials-interfaced cells have been demonstrated to transform poorly water-soluble substrates into fine chemicals, pharmaceuticals, and fuels [77]. The efficient biocatalysts should not only be long-term stable in the hostile environment (e.g. organic solvents) [78], but also overcome the diffusional limitations to achieve the catalytic functions.

A robust and recyclable Pickering interfacial biocatalysis has been fabricated by integrating *Alcaligenes faecalis* cells with CaP mineral shell and Fe_3O_4 nanoparticles [66]. This CaP mineral shell can effectively protect the biocatalysis from long-term organic-solvent stress, meanwhile, the Fe_3O_4 nanoparticles provide the magnetic separation and recycling. At the interface of two immiscible solvents, the adsorption of MDP-Na on the mineral shell could simultaneously stabilize Pickering emulsions (Fig. 9(A)). This rational design of shell on biocatalysis greatly enhances the catalytic capacity and the efficient reusability (up to 30 cycles) [66]. In addition, a shell with multienzyme activity on yeast cell surface has been fabricated by manganese dioxide nanozymes [67]. It is worth noting that the continuous MnO_2 shells can not only strengthen the cellular tolerance against multiple stressors (e.g. dehydration, lethal lytic enzyme and UV radiation), but also maintain the high catalytic activity and stability for two weeks' storage, revealing the capacity for further cytoprotective usages. During the assistance of these nanozyme shells, superoxide radical and $\text{OH}\cdot$ radical can be efficiently removed in nitro blue tetrazolium and terephthalic acid reaction assay system respectively (Fig. 9(B)), which demonstrate the multienzyme activity of the organism-material hybrids [67].

The incorporation with biomimetic materials is the appropriate strategies to fabricate the demanding biocatalysts. By integrating the mineral materials, individually encapsulated organisms become robust in hostile biocatalytic environments to retain high stereo selective catalytic activities and cell viabilities. Moreover, due to the specific structures of functional materials, the biocatalytic performances could be highly enhanced. Therefore, it is reasonable to expect that the functionalized organism-material hybrids can be further developed for applications in efficient and practical whole-cell biocatalysis.

3.1.4. Functionalization

The combination on living organisms with biomimetic mineralization can create several chemical and biological functionalities,

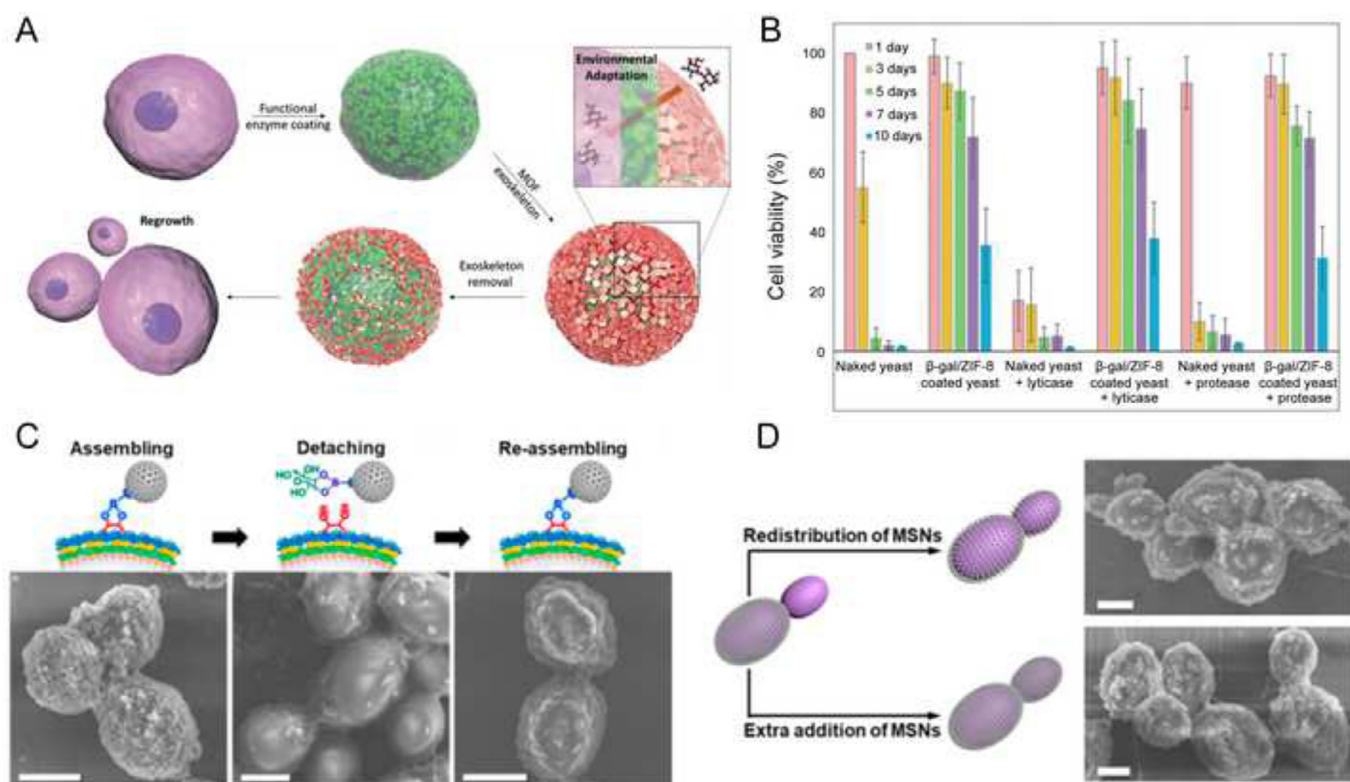


Fig. 8. (A) Scheme of construction and removal of the bioactive porous (β -gal/ZIF-8) shell for synthetically adaptive cell survival. (B) Relative cell viability of naked yeast and yeast cells coated with biocomposite MOF in oligotrophic cell media containing lactose. Reproduced with permission [65]. Copyright 2017 John Wiley and Sons. (C) Reversible MSN-B(OH)₂ coating of yeast cells. The SEM image of MSN-B(OH)₂-coated cells (left) before and (medium) after MSN-B(OH)₂ dissociation promoted by addition of glucose, and (right) following reassembly caused by glucose removal (scale bar 3 μ m). (D) Two methods of encapsulating daughter cells. The redistribution of MSN-B(OH)₂ over daughter cells by glucose addition and dilution (up). The complete restoration of encapsulation of daughter cells by addition of extra MSN-B(OH)₂ (down) (scale bars 2 μ m). Reproduced with permission [50]. Copyright 2019 American Chemical Society.

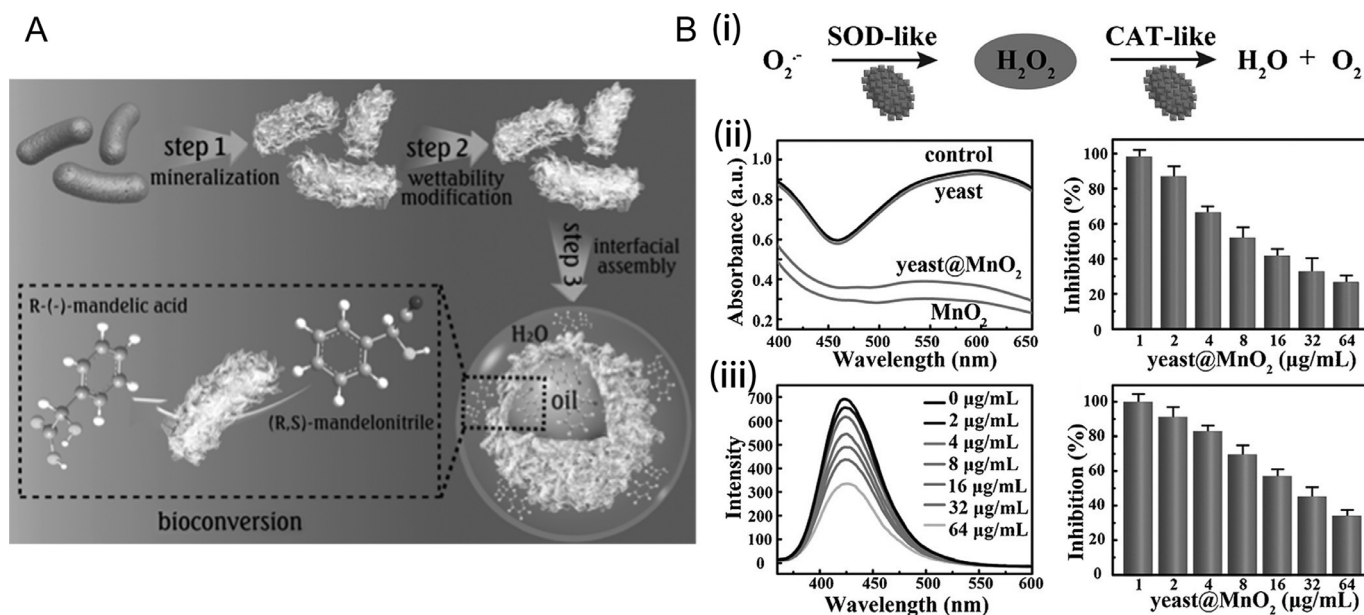


Fig. 9. (A) Preparation of robust Pickering interfacial biocatalysts based on the individual bacterium encapsulation technique and their application in phase-transfer stereoselective bioconversion. In step 1, a calcium phosphate mineral shell doped with Fe₃O₄ nanoparticles was deposited onto the bacterial surface. In step 2, the wettability of the mineral shell was tailored by adsorption of MDP-Na. In step 3, individually encapsulated bacteria were assembled at Pickering interfaces for hydrolyzing hydrophobic (R,S)-mandelonitrile in the oil phase into hydrophilic R(-)-mandelic acid. Reproduced with permission [66]. Copyright 2015 John Wiley and Sons. (B) The superoxide dismutase (SOD) and catalase (CAT) mimic activities of MnO₂ coating. (i) Schematic illustration; (ii) SOD like activity and percent inhibition of oxidation; (iii) CAT like activity and percent inhibition of oxidation. Reproduced with permission [67]. Copyright 2017 John Wiley and Sons.

