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Review

Core–shell designed scaffolds for drug delivery and tissue engineering

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ABSTRACT

Scaffolds that secure and deliver therapeutic ingredients like signaling molecules and stem cells hold great promise for drug delivery and tissue engineering. Employing a core–shell design for scaffolds provides a promising solution. Some unique methods, such as co-concentric nozzle extrusion, microfluidics generation, and chemical confinement reactions, have been successful in producing core–shelled nano/microfibers and nano/microspheres. Signaling molecules and drugs, spatially allocated to the core and/or shell part, can be delivered in a controllable and sequential manner for optimal therapeutic effects. Stem cells can be loaded within the core part on-demand, safely protected from the environments, which ultimately affords ex vivo culture and in vivo tissue engineering. The encapsulated cells experience three-dimensional tissue-mimic microenvironments in which therapeutic molecules are secreted to the surrounding tissues through the semi-permeable shell. Tuning the material properties of the core and shell, changing the geometrical parameters, and shaping them into proper forms significantly influence the release behaviors of biomolecules and the fate of the cells. This topical issue highlights the immense usefulness of core–shell designs for the therapeutic actions of scaffolds in the delivery of signaling molecules and stem cells for tissue regeneration and disease treatment.

1. Introduction

Over the past decades, scaffolding materials have been developed to deliver therapeutic molecules and cells, with the goal of repairing and reconstructing diseased and defective tissues. A series of material actions that favor and even stimulate biological processes in the body in terms of orienting protein adsorption, guiding cellular anchorage and migration, and driving progenitor character into specified cellular lineages, have thus been substantially researched [1–5].

Some key solutions on how to secure drugs and protein molecules within the composition and controllably deliver the molecules to the target sites have been sought to overcome the innate power of synthetic scaffolding materials [3,6,7]. Furthermore, how to safely load tissue cells at relevant quantities, particularly preserving potent stem cell characteristics, and effectively transplanting them into the damages that need regenerative actions, have also been the key scaffold-based issues in engineering tissues [3,8,9].

Among the accumulative technologies of scaffolding materials for therapeutic molecules and stem cells, the core–shell design has emerged as a promising approach. The cored inner layer with a shelled outer layer, a typical design feature, enables a number of faceted characteristics that have potential for the delivery system and tissue engineering. Typically, the therapeutic molecules and cells can be secured and partitioned within the layered core–shell structure, and can be delivered to target defects. Furthermore, the capacity to load molecules and cells safely, the tunability of material compositions and parameters to proper shapes and sizes, and the secreting actions of the design, are the beneficial faces of the core–shell structure for use as scaffolding systems. Various shapes, including fibers and spheres, are possible by utilizing different techniques; and a wide range of sizes from submicrometers to millimeters allow for the application of the system in diverse fields from the delivery of small therapeutic molecules to the transportation of tissue cells. Furthermore, the fine-integration of the core–shell building blocks enables tissue-level engineering of cells and extracellular matrices (ECMs).

Consequently, core–shell designed systems are considered to have a multi-faceted nature, providing on-demand biomaterial platforms for drug delivery and tissue engineering. Here, we summarize the core–shell designed scaffolds and materials that find useful applications in drug delivery and tissue engineering. While

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many different types of scaffolds and nanomaterials have been developed separately, this review is intended to collect for the first time the information available under this theme. It is thus reviewed first to describe general features of core–shell structures, then to identify the production methods and the typical types, and finally, to detail the applications of the core–shells in drug loading and delivery as well as in cell encapsulation and tissue engineering.

2. General feature of core–shell structures

The core–shell structure features two discrete parts, with one inner part ('core') and the outer part ('shell') completely enclosing the inner portion. As they are partitioned in space, each core and shell can perform independent functions, such as incorporating two different molecules. However, they are both interfaced and molecular-permeable, thus molecular interactions between them are possible, and one side can affect the other. The core–shell can be shaped in either a continuous or a discrete manner. The former gives rise to a fibrous shape while the latter generates a spherical form. Only when the size (diameter) of the core part is large enough (tens to hundreds of micrometers) does it allow for loading cells. On the other hand, exogenous signaling molecules can be incorporated without regard to the core size and can be loaded in the shell as well. The role of the core is thus considered as either to load therapeutic molecules for delivery or to hold tissue cells and provide them with 3D culture environments. The shell protects the inner biological ingredients, governing the release kinetics of the core-contained molecules and protecting the viable cells. Fig. 1 depicts the general features of the core–shell designs that are useful for cell-encapsulated tissue engineering as well as for the delivery of therapeutic molecules.

