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Review

Particle assemblies: Toward new tools for regenerative medicine

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ABSTRACT

Regenerative medicine is a demanding field in terms of design and elaboration of materials able to meet the specifications that this application imposes. The regeneration of tissue is a multiscale issue, from the signaling molecule through cell expansion and finally tissue growth requiring a large variety of cues that should be delivered in place and time. Hence, the materials should be able to accommodate cells with respect to their phenotypes, to allow cell division to the right tissue, to maintain the integrity of the surrounding sane tissue, and eventually use their signaling machinery to serve the development of the appropriate neo-tissue. They should also present the ability to deliver growth factors and regulate tissue development, to be degraded into safe products, in order not to impede tissue development, and finally be easily implanted/injected into the patients. In this context, colloid-based materials represent a very promising family of products because one can take advantage of their high specific area, their capability to carry/deliver bio-active molecules, and their capacity of assembling (eventually in vivo) into materials featuring other mechanical, rheological, physicochemical properties. Other benefits of great interest would be their ease of production even via high through-put processes and their potential manufacturing from safe, biodegradable and biocompatible parent raw material. This review describes the state-of-the-art of processes leading to complex materials from the assembly of colloids meeting, at least partially, the above-described specifications for tissue engineering and regenerative medicine.

Contents

Abbreviations: dex-HEMA, dextran-hydroxyethylmethacrylate carbonate derivative; DMAEMA, dimethylaminoethylmethacrylate; ECM, extracellular matrix; G′, elastic modulus; G″, viscous modulus; GMPs, gelatin microparticles; LCST, lower critical solubility temperature; MAA, methacrylic acid; mPEG, methoxy poly(ethylene glycol); MSCs, mesenchymal stem cells; NIPAM, N-isopropyl acrylamide; ODLLA, D,L-lactic acid oligomer; OPF, oligo(poly(ethylene glycol)fumarate); PCL, poly(ε-caprolactone); PEG, poly(ethylene glycol); PEGEEMA, poly(poly(ethylene glycol ethyl ether methacrylate)); PEGMEMA, poly(poly(ethylene glycol methyl ether methacrylate)); PEMA, poly(ethylene-co-maleic acid); PLA, poly(lactic acid); PLGA, poly(D,L-lactide-*co*-glycolide); pNIPAM, poly(N-isopropyl acrylamide); POA, poly(octadecanedioic anhydride); PPGMA, poly(propylene glycol methacrylate); PVAm, polyvinylamine; SMSs, sintered microspheres; tan(δ), loss factor; τ_y, liquefaction stress; Tg, glass transition temperature; VEGF, vascular endothelial growth factor.

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1. Introduction

Particles have long been used in life sciences as drug or vaccine delivery systems [1,2] or in biotechnology for cell culture in bioreactors [3]. From the field of tissue engineering, new needs in terms of materials have emerged with particular specifications such as the capacity *i*) to allow cell growth in a highly hydrated 3D environment allowing diffusion of the nutriments and various chemokines, *ii*) to fit into a defect for optimum regeneration properties, *iii*) to be easily implanted in patients, *iv*) to feature mechanical properties matching those of a living tissue (elastic moduli ranging from less than 1 kPa for brain tissues to dozens of GPa for bones [4,5]), *v*) to be non cytotoxic and *vi*) to deliver growth factors with temporal and spatial control. Ideally, the properties of the materials should be flexible depending on the need or should evolve with time as the regeneration of the tissue takes place.

Particle assemblies constitute a new generation of materials obtained from the associations of micro or nanospheres, which meet some of the above constraints, in particular their mechanical properties can easily be tuned, they lead to porous materials potentially allowing cell colonization and they are capable of delivering biological cues via the encapsulation or the physical adsorption of various molecules. The particle associations can be achieved either by entrapment within a polymer network obtained by a polymerization reaction, physical interactions, physical processing (Fig. 1A), or by physicochemical interactions between the particles dispersed in an aqueous continuous phase (Fig. 1B). This paper aims at reviewing the current strategies used to obtain new materials from the controlled assembly of micro/nano-particles and their potential applications in the demanding field of regenerative medicine. We have chosen to divide this paper into two parts corresponding to the two main elaboration processes of micro/nano-particle-based 3D networks (Fig. 1).

2. Particle-polymer assemblies (composite gels)

Hydrogels are very attractive in tissue engineering because they are 3D structures that, similar to the extracellular matrix (ECM), contain a high water content, thus providing a favorable environment for cell expansion and tissue regeneration [6]. The interest for composite gels, i.e. gels loaded with particles, has been increasing steadily because *i*) they allow the improvement of the mechanical properties in comparison with non-composite systems, *ii*) they favor cell expansion and differentiation, *iii*) the particles can be loaded with bioactive molecules involved in tissue regeneration and *iv*) the particles can modulate the biodegradability of the composite material. We can differentiate two types of particle-polymer assemblies, those resulting from the entrapment of particles within a polymer gel matrix, from those where the interactions between the dispersed phase and the polymer lead to the assembly.

2.1. Assemblies via particle entrapment in a polymer gel matrix

2.1.1. Chemically crosslinked matrix

In 2003, Mikos and co-workers reported a composite gel comprising of oligo(poly(ethylene glycol)fumarate) (OPF) and gelatin microparticles (GMPs) [7]. The gelation at physiological conditions took place in 8–10 min thanks to the addition of an ammonium persulfate initiator and a poly(ethylene glycol)-diacrylate cross linker. They showed that the transforming growth factor-β1 could be loaded in GMPs through polyionic complexation, and its in vitro release could be controlled by modulating the swelling properties of the OPF–GMPs composite gel. The authors showed that the in vitro burst release of the growth factor from OPF hydrogels was approximately 53% while it was reduced to 29–32% from composite gels (both with a similar mesh size of 136 Å). In physiological or biological media, GMPs appeared to act as sacrificial templates enzymatically generating pores, allowing a better control of the protein release, and increasing the kinetics of the hydrogel degradation [8].

Moving to implantable biodegradable scaffolds for cell culture, Mikos and co-workers associated chondrocytes or mesenchymal stem cells (MSCs) to the above composite gels, the particles serving as cell-adhesion points. Indeed, the presence of GMPs increased cellular proliferation and, with GMPs loaded with growth factors, the phenotype of chondrocytes was maintained [9], and the differentiation of MSCs into chondrocytes was induced [10,11]. In the latter case, the MSCs differentiation increased with the swelling ratio of the matrix, which was related to the molar mass of the poly(ethylene glycol) (PEG) entering in the formulation of the OPF [12]. In vivo, the filling of osteochondral defects with the composite gel embedding MSCs and GMPs loaded with growth factors was well tolerated after 12 weeks post implantation [13]. However, the histological investigation revealed that the newly formed tissues could still be perfectible.

To improve the performance of their composite gels, Mikos and co-workers developed the concept of a bilayer structure for the regeneration of bone and cartilage, represented in Fig. 2. The lower layer of the gel was designed to favor bone growth whereas the upper layer was devoted to cartilage regeneration. To reach these objectives, the lower layer consisted in a crosslinked OPF hydrogel containing or not empty GMPs; the upper layer contained GMPs