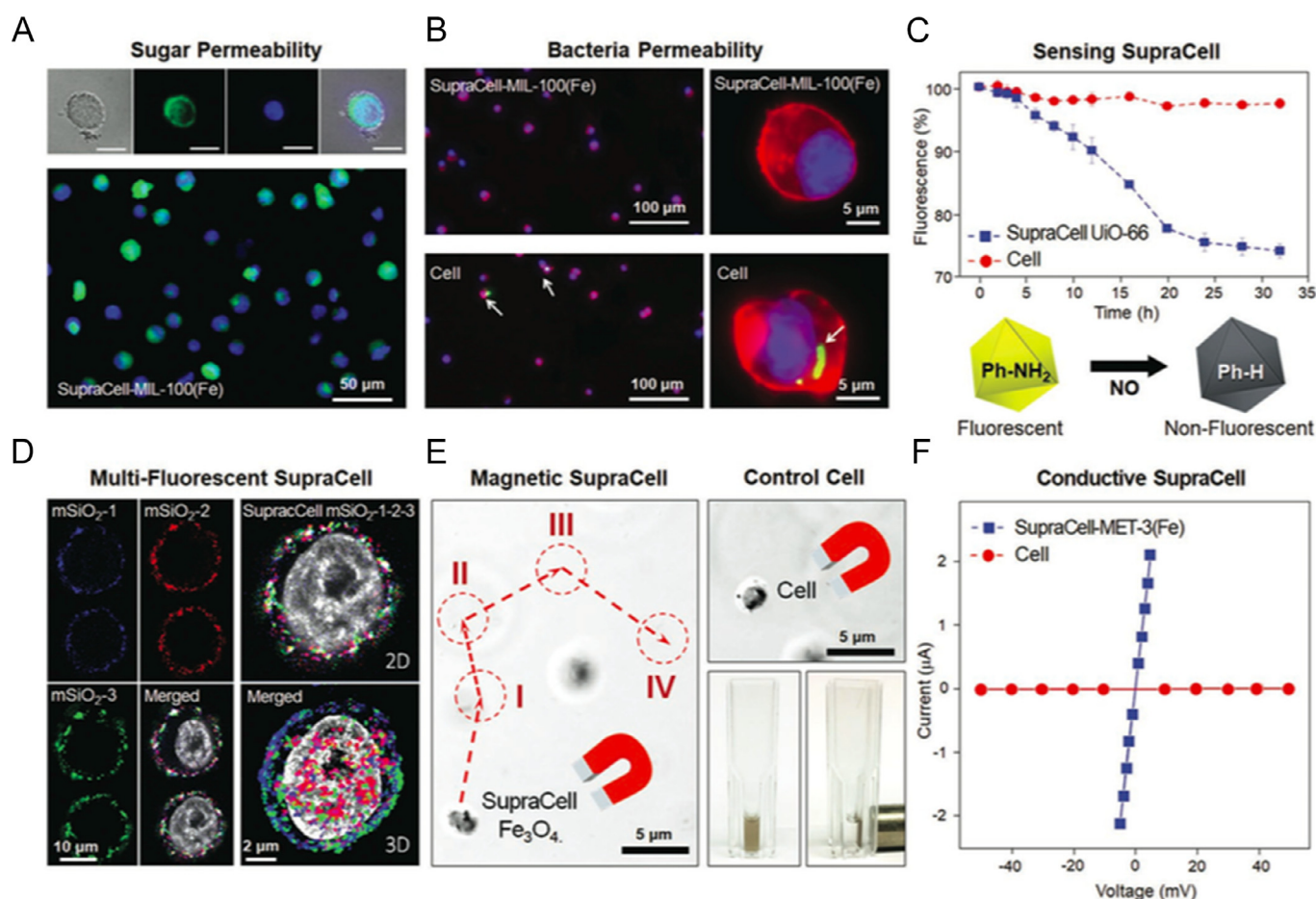


Fig. 10. (A) and (B) Size-selective permeability studies involving sugar permeation and bacteria nonpermeation. (C) Timeline of the fluorescence of cellular NO-sensing coated cells based on fluorescent UiO-66(Ph-NH₂) nanobuilding blocks upon NO detection. (D) The confocal images of multifluorescent cells based on three different fluorescent nanobuilding blocks. (E) Bright-field microscopy images of magnetically actuated Fe₃O₄ coated cells or immobile normal cell. Photographs of a dispersion of coated cells before (left) and after (right) placing a magnet on its side. (F) Current–voltage plot demonstrating the conductivity imparted to the coated cells via MET-3(Fe) MOF NP-based exoskeletons. Reproduced with permission [29]. Copyright 2019 John Wiley and Sons.

which is introduced by integrating the functional groups with non-toxicity and cytocompatibility onto the biomimetic encapsulated organisms [64, 79, 80].

The functional mineral shells import various functions to biological systems. For example, thiol-functionalized silica shells are generated by adding (3-Mercaptopropyl)trimethoxysilane (MPTMS), which are the silanol derivatives containing functional groups [79]. The thiol group in the artificial shell specifically reacts with maleimide derivatives. Thus, this biomimetic coatings can be integrated with biotinyl functional group on yeast cell surface to introduce various functions, such as fluorescent dyes, chemical moieties or proteins, the site-specific immobilization of living cells [79]. This method has been also be extended to mammalian cells (e.g. HeLa cells), which is useful for the fabrication of cell-based sensors and cells-on-a-chip by the site-specific localization of cells [64].

In addition, the NPs with diverse functionalities and natural coherence may be ideal candidates for cellular engineering and provide a convenient versatile platform to fabricate multiple functional organism-material hybrids. For instance, the artificial shell composing with TA and various kinds of NPs shows a unique semi-permeability, which allows nutrients but prevent pathogen from attacking cells. The different types and combinations of NPs demonstrate the versatile functions, containing multi-fluorescent labeling, sensing, magnetic, and conductive properties (Fig. 10) [29].

In general, the field of functionalized organism-material hybrids is rapidly developing. The chemical and biological functionalities could incorporate with living organisms, following the different integration with biomimetic materials. It is therefore anticipated that the organism-material hybrids with versatile functions would make a significant step towards various areas, such as cell-based sensors, reactors, and devices.

3.2. Artificial organelles

Rather than the formation of shell structures, the biomimetic materials can be implanted into cells to develop more available functions, which are considered as artificial organelles. The studies of artificial organelles can be extended to the diversified functionalities and potential applications, such as robust stability [81], energy production [82], environmental protection [58] and biomedical therapy [59, 81, 83].

For example, it has been documented that the solar power can be effectively utilized by photosynthetic biohybrid system of “artificial organelle” and bacteria for fuel production [82]. The gold nanoclusters (AuNCs), biocompatible light absorber, are preferentially taken up by *M. thermoacetica*. The ultra-small AuNCs serve as the intracellular photosensitizers for non-photosynthetic bacteria to harvest solar light. The photo-excited electrons form AuNCs transfer to cytoplasm-distributed redox mediators for CO₂ fixation.

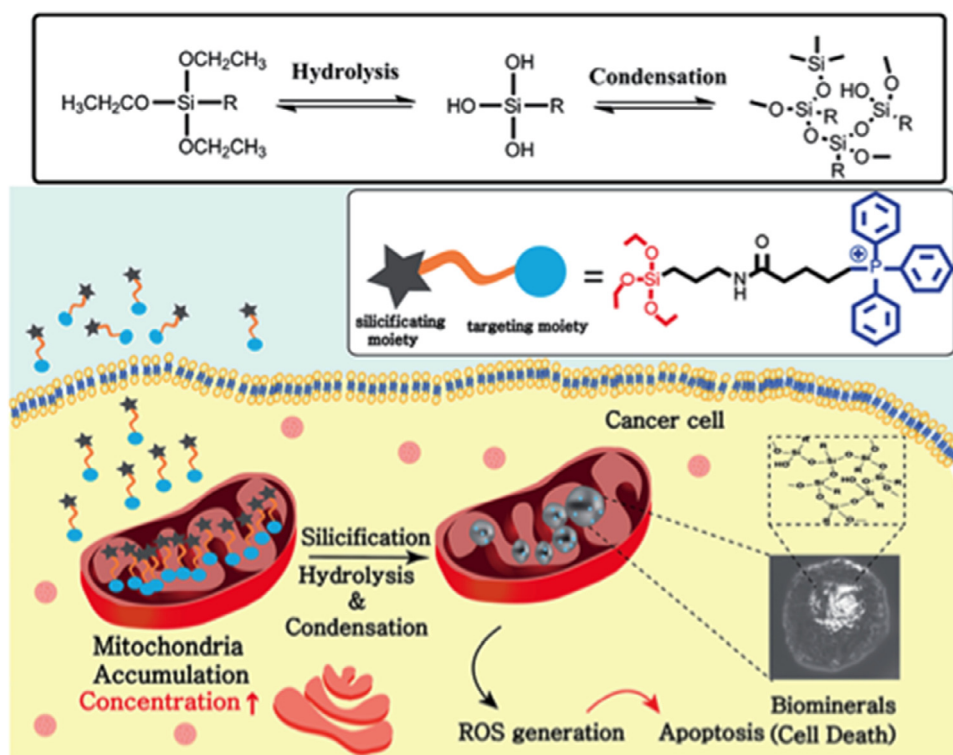


Fig. 11. Schematic illustration of the target accumulation of trialkoxysilane-TPP in cancerous mitochondria. It could lead to mitochondria-specific silicification to form biominerals that induce cellular apoptosis. Reproduced with permission [83]. Copyright 2018 Royal Society of Chemistry.