3. Methods to prepare core–shell structures

To generate core–shell structures, the general approach is either top-down or bottom-up. The top-down approach involves an apparatus either designed simply with co-concentric nozzles or more powerfully with microfluidic devices. While a continuous nozzling of core and shell components produces fibrous shapes, the periodic discontinuity in the device generates discrete particulate forms. The top-down approach can generate core–shelled fibers and spheres easily with hundreds/tens of micrometers and sometimes even down to a few micrometers. Conversely, the bottom-up approach utilizes chemical reactions in confined conditions to form phase-separated core–shelled particulates, mainly nanoparticles. This is possible either by in situ phase-separation reactions or by the post-shelling approach. This section outlines the top-down and bottom-up approaches to generating core–shell structures.

3.1. Co-concentric nozzle extrusion

Concentric nozzle is an easy and simple approach to obtain two well-defined structures in a coaxial manner. In order to do so, the basic design consists of a central nozzle, usually made of metal to avoid deformation during injection, around which a second nozzle larger in diameter is placed. The design can be achieved through the use of highly sophisticated nozzles or with homemade nozzles. Hydrogel injection and electrospinning based techniques often require these types of nozzles that allow the injection of two different solutions allocated in well-defined compartments. In order to be successful, the injection speed for both solutions needs special care. The hydrogel can be formed into microspheres if the flow is disrupted periodically during the injection.

3.2. Microfluidics generation

Hydrogels are generally used for microfluidics. Microfluidics allows for the generation of small size channels with perfectly designed and symmetric structures. The sizes produced by microfluidics are more homogeneous than those by other methods. The principle of microfluidics is the use of micrometer scale channels that create a stream of polymeric precursor solution. This solution is allowed to flow continuously through one of the streams, but is then broken in a controlled manner by interaction with a second flow composed of an immiscible fluid. By controlling the viscosities, flow rates and dimensions of the channels among others, microspheres are produced which then become in the formed shape [10–12]. In the case of the core–shell microspheres, the shell is usually made of the gelling agent, whereas the core is able to carry the desired payload, such as cells or drugs [13]. This technology has also allowed for the fabrication of core–shell structures using stimuli responsive materials that are able to release the payload according to external stimuli [14]. The incorporated anticancer drugs within core–shell particles can be released selectively by the surrounding pH change, which is effective for the selective treatment of cancer or chronic wounds [14].

3.3. Chemical confinement reactions

Chemical reactions are mainly applied for the preparation of core–shell nanoparticles. Two main routes have been described to fabricate them. The first route consists of the preparation of core particles which are then surface-modified to allow for coating with the shell material [15–20]. The second process consists of the synthesis of the core particle in situ followed by the synthesis of the shell coating [21]. Both methods have coating to form the shell, although the second method uses specific reagents with growth inhibitors, forming the shell after the core reaction is complete. In both cases, it is important to achieve homogenous shells in

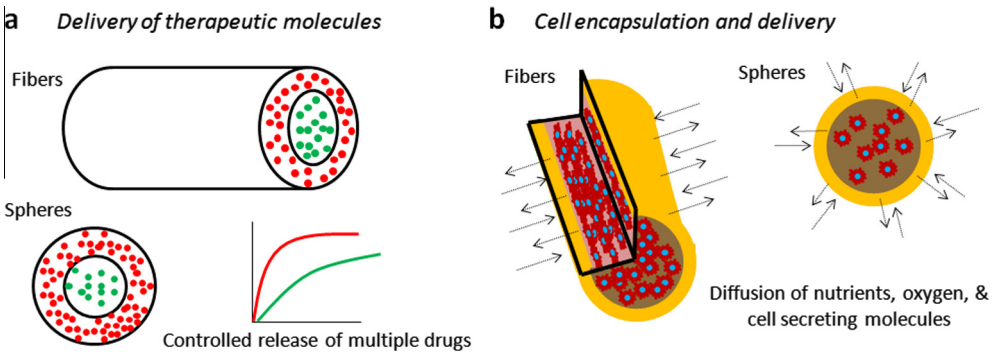

Fig. 1. Illustration of the general features of core–shell designs that are useful for the delivery of therapeutic molecules (a) and for the cell encapsulated tissue engineering (b).