EDITORIAL

Innovations in living biomaterials

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Living biomaterials refer to composite materials made from living cells integrated with synthetic or biological materials. They have feature remarkable characteristics such as self-growth, self-repair, self-organization, adaptability, and responsiveness to the environment. These properties allow for controlled and predictable interactions with biological systems.[1]Traditional biomaterials, despite their extensive applications in healthcare, are limited by central critical factors. For example, one of the critical limitations of traditional biomaterials is their inherent inertness, which impedes their ability to dynamically respond to changes in vivo and restricts the effectiveness of potential therapeutic modalities. Recent convergent advances in synthetic chemistry, soft matter, molecular self-assembly, and the-omics era collectively signal the dawn of a new generation of biomaterials, heralding unprecedented innovation and development in the field of biomedicine. Therefore, as we explore the current state and potential advancements in biomaterials, it becomes evident that living biomaterials hold the key to unlocking new frontiers in biomedicine, offering promising strategies to overcome complex diseases.[2]

Living biomaterials presenting an intriguing research area centered on imparting life-like capabilities and functions to materials in an integrative and programmable manner. For instance, porous silica structures encapsulating diatom cells (diatom frustules) not only provide robust mechanical support but also actively engage in cellular metabolic processes, such as chlorophyll synthesis. Currently, living biomaterials attract great attention in green energy production, bioremediation, bioimaging, disease treatment, which is increasing surpassing those of many existing materials. It is worth noting that the direct application of bioactive ingredients in biomedicine face considerable challenges, primarily owing to the instability and susceptibility to rapid inactivation. The development of living hybrid systems, integrating materials with active biological components through nanobiotechnology, protects the inherent biology activity of living organisms for disease treatment.

The synergistic advantages of integrating living organisms with materials are evident in engineering living biomaterial systems. To optimize the biomedical potential of the entities and maintain their viability, a range of construction strategies have been developed: (i) physical strategies such as electrostatic interaction, physical encapsulation, and 3D printing; (ii) chemical strategies including covalent conjugation, noncovalent conjugation, and in-situ reaction; and (iii) biological strategies such as biomineralization and biosynthesis (Figure 1A). These approaches not only successfully mitigate the potential toxicity, pathogenicity, and immunogenicity induced by the living organisms,[3] but also effectively protect living organisms from physiological threats such as gastric acidity, intestinal adverse conditions, and enzymatic interference in the bloodstream.

The design of living biomaterials is a pivotal step in determining their efficacy for biomedical applications. Among diverse physical modification meth-