The AuNCs not only maintain high proliferation rate and cell viability, but also possess the capacity to eliminate ROS to stable states [82].

In addition, the intracellular targeting strategies incorporating the artificial organelle can achieve targeted delivery and reduce side effects in biomedical therapy. A number of particular organelles have been investigated for enhancing anticancer efficiency [81, 83]. For instance, triphenylphosphonium (TPP)-conjugated trialkoxysilanes could particularly target and disrupt the mitochondria of cancer cells. [83] It is considered as an artificial organelle on mitochondria-targeting medium, which can introduce intracellular biomimetalization. In other words, the TPP can target on mitochondria of cancer cells, while the silicification can be induced by trialkoxysilanes (Fig. 11) [83]. This approach depolarizes and disrupts mitochondrial membrane, leading the dysfunction of mitochondria and activate apoptotic pathways, and finally resulting in the tumor inhibition *in vitro* and *in vivo*.

At the meanwhile, chemotherapy is an effective treatment in cancer therapy [84]. The pharmacotherapy, such as doxorubicin (DOX), inhibits DNA replication and induce apoptosis, but cannot distinguish between healthy and diseased cells [85]. It is known that the GC-rich oligonucleotides (ODNs) can eliminate DOX from normal cells due to the high affinity of DOX for DNA [86]. However, the utilization of ODNs *in vivo* is limited by rapid degradation of nucleases [87]. The gold-oligonucleotides (Au-ODN) nanomaterials have been designed as artificial organelles, which resist degradation of DNase I. The nanomaterials are implanted into normal cells to capture intracytoplasmic DOX to reduce the DOX-induced cytotoxicity [81]. Owing to the selective action of these nanocomposites, the intracellular implantation of the Au-ODN is concentrated in the liver to establish an effective defense. The low concentration of Au-ODN in tumor implied the therapeutic effect of DOX on the tumor can be ignorable (Fig. 12). Meanwhile, DOX can be released in cancer cells by near-infrared (NIR) illumination, which further

cause ODN denaturation from the photothermal heating of the Au nanocage [81].

Moreover, the endogenous CaCO_3 nanoparticles, as artificial organelles, in yeast cells by intracellular mineralization possess the potential for application in the development of cancer therapy and environmental protection [58]. The CaCO_3 artificial organelle is considered as a pH-sensitive drug carrier, which promotes the release of drugs into tumor tissues (pH 6.0) or lysosomes inside cancer cells (pH 4.5) and enhance drugs' cytotoxicity by increasing cellular uptake. Besides, the other advantage of CaCO_3 artificial organelle is to remove heavy metals ions from aqueous solutions. For example, the precipitation transformation from CaCO_3 to PbCO_3 facilitates the biosorption of Pb^{2+} . The biocompatible HAP particles, which can combine with the hemoglobin, are artificially compounded into the RBCs to serve as the organelles. This engineered RBCs possess improved direct electron transferring activity and electrocatalytic oxygen reduction ability, which can be developed as the biological battery [60].

More generally, the biomimetic materials can develop a promising strategy for intracellular multifunction. The implantation of artificial organelles into cells demonstrates the biocompatible in a molecularly crowded cytoplasm and provides a different way to regulate cellular improvements with enhanced stability and new functions. We believe that the construction of artificial organelle could expand considerable potential application in diversified research fields, such as development of energy sources, environmental protection and biomedical therapy.

3.3. Other hybrids

The biomimetic materials can integrate with organisms for construction of artificial shells or organelles, as well as other biomacromolecules (e.g. enzymes and antibodies) for formation of inorganic-biological composites.

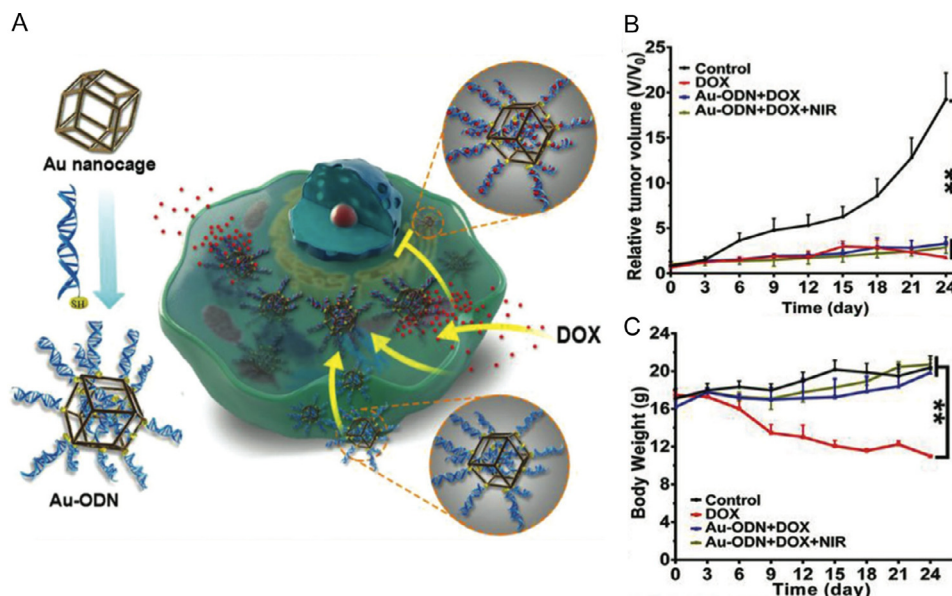


Fig. 12. (A) Scheme of formation of Au-ODN and its working principle as an artificial organelle within the cell. (B) Tumor growth curves in the control, DOX, Au-ODN+DOX and Au-ODN+DOX+NIR treatment groups (volume vs time). (C) Body weights of mice after the different treatments [81]. Reproduced with permission. Copyright 2018 John Wiley and Sons.

Nowadays, the biomacromolecules have been widely used in biomedical therapy and industrial production of catalysts [88]. However, due to their highly heat-sensitivity, they are easily changed in tiny variation of environmental temperature [89]. It is desired to improve the thermal stability of biomacromolecules, which can promote their potential applications. The biomacromolecules with incorporation of biomimetic materials could be beneficial to the thermal stability of them. The catalase (CAT) as an example, Yang et al. found that the combination with amorphous calcium phosphate (ACP) can enhance the thermal stability of CAT [90]. The CAT is *in situ* mineralized in ACP, which is suppressed the phase transformation from amorphous to crystalline (e.g. HAP) with the stabilization effect from Mg^{2+} . On account of rigid inorganic structure, the interaction between protein and protein can be reduced to suppress the probability of denaturing unfolding-refolding motions. There are abundant internal water molecules in ACP and they are more stable in comparison with the free ones. These structures constructed a relative steady condition to protect proteins from destructive molecule mobility. Accordingly, the *ex situ* mineralization is useless for improving heat tolerance, and the *in situ* mineralization is the key to stabilize the conformation of the enclosed protein, since it can decrease the hydrogen bond exchange [90].

Antibodies play an important role in the immune system, which can specifically recognize and neutralize foreign organisms or antigens [91]. Thereinto, the monoclonal antibodies (mAbs) with high specificity and effective recruitment is potentially applied in biomedical therapy [92]. Although the mAbs efficiently target viral surface proteins, this targeting process only occurs on extracellular virions [93]. The mAbs can be biomaterialized with CaP, which is developed an efficient strategy of intracellular therapy against viral infection [94]. The mAbs by CaP encapsulation retained their original antigenicity, including the direct interaction with specific antigen of Fab fragment and Fc region. Due to the favorable dimensional CaP nano vector, the modified mAbs can be delivered into cells, by contrast the native mAbs cannot. Meanwhile, the mAbs modified by CaP can be rapidly dissolved in the acidic solution. It is beneficial to release mAbs into cytosol, owing to the internal acidic environment in the lysosome, which can react with their target for intracellular therapy. Fortunately, the mAbs hybrids can

significantly decrease the expression of target proteins and inhibit intracellular viral replication in infected cells [94].

The inorganic-biological composites are further performed to “transform” the biomacromolecules. With the rigid and available structures, their properties (e.g. thermal stability [90]) can be remold. It also shows the distinct functions of biomacromolecules, such as capacity of entering into cells [94], which reveals another important biological issue for biomedical therapy.

