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Review

Bio-inspired encapsulation and functionalization of living cells with artificial shells

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ABSTRACT

In nature, most single cells do not have structured shells to provide extensive protection apart from diatoms and radiolarians. Fabrication of biomimetic structures based on living cells encapsulated with artificial shells has a great impact on the area of cell-based sensors and devices as well as fundamental studies in cell biology. The past decade has witnessed a rapid increase of research concerning the new fabrication strategies, functionalization and applications of this kind of encapsulated cells. In this review, the latest fabrication strategies on how to encapsulate living cells with functional shells based on the diversity of artificial shells are discussed: hydrogel matrix shells, sol-gel shells, polymeric shells, and induced mineral shells. Classical different types of artificial shells are introduced and their advantages and disadvantages are compared and explained. The biomedical applications of encapsulated cells with particular emphasis on cell implant protection, cell separation, biosensors, cell therapy and tissue engineering are also described and a recap of this review and the future perspectives on these active areas is given finally.

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1. Introduction

In the evolution of natural systems, living organisms have developed various mineralized structures, such as teeth, bones, shells, talons, carapaces, and spicules [1–7]. Those composite biomaterials often exhibit complex hierarchical structures, possessing important functions such as mechanical support, protection, motility, and sensing of signals [8]. Certain biological systems, such as mollusks, arthropods, radiolarians, diatoms, and fungi, have evolved to preserve their species under unfavorable harsh environments by protecting their genetic information with a hard shell. However, most single cells in nature do not have structured shells to provide extensive protection. During the past decade, exploration of novel bioinspired strategies for self-assembling or surface-assembling molecules or colloids to generate artificial shell on cells is one of the hottest current research subjects in the material chemistry and its cutting-edge fields [9]. Fabrication of biomimetic structures based on living cells encapsulated with artificial shells lies on the border between chemistry, biology and materials science, therefore the tutorial review covering the recent advances in this pioneering research is important and will inspire a wide community of researchers to contribute to this exciting new area [10].

Coating isolated cell with hydrogels, sol-gel shells, various polymer nanofilms, and mineral shells has come to a focus of recent interest because of the importance and the potential to design new materials and devices in various fields such as whole cell biosensors [11,12], toxicity microscreening devices [13], microelectronics [14], tissue engineering [15] and bioanalytical chemistry [16]. For example, microbial spores have been employed for analyte detection [17] and cell patterns [18,19], based on the benefits of the robust shells in increasing the stability of cell-based sensors. Many attempts have been made to fabricate artificial shells directly onto cells or to confer to cells an ability to form their own shells. A rapid increase of research concerning the new fabrication strategies, functionalization and applications of this kind of encapsulated cells was witnessed in the past decade. Spore-like structures have recently been generated chemically by encapsulating individual living cells within artificial shells, such as silica [20], calcium phosphate [21], calcium carbonate [22], and multilayers of polyelectrolytes [23–27]. Microbial and mammalian cells have been intensively used as versatile templates for deposition of functional polymer multilayers [28], in conjunction with nanoparticles [29] or by direct deposition [30] of nanomaterials onto the cell membrane. On the other hand, the viability of magnetically-responsive cells used as biosensing elements in microfluidic devices is of paramount importance, hence more bio-compatible techniques for coating of the cells with magnetic nanoparticles are required. Cell-surface modification is another important issue for the application of living cells [31]. It has been achieved by complicated methods, such as the introduction of nonbiogenic functional groups by metabolic or genetic engineering [32–36]. Noncovalent adsorption of macromolecules onto the cell surfaces has also been attempted in order to introduce chemical functionalities into living cells [37,38]. Biomimetic encapsulation of cells in inorganic microshells has become a subject of increased interest over the past few years [39,40]. A range of cells, including bacteria, yeast, human normal and cancer cell lines, and even microscopic multicellular species are intensively being used in applications requiring surface functionalization.

In this review, the latest developments in the bio-inspired cellular shellization are discussed. First, the general crystal growth modes and the effect of selective adsorption on crystal growth will be the topic of Section 2. Then some prominent examples of cellular exterior coats in natural living organisms will be given in Section 3. Section 4 will give an intensive review on the latest fabrication strategies on how to encapsulate living cells with functional shells. The biomedical applications of encapsulated cells with particular emphasis on cell implant protection, cell separation, biosensors, cell therapy and tissue engineering will be the focus of Section 5. Finally, a recap of this review and the future perspectives on these active areas is given in Section 6.

2. Growth and form of cellular exterior coats

The majority of biominerals produced by unicellular eukaryotes, such as the delicate micro-skeletons of radiolarians, elaborately patterned scales of coccolithophorids and diatoms, or the denser more robust shells of foraminifera, have complex but regular forms that cannot be explained by contingent modification of inorganic crystallization [41]. It is important to stress that the cellular boundary edges and interstitial mineralization sites are delineated by membrane-bound structures in each of these examples so that mineralization in the geometrically defined space is under strict biological control. In general, the fashioning of these biominerals is prescribed by confining the mineralization process within vesicles, vacuoles or polymeric matrices that are assembled and organized using structural scaffolds and associated directing agents. The chemistry of these localized sites is regulated by ion and molecular transport into and out of the shaped reaction environments such that mineralization and organic pattern formation are termed “biologically induced mineralization” [42]. In “biologically controlled mineralization”, the organism directly controls the mineralization process, having evolved specific strategies to produce minerals of selected size, morphology, structure, and orientation [2,4]. These strategies rely upon organic molecules to control mineralization: confining a space, forming an organic matrix framework, controlling ion input, constructing a nucleation site, controlling crystal orientation and growth, and terminating crystal growth. Some or all of these processes may be involved in the precipitation of a given mineral. Exhibiting a degree of control that is currently beyond that which can be achieved synthetically, these biological mechanisms offer a unique inspiration for “biomimetic” crystal growth experiments and provide the basis for the design and synthesis of novel materials.

2.1. Organic matrix in organized reaction fields

Fundamental to all biologically controlled biomineralization processes is that mineralization always takes place within a designated space that is delineated by a structured organic matrix. The organic matrix defines the mineral-deposition site and enables an organism to control the composition and concentration of the precipitation solution. As an important mechanism of morphological