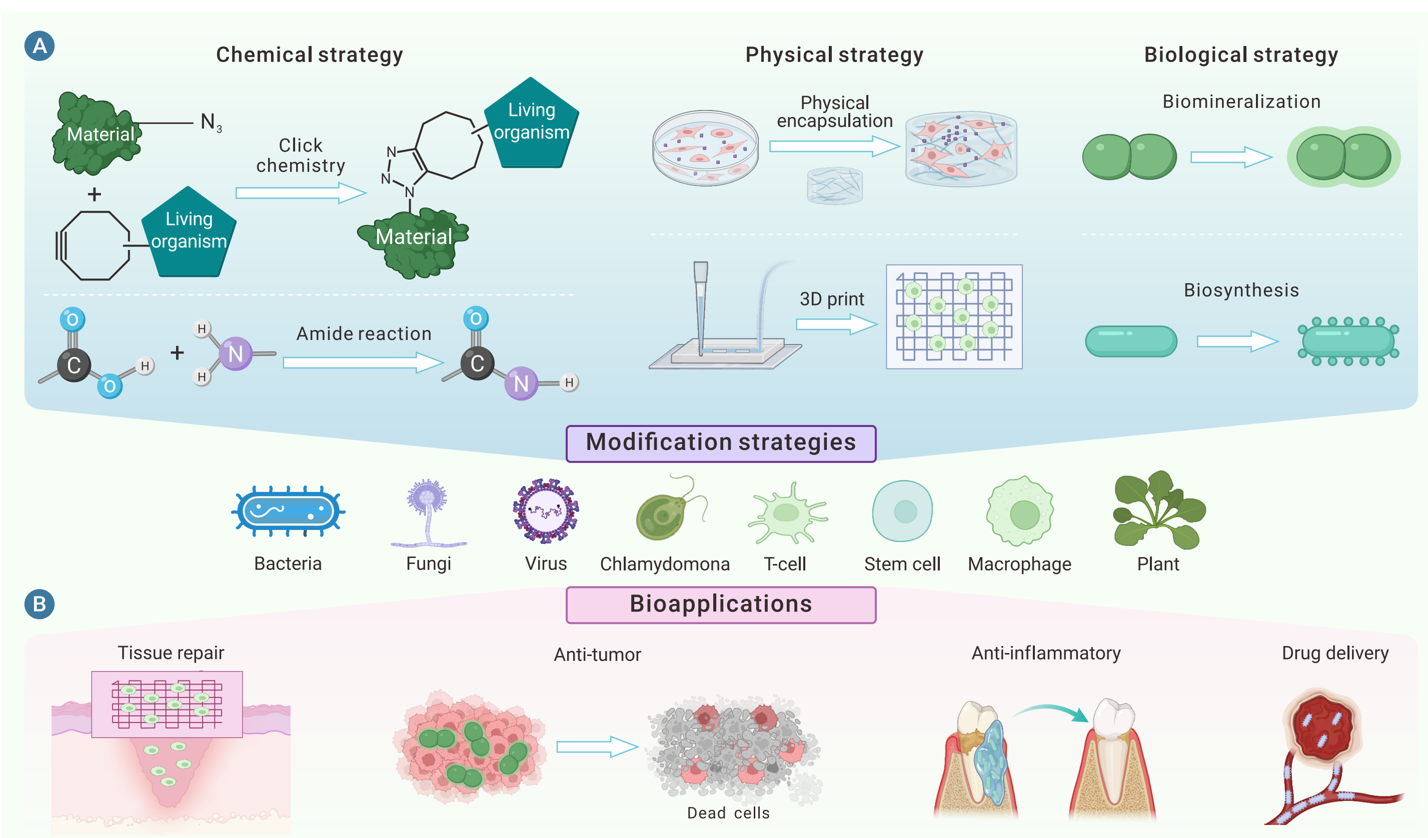

Figure 1. Living biomaterials constructed by different methods and used for different biomedical applications (A) Representative methodologies employed in the construction of living biomaterial system using chemical, physical, and biological strategies. (B) Respective biological applications of living biomaterial systems, including tissue repair, anti-tumor, anti-inflammatory, and drug delivery.

ods, electrostatic interactions and physical encapsulation are prevalently utilized. An example of employing electrostatic interactions in physical strategies for the preparing microbial-hybrid materials is demonstrated in the fabrication process involving *Streptococcus* mutans. A notable instance of employing electrostatic interactions in the realm of physical strategies for fabricating microbial-hybrid materials is demonstrated in the preparation process involving *Streptococcus* mutans. In this approach, liposomes, which are meticulously constructed using cationic lipids, are strategically deposited onto the surface of *Streptococcus* mutans. In physical encapsulation, different organisms, including microorganisms (virus, bacteria, fungi, and algae), animal cells, and plants have been incorporated into materials such as silk, concrete, and hydrogels. This integration is aimed at engineering living hybrid materials for various application purposes. Furthermore, chemical modification methods constitute another crucial aspect in constructing living biomaterials, which broadens the material spectrum and provides tailored functionalities. Covalent conjugation methods, mainly categorized into amine-carboxylic acid coupling, thiol-based crosslinking, and bioorthogonal conjugation, utilize different bonding groups. Additionally, non-covalent interactions such as bioconjugation and coordination interactions, exploiting specific molecular affinities, have been explored for living organism modification.[4] Moreover, living organisms can autonomously synthesize substances in situ for self-protection, including dopamine-mediated in situ polymerization, bacterial-mediated radical polymerization, and biomineralization. Microorganisms, functioning as efficient manufacturing factories, has garnered extensive attention in nanomedicine, particularly in functional nanomaterials synthesis. For instance, *Bacillus subtilis* has shown the capability to reduce Au^{3+} ions to Au nanoparticles within the cell wall, with sizes ranging from 5 to 25 nm.[5] These methods enhance the material functionality and augment the adaptability of living biomaterials to environmental changes.

Living biomaterials have undergone significant refinement and customization, enabling them high performance in biomedical applications, such as biosensors, wound healing, drug delivery, immunotherapy, antitumor therapy, and tissue engineering (Figure 1B). For example, bacteria can secrete or express active factors for disease diagnostics. Development of whole-cell microbial biosensor and engineering of microbial gene expression, responsive to medically relevant molecules, facilitate applications in protein activation and disease detection. The unique properties of materials and bacteria have been leveraged to create nanotherapeutic systems for tumor treatments through radiotherapy, photodynamic therapy (PDT), photothermal therapy, and chemodynamic therapy. In nanomedical applications, bacterial are harnessed for drug delivery due to their nature tropism, including anaerobic targeting, magnetic targeting, and optical tendencies. These properties aim to improve the site-specific accumulation and precision of therapeutic drug molecules within the body. Facultative anaerobes can target specific tumor areas because of their intrinsic tropism toward internal and/or external environmental signals. Recent developments in cancer immunotherapy facilitated by living biomaterials, particularly microbe-based approaches, have garnered significant attention. Various microbes, including bacteria, oncolytic virus, and fungi, are strategically used to activate innate immunity and enhance adaptive immune responses, amplifying antitumor immune reaction. The engineered living biomaterials with promising therapeutic outcomes in disease treatments, have been poised to revolutionize the biomedical field. The fabrication of living biomaterials employs diverse techniques, encompassing physical interactions, chemical modifications, and biological strategies. The engineered living biomaterials are unique capable of sensing and responding to environmental changes, such as variations in pH, temperature, and biochemical composition. The responsiveness of drugs or biomolecules release can be finely tuned for activation by specific stimuli, including light or small molecules. Nonetheless, there are still substantial obstacles to overcome in the creation of living biomaterials that can activity sense and respond to their surroundings.

To date, the engineered living biomaterials have predominantly been confined to laboratory research, with only a few instances transitioning into clinical trials. For example, genetically modified common probiotic lactic acid bacteria are currently under clinical investigation on the basis of their ability to secrete anti-inflammatory drugs, offering potential treatment for inflammatory bowel diseases. The implementation of living biomaterials in disease treatment faces three primary challenges: (i) An enhanced understanding of the interactions between microorganism and materials is crucial for tailoring designs that can facilitate personalized therapy. (ii) Biocompatibility and immunogenicity of living biomaterials within the body of host must be carefully addressed. (iii) Safety concerns regarding the unintended spread or leakage of living biomaterials into the environment remain a gordian knot. Importantly, the prospective therapeutic applications of living biomaterials necessitate rigorous regulatory approval for clinical translation, which poses an additional challenge. Therefore, to propel the field of engineered living biomaterials forward, a multidisciplinary approach is required. By synergistically combining diverse strengths, we can optimize the design of functional living materials, and effectively tackle challenges related to adaptability, biosafety, and immunogenicity. The advancement of engineered living biomaterials is anticipated to be significantly bolstered by the progress in development of material science, microorganism and materdicine.

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DECLARATION OF INTERESTS

The authors declare no competing interests.