4. Application of organism-material hybrids

4.1. Vaccine improvement

Vaccination is the most effective medical intervention for the infectious diseases by viruses, which had posed great threats to public health every year [95]. Unfortunately, the limitation of vaccines still exists in the poorest countries, where are severely affected the survival of human [96]. In general, the dissociation of picornavirus in elevated ambient temperatures initiates virus swelling, conformational alteration, loosening of bonds and RNA release [97]. Due to the heat sensitivity of live attenuated vaccines, vaccines cannot be stored at room temperature, so that it is essential for refrigerating to maintain their quality [98]. However, it is difficult and expensive for the cold chain to preserve the vaccines, especially in developing countries. Inspired by the mineralized state of virus, the biomineralization-based strategy is used to improve the vaccines [75]. Therefore, several attempts have been reported in artificial biomineralization of virus to enhance the thermostability and immunogenicity [23, 35, 99]. The rational design of biomimetic materials on virus can make thermostable vaccines to improve the vaccines storage. Wang et al. endowed JEV with CaP mineral shells by *in situ* biomineralization [23]. This CaP shell makes the JEV robust, exhibiting overall increased thermostability for storing at room temperature for 7 days. Surprisingly, this approach can preserve vaccines without refrigeration and maintain its original immunogenicity. Besides, EV71, a typical nonenveloped picornavirus as a model, can rapidly *in situ* individual silicified in freshly prepared silicic acid [99]. The silica exterior can increase the temperature and energy required for conformational changes and denatures of the viruses, and prevented RNA

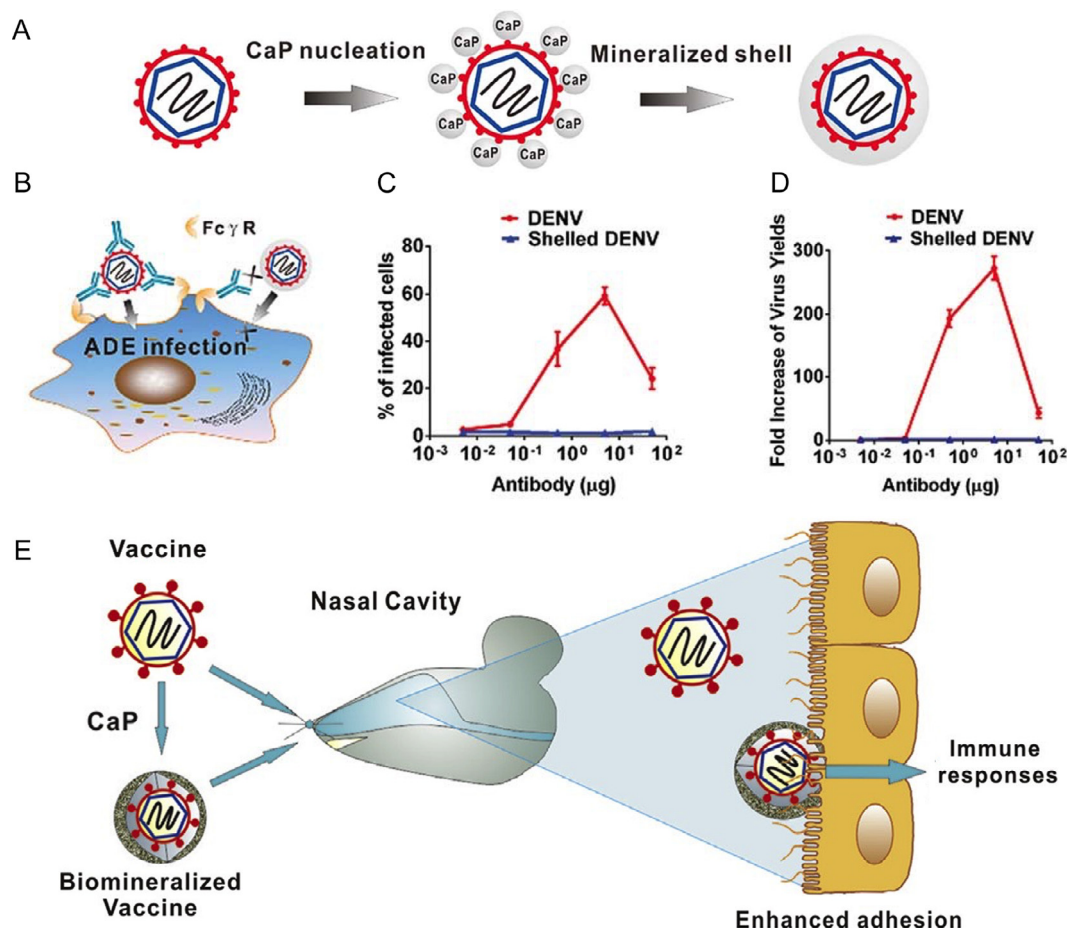


Fig. 13. (A) Scheme of the formation of calcium phosphate nanoshells on viral surfaces. (B) Scheme represents that CaP camouflage could inhibit antibody recognition and ablates the FcγR dependent virus infection. (C) Number of infected cells by DENV or shelled DENV at the first opsonization. (D) Antibody-enhanced viral production after being opsonized with the pre-existing 4G2 antibody. Reproduced with permission [105]. Copyright 2017 Royal Society of Chemistry. (E) Schematic description of biomineralized vaccine nanohybrid for intranasal immunization. Reproduced with permission [106]. Copyright 2016 Elsevier Science.

release at high temperatures. The amorphous silicified coating and nearby water molecules form a hydration layer that exhibited improvement of thermal stability [99]. EV71 viral particles can also be coated an alumina gel-like structure, which are spontaneously biomineralized through electrostatic interaction [35]. It is noted that the alumina modification made the viral particles coagulated to easier separate and concentrate than the native ones. The thermostability is enhanced by an efficient suppression of the hydrogen exchange between free water and protein. The nano-alumina particles with a size of <500 nm can induce more cellular immune responses by antigen-presenting cells [35] such as dendritic cells and macrophages [100]. Except for the inorganic shells, the hybrid organic-inorganic materials (e.g. MOFs) have provided the more versatile and general method for encapsulating biomacromolecules including proteins, DNA and enzymes via a biomimetic mineralization process [101], which give superior protection than the co-precipitation method. It can maintain the bioactivity and render the protection from biological, thermal and chemical degradation. This kind of materials can be applied on virus surface as well. The tobacco mosaic virus (TMV), a tubular viral particle with anisotropy and robustness, is a bio-template for manufacture of organic or inorganic materials [102]. The shell of hydrolytically stable ZIF-8 can be generated on TMV surface with highly symmetric quaternary structures. It is shown that composites of TMV and ZIF-8 with tunable shell thickness demonstrate nice stability in or-

ganic solvents (e.g. methanol) and at high temperature. Moreover, this strategy provides a possibility to functionalize the exterior of the viral by using a diazonium coupling reaction [102].

Moreover, the efficacy of current vaccine is highly restricted by unwanted immune responses [103]. The pre-existing immunity can lead to the risk of fatal antibody-dependent enhancement (ADE), which is critically serious in dengue virus (DENV) infection due to secondary exploration [104]. The biomimetic mineral coating (e.g. calcium phosphate) onto the outside of a vaccine can facilitate the stealth effect to circumvent body clearance and chaperone antigens to intestinal immune cells [105] (Fig. 13(A)–(D)). The biomineralization of DENV is advantageous for pH sensitive biodegradation in endosomal pH conditions to maintain the original immunogenicity. Moreover, the CaP coating with enhanced infectivity and expanded tropism can circumvent neutralizing antibodies and bypass the receptor barriers to ensure systemic administration of the virus in low dosage [105]. The biomimetic mineralization modification is designed for change the method of vaccinations [106]. Most of the currently available vaccinations have some drawbacks, such as needle-stick injuries, the require for qualified medical practitioners and the risk of spreading the infection by conventional syringe delivery [107]. A promoting approach for the vaccination is through the nasal mucosa with CaP shell to improve adhesive property and modulate the immunity (Fig. 13(E)) [106]. In addition, the improved vaccine by virus-templated biomineralization can pro-

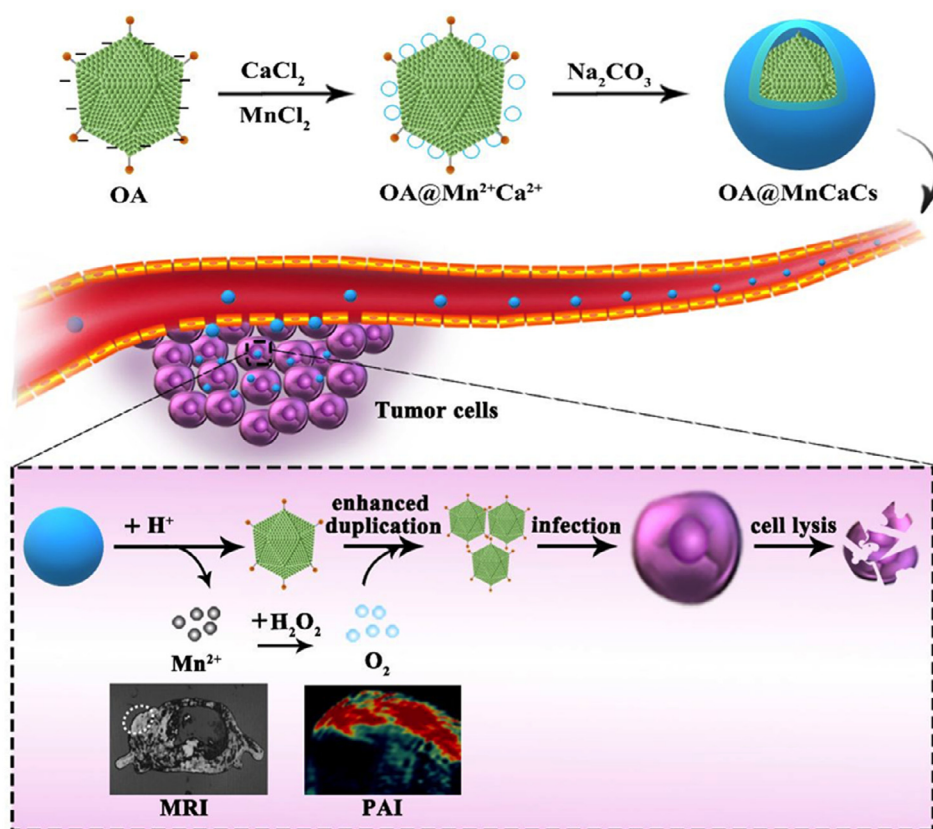


Fig. 14. Scheme of the preparation of OA@MnCaCs nanoparticles and their application for tumor therapy, such as magnetic resonance imaging and photoacoustic imaging. Reproduced with permission [109]. Copyright 2019 American Chemical Society.

mote the antigen-specific systemic humoral and cellular immune response, which is efficient, safe and controllable. The biomaterialized virus is an ideal candidate for clinical anticancer treatment, which can specifically replicate in tumor cells with high titer [108]. Oncolytic adenovirus (OA), with calcium and manganese carbonates (MnCaCs) biomaterial shell, can prevent the host immune system from eliminating virus and prolong the circulation of virus *in vivo*. While the engineered viruses accumulated in tumor sites, MnCaCs shell are rapidly dissolved in the acidic conditions, along with Mn^{2+} released, which can be used for magnetic resonance imaging. Meanwhile, the Mn^{2+} can be oxidized to MnO_2 and further decomposes endogenous H_2O_2 to generate O_2 , relieving the hypoxia situation in tumors for tumor therapy (Fig. 14) [109].

The combination between biomimetic materials and vaccines improves the limitations of the native vaccines, strengthening thermostability and immunogenicity. Therefore, it can promote the vaccine application, such as storage of vaccines at room temperature, improvement of the vaccine transportation, safety and efficacy. In the meantime, it is an efficient strategy to develop the multiple functions and applications of virus with therapeutic potential (e.g. drug delivery, imaging, sensing, and catalysis, etc.).

4.2. Energy production

Nowadays, owing to the over-consumption of fossil fuels, the energy resources are in short supply, which may greatly restrict the economic and social development of humans. Meanwhile, many serious environmental problems have been caused, such as the greenhouse effect, acid rain, atmospheric pollution and ozone destruction [110]. Thus, the developments of the renewable and clean energy resources are highly desirable to work out these problems. On Earth, solar energy is the most common renewable en-

ergy resource, but it is difficult to be utilized owing to its low conversion efficiency. The effective utilization of photosynthesis to produce renewable and clean energy resources, such as hydrogen or other fuels, is urgently required [69].

The tremendous progress has been made in combination of the biomimetic materials and living organisms consequently emerged in the utilization of solar energy for the energy resources production [111]. The nonphotosynthetic organisms convert into self-photosensitization by integrating with semiconductor nanoparticles and potentially exceed the natural photosynthesis. For example, the nonphotosynthetic CO_2 -reducing bacterium *Moorella thermoacetica* (*M. thermoacetica*) biological precipitated CdS nanoparticles onto surface (Fig. 15(A)) [112]. The illuminated CdS nanoparticles can generate photogenerated electrons, and *M. thermoacetica* use them to carry out photosynthesis. Afterwards, acetic acid is synthesized from CO_2 through the Wood-Ljungdahl pathway (Fig. 15(B) and (C)) [112]. Moreover, the highly efficient light-harvesting indium phosphide (InP) nanoparticles can be used for the energy production. It is modified on the genetically engineered *S. cerevisiae*, a workhorse microorganism in biomanufacturing, by polyphenol-based assembly (Fig. 15(D)). The hybrid yeast cells harvest photogenerated electrons from the illuminated InP nanoparticles and utilized for cytosolic regeneration of redox cofactors to facilitate a carbon-and energy-efficient production (Fig. 15(E)) [113].

Due to the high conversion efficiency, environmental friendliness and superior energy capacity of hydrogen, it is considered to be a new energy to substitute for fossil fuels and will play an important role in overcoming the increasing energy requirements [114]. The biomimetic silicification provides *Chlorella* cells a new capacity of photobiological hydrogen production under natural conditions. In the aerobic conditions, the native *Chlorella* cells perform photosynthetic O_2 evolution without H_2 production, owing to

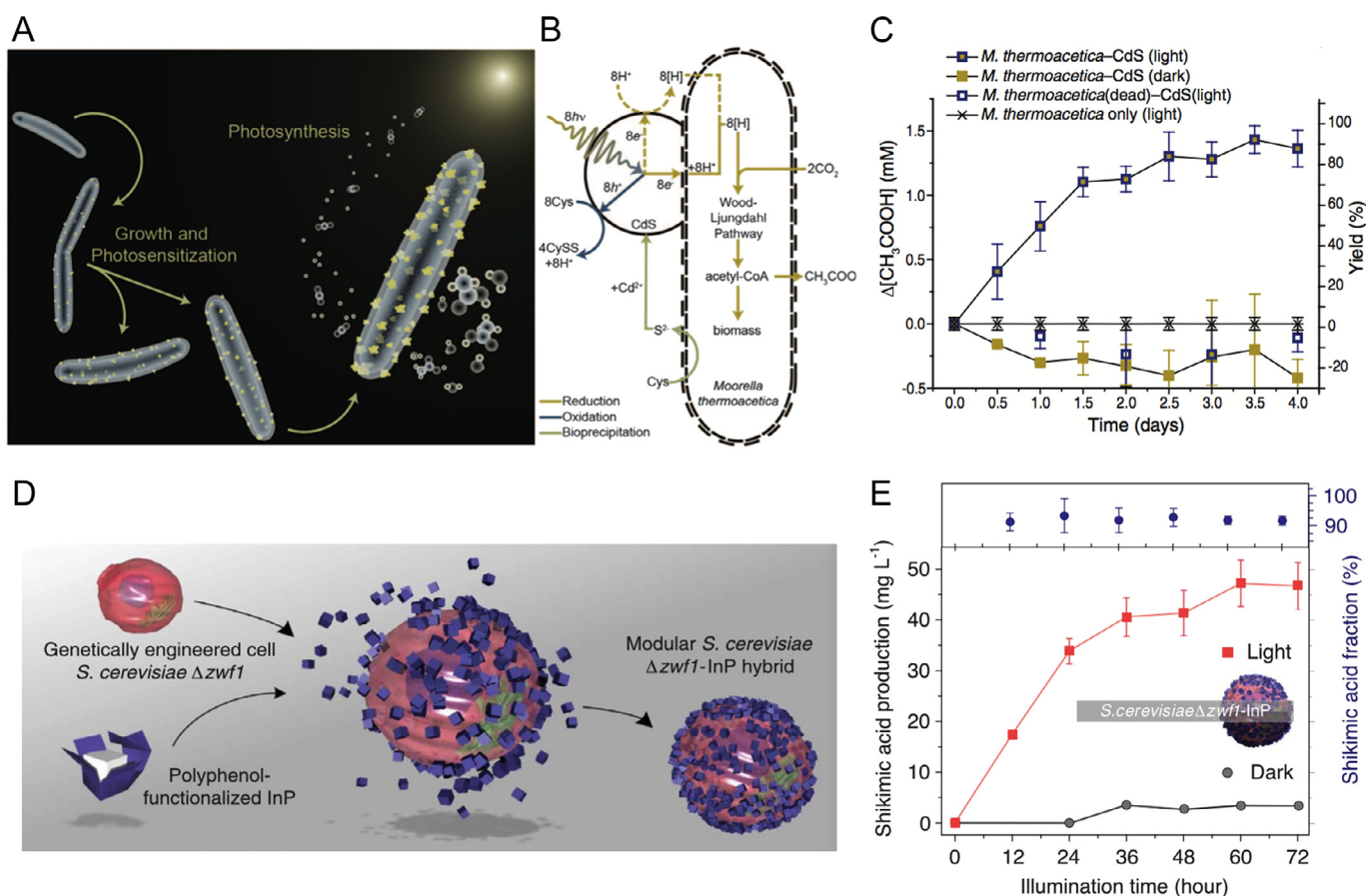


Fig. 15. (A) *M. thermoacetica*-CdS reaction schematics. The CdS nanoparticles (shown in yellow) on cell surface could promote the conversion of CO_2 (center right) to acetic acid (right). (B) Pathway diagram for the *M. thermoacetica*-CdS hybrid system. (C) Photosynthetic production of acetic acid by *M. thermoacetica*-CdS hybrids system. Reproduced with permission [112]. Copyright 2016 American Association for the Advancement of Science. (D) InP nanoparticles were functionalized with polyphenol moieties and further assembled on the surface of genetically engineered *S. cerevisiae* to form modular inorganic-biological hybrids. (E) The shikimic acid production profiles under light and dark conditions. Reproduced with permission [113]. Copyright 2018 American Association for the Advancement of Science.

the inactivation of hydrogenase. The aggregation of silica nanoparticles on cells reduced the zeta potential of cell surface, resulting in the self-aggregation of cells. It can build the oxygen-deficient microenvironment to activate hydrogenase, while hardly affecting the PSII reaction center generate photosynthetic electrons to product H_2 (Fig. 16(A) and (B)) [115]. The anaerobic microenvironment can also be manufactured by using polydopamine, laccase, and tannic acid as oxygen-consuming confined space on *Chlorella* cells surface. It is known that hypoxic environment can offer several pathways to enhance photolysis of water for hydrogen production by the activation of hydrogenase. At the meantime, the H_2 production can be modulated by controlling the amount of the substrate TA to impact the O_2 concentration (Fig. 16(C)) [116]. In addition, an engineered *Escherichia coli* (*E. coli*) has been developed for hydrogen photosynthesis under aerobic conditions, by combining with the biomimetic silicon encapsulation and CdS nanoparticles (Fig. 16(D)) [117]. The biomimetic silica encapsulation induced the aggregation of *E. coli* cells and created an anaerobic environment for the *E. coli* cells in the core to protect the catalytic activity of the expressed hydrogenase. The *in situ* biosynthesized biocompatible CdS semiconductors provided the light-harvesting capability to harness solar energy for hydrogen production (Fig. 16(E) and (F)) [117].

Therefore, the biomimetic materials endow the advanced functions into biological organisms for the conversion of solar energy into the valuable products, which can be used to develop advanced solar-to-chemical synthesis platforms. The production of renewable

and sustainable energy resources form organism-material hybrids is feasible, inexpensive, and effective. More generally, this bioinorganic hybrid system based biomimetic mineralization can become a useful tool for the convenient utilization of solar energy to product renewable biofuel.

4.3. Environmental protection

Due to the heavy exploitation and utilization of energy resources, there are several serious environmental problems of adverse effects on the ecological environment and human health, such as water pollution, heavy metal pollution, etc. [118]. To achieve the sustainability of our society, the environmental protection is the most important issue to develop in the world [119]. Recently, the organism-material hybrids systems are developed to realize environmental protection via the biomimetic approach. For example of water pollution, the exponential and uncontrollable reproduction of cyanobacteria with rapid mortality in water causes a harmful cyanobacterial bloom [120]. If the cyanobacteria bloom, it can poison the animals and humans, resulting the large-scale death of aerobic organisms, and destroy aquatic ecosystems. Inspired by the aggregated cyanobacteria cells [115], the *Microcystis flos-aquae* can incorporate silica via PDADMAC coating. The aggregation of silica on cell surface decreased the surface potential, leading to the aggregation of the cells to a size of 10–100 μm (Fig. 17(A)–(C)). Due to the relatively high spe-

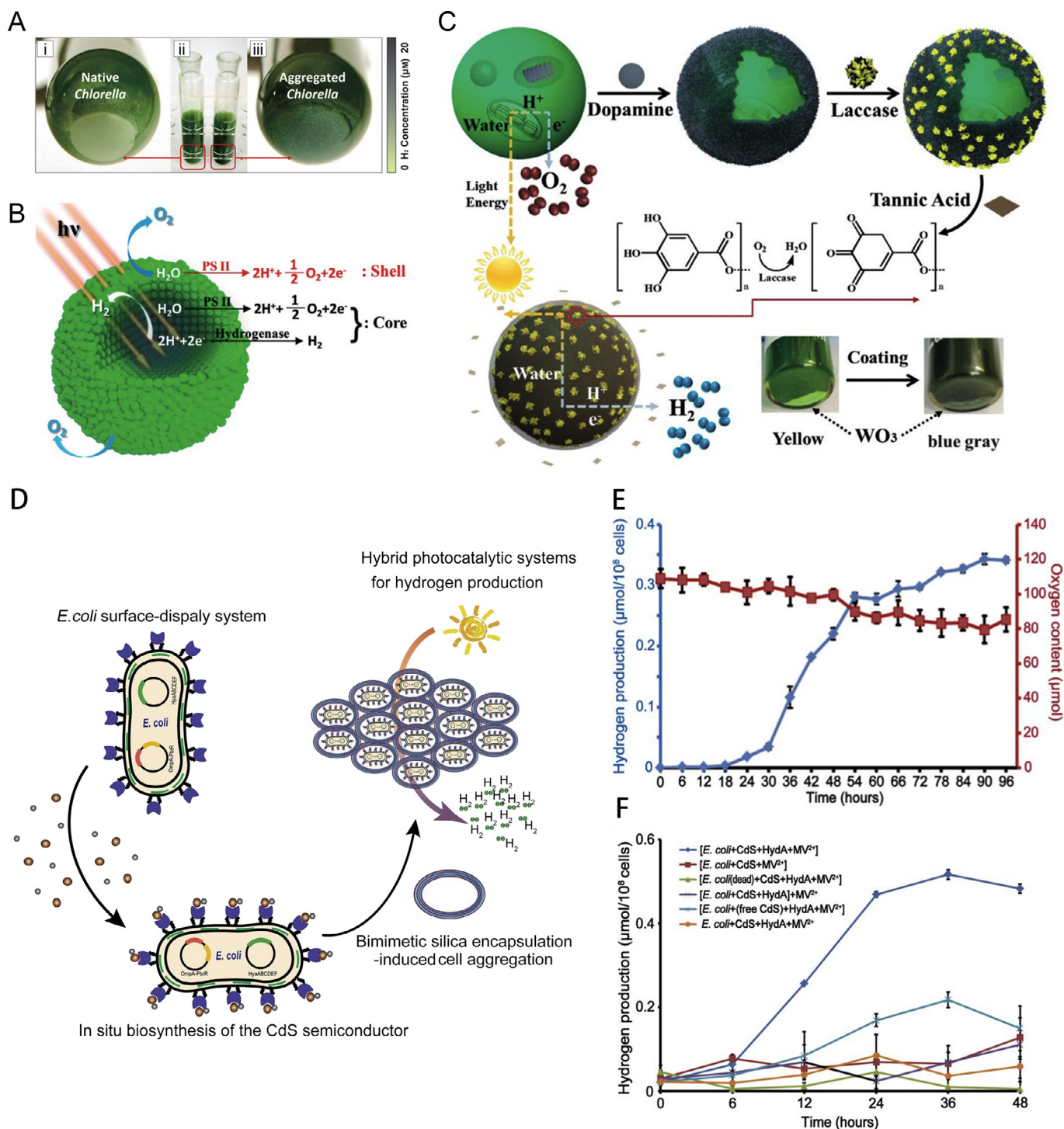


Fig. 16. (A) Native *Chlorella* cells and their aggregates. (i) Native *Chlorella* with WO_3 powders (bottom of the tube). (ii) Native and aggregated *Chlorella* culture medium with WO_3 powders in the tubes. (iii) Aggregated *Chlorella* with WO_3 powders (bottom of the tube). The bar indicates the standard color changes of WO_3 in the presence of H_2 production. (B) The scheme of aggregated *Chlorella* cells about the Spatial-functional differentiation. Reproduced with permission [115]. Copyright 2015 John Wiley and Sons. (C) Schematic illustration of the laccase-modulated anaerobic layer around individual *Chlorella* cells to H_2 production under aerobic conditions. Reproduced with permission [116]. Copyright 2019 John Wiley and Sons. (D) *E. coli* surface-display system *in situ* biosynthesis of the CdS semiconductor and further encapsulate biomimetic silica to induce cell aggregation for hydrogen production in air. (E) Measurements of continuous hydrogen production in hybrid photocatalytic systems. (F) Measurements of the amount of hydrogen produced by the various biohybrid systems. Reproduced with permission [117]. Copyright 2018 American Association for the Advancement of Science.

cific gravity of silica, the cyanobacteria with silica can deposit to the bottoms, inhibiting rapid cell breed and subsequent death (Fig. 17(D)). The SiO_2 -incorporated cell structure efficiently inhibit cyanobacterial photoautotrophic growth and cell proliferation, and that pose unobvious death for preventing some harmful ef-

fects of the blooms (Fig. 17(E)) [121]. It indicates the strategy of organism-material hybrids is an available environmental protection approach for ecological controls. In future, it may extend to more living organisms for solving more extensive environmental problems.

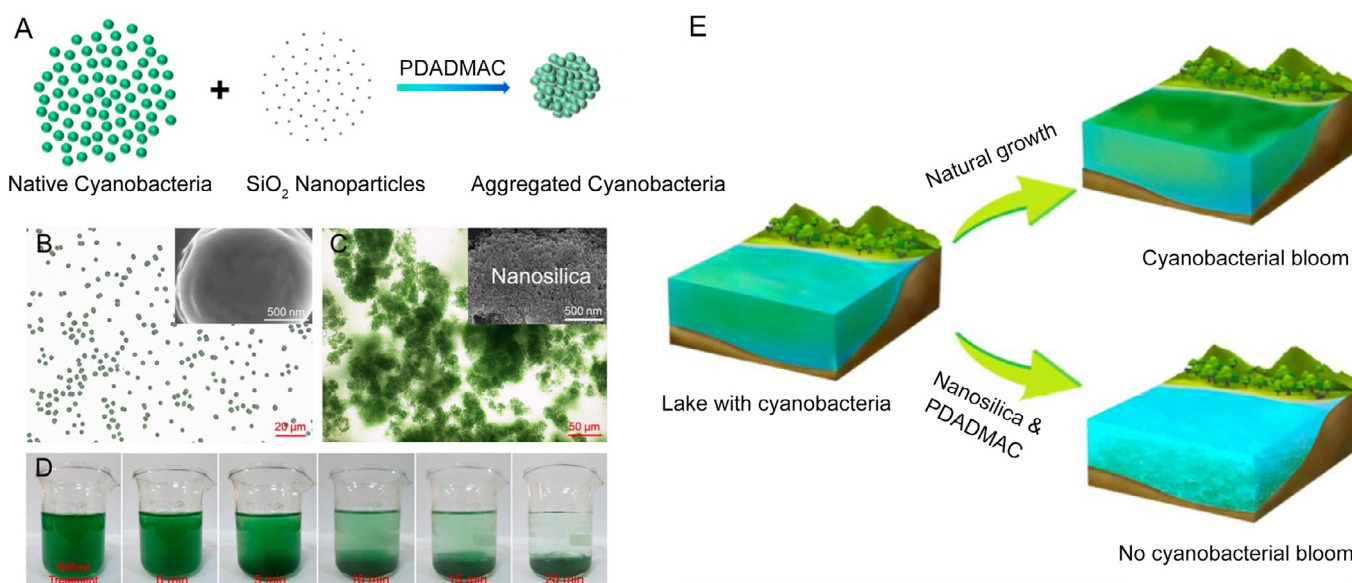


Fig. 17. (A) Scheme of the direct incorporation of SiO₂ nanoparticles on the *Microcystis flos-aquae* cells using PDADMAC to aggregate cyanobacteria. The optical microscope image and SEM image of (B) native cells and (C) aggregated cells, which demonstrate the nano-silica particles on their surface. (D) Performance of aggregated cells in the beaker (100 mL) at different times. (E) Schematic illustration of the prevention on cyanobacterial bloom inducing sedimentation by silica and PDADMAC. Reproduced with permission [121]. Copyright 2017 American Chemical Society.

4.4. Biomedical therapy

The organism-material hybrids structures are potentially applied in biomedical therapies. The lymphocytes in humans, including T cells, B cells, and natural killer cells, are the major executive cells in the immune system, producing immune response to keep human healthy [122]. For instance, in chimeric antigen receptor T-cell therapies, the T cells are genetically modified *in vitro* to express a receptor for a specific antigen on tumor cells [123]. The fragility of cells makes it more difficult to fabricate the engineered T cells, so that it is essential to protect the cells from outside aggressors *in vitro* for the manipulation, handling, and preservation of cells [124]. The bioinspired TiO₂ shells are coated on Jurkat cells, which belong to immortalized leukemic T-cell line, achieved by peptide-modification without significant loss of cell viability (Fig. 18(A)) [125]. The TiO₂ coating not only enhances the long-term viability of Jurkat cells under ordinary-life conditions and high temperature, but also enables juxtacrine interactions and cytokine secretion (Fig. 18(B) and (C)) [125]. Among the functional cells in the field of biomedical therapy, the red blood cells (RBCs) is one of the simplest but highly important cells due to their deliver of necessary oxygen and energy to all parts of the body [126]. The type mismatch of RBCs causes the severe problems in blood transfusion, because of immune responses between the antigen on RBC surface and antibody in blood serum, resulting in agglutination and hemolysis [127]. To solve these problems of blood transfusion, the biomimetic materials (e.g. polydopamine [46], TA-Fe^{III} [128], etc.) can form the shell structure to shield the epitopes on RBC surface for avoiding the unexpected immune responses (Fig. 18(D) and (E)). At the meantime, due to allogeneic host immune rejection, it is also required to track and monitor the administered cells for evaluating the efficacy of cell therapies. Multifunctional nanoparticles can be used for integrating the cell surface after mild modifications (e.g. reduction of disulfides). The attached glycoproteins on modified cell surface retained, implying that functionality of the surface ligands and receptors is reserved. The near-infrared fluorescent MSNs coated on cells can track the location of cells *in vivo* during the early stages of cell therapy [49].

Moreover, among the cell therapies, the cancer treatment is very important. Nowadays, the cancers cause the extraordinarily high mortality in the world, and it is increasing by years [129]. Due to the limitations for current cancer treatments, such as the adverse influences of chemotherapy and radiotherapy [130], spread and metastasis of surgery [131], ensuring the efficiency of cancer therapy is a great challenge. Recent rapid progresses in biomimetic mineralization have contributed greatly to cancer treatment, one of which is the selectively calcified tumor without injury on normal cells [132]. The folate receptors (FR) with high expression in many human carcinomas are the key factor for the specific mineralization [133]. Due to their targeting effects on tumor, the biological fluids of Ca²⁺ can specifically bind on FR, which accumulate folic acid (FA) molecules to induce the calcium mineral nucleation on tumor cells (Fig. 19). Notably, the calcification of the tumor tissue can intrinsically facilitate the cancer cells dysfunction and death, and suppress tumor metastasis without damage to other tissues or organs as well [132]. On the basis of the unique cytotoxicity mechanism of Ca²⁺, it is desirable to develop an effective strategy for tumor therapy. The calcium peroxide nanoparticles (CaO₂ NPs) are designed with pH-sensitive sodium-hyaluronate-modified for creating an artificial calcium overloading stress in tumor cells, leading the cancer cells to death [134]. In the acidic tumoral microenvironment, CaO₂ NPs can slowly decompose into free Ca²⁺ and H₂O₂, which may change the calcium channels, hinder the accurate transmission of calcium signals and induce cell death. At the meantime, the tumor calcification tends to generate in the enrichment of Ca²⁺, and it is benefit to facilitate tumor inhibition *in vivo* and computed tomography (CT) imaging to monitor the treatment efficacy. On the contrary, the normal cells have sufficient catalases to allow exogenous Ca²⁺ pump out or store through calcium channels (Fig. 20), which are more tolerant than the negative effects of NPs. This calcium-mediated tactic could inhibit tumor and further show its great potential in clinical cancer treatment [134].

In general, the therapeutic potential of organism-material hybrids has generated in a wide variety of clinical applications. The combination of living cells and biomimetic materials could make some improvements for cells, such as protect immune cells for therapy, shelter the antigens for transfusion and kill cancer cells for

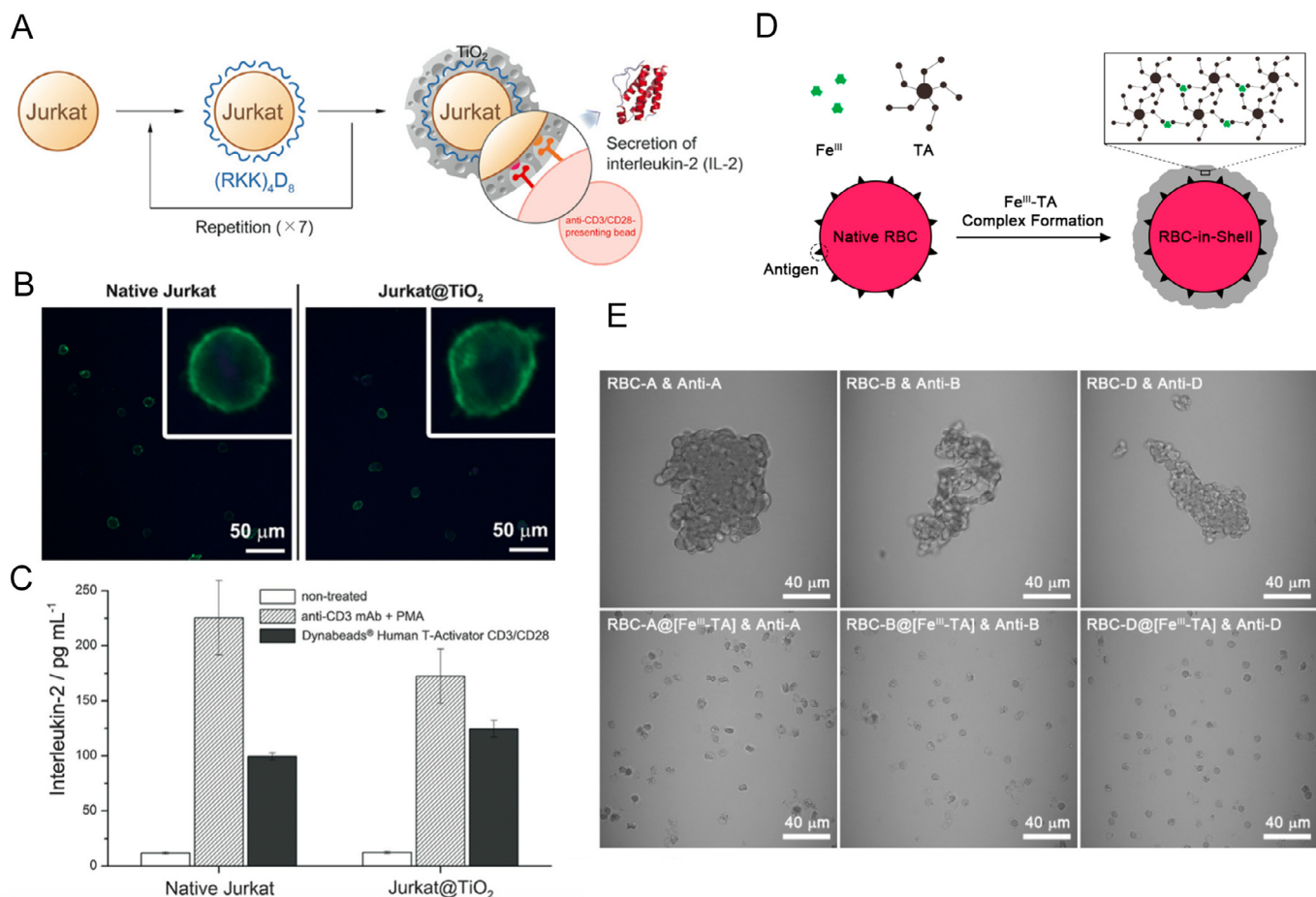


Fig. 18. (A) Representation of the individual encapsulation for Jurkat cells within the cytoprotective TiO₂ shells, which could ensure the antigen-antibody interactions and cytokine secretion. (B) The CLSM images after treatment with anti-CD3 mAb and donkey anti-mouse secondary antibody, which shows CD3 on Jurkat cells is accessible to anti-CD3 mAb for binding. (C) Secreted amount of IL-2 after stimulation. Reproduced with permission [125]. Copyright 2017 John Wiley and Sons. (D) Schematic illustration of the shell formation of ferric ion and tannic acid to mask the antigens on RBCs surface. (E) Antibody-mediated agglutination assay of native RBCs and engineered RBCs. Reproduced with permission [128]. Copyright 2017 Multidisciplinary Digital Publishing Institute.

tumor treatments. Based on these achievements, these biomimetic strategies are anticipated to more extensive applications in various biomedical and biotechnological areas, including the cell-based sensors, regenerative medicine, as well as 3D cell printing and tissue engineering.

5. Future perspectives

The applications of organism-material hybrids by biomimetic mineralization have successfully been employed in multiple fields, including biological research, biomedical therapy, energy production and environment protection. These advances demonstrate an effective tactic of material-based biological enhancement, which provide organism more powerful performance and more useful functions. In some ways, it plays an important role to combine the inorganic materials and living organisms to make artificial biological evolutions. Despite the great processes in this research field, the ideal combination of biomimetic materials and living organisms for organism-material hybrids construction remains several challenges to exploit.

Although we have enumerated various kinds of biological organisms, including microorganisms and animal cells, a majority of them have not been utilized yet. For fungi, the yeast cells have been served as a model system to explore the advantages of these techniques. However, the progress is limited in the simplex system, and more organisms with specific functions should be con-

sidered. For example, the decomposer (e.g. bacteria, fungi) could break down organic matters in specific condition by integrating the biomimetic materials with decomposers [135], which may create robust and high-efficient decomposer-material hybrids. Thus, it is necessary to screen more classes of functional organisms for being candidates in this research.

Secondly, more synthetic methods for material preparation should be introduced for organism-material hybrids construction. In most situations, the materials are rigid and noxious to biological system. Due to the synthetic conditions, including the precursor chemistry, pH, temperature, solvent, and reaction time, the high biocompatibility is always limited. To keep the bioactivity of living organs, the dosage of materials should be decreased at low level. But the low concentration of materials makes no effect for the living organisms. A specific material and synthetic method may be needed for sustaining their viability during and after organism-material hybrids. Thus, optimization of the synthetic strategy and biocompatibility for materials should be imperative, which can adapt the mild biological environment for preferably integration. For example, the biomimetic mineralization methods used for shell production are commonly realized by simply increase the supersaturation of the solutes. These classical crystal growth methods are slow and need excess ions, which may raise side effects to the living organisms. Many precursors [136] rather than solutes for crystal growth have been established, such as the amorphous nanoparticles [137], polymer-induced liquid precursors [138], and

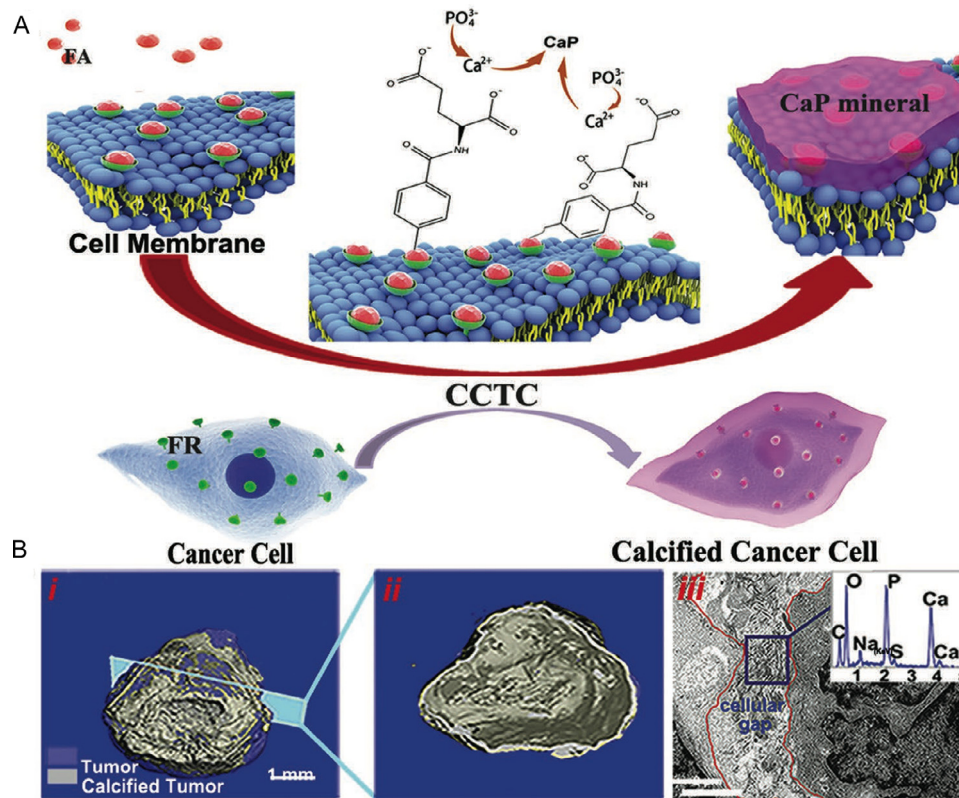


Fig. 19. (A) Schematic of cancer cell targeted calcification. The folate receptors on cancer cell surface could specifically bind to folic acid molecules, which actively induce calcification owing to its carboxylate residues. (B) It could specifically bind Ca^{2+} from biological fluids to facilitate calcium mineral nucleation on cancer cells. Reproduced with permission [132]. Copyright 2016 John Wiley and Sons.

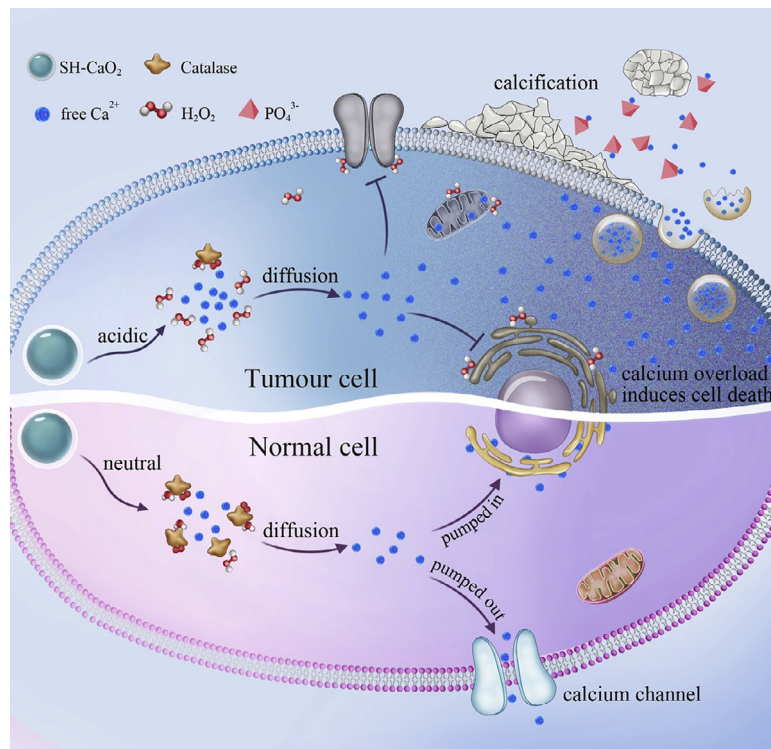


Fig. 20. Schematic Representation of the Functional Pattern of SH- CaO_2 NPs for cancer therapy. For the tumor cells, the low expression of catalase causes the abnormal cellular H_2O_2 accumulation and an imbalanced calcium transport pathway, thus, resulting in an efficient cellular calcium overload and subsequently the induction of cell death. Meanwhile, the high local concentration of Ca^{2+} increases the likelihood of tumor calcification. For normal cells, a sufficient amount of catalase could prevent oxidative activation of the cells and allow the exogenous Ca^{2+} to be more efficiently pumped out or stored through calcium channels. Reproduced with permission [134]. Copyright 2019 Elsevier Science.

inorganic ionic oligomers [139, 140], etc. And we believe these methods can improve the present techniques, both in efficiency and biocompatibility, for biomimetic mineralization.

In addition, the major improvement of organism-material hybrids is protecting the organisms against extreme conditions, but the researches that focus on the developments of extended functions are limited. Although the high mechanical strength is the advantage of biomimetic materials, other superior performances could also be utilized for diverse applications. For instance, the intelligent materials could responsive to the change of environments and might manipulate the organisms to do what is in-demand. The self-repairing organism-material hybrids might be an available tool for wound healing and tissue engineering. Therefore, the idea of expanding the multi-functionalities of organism-material hybrids would offer a promising avenue.

Last but not least, the organisms themselves are “live materials”, which possess the ability to sense, respond or adapt to the sporadic fluctuation of outside *in vitro* (and *in vivo*) conditions. Thus, the organisms may also have the ability to selectively combine with specific materials. In other words, organisms can “choose” the materials, which are suitable for them. Thus, we can quickly find suitable materials for organisms, and this may be beneficial for the development of more autonomous and smarter organism-material hybrids.

In summary, despite remarkable achievements have been made to date in the improvement of living organisms by biomimetic materials, there are still many challenges and opportunities remaining for the further development with superior performance. The development of expansive functional organism and material, more biocompatible mineralization techniques will make the organism-material hybrids increasingly applicable.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Grants 21625105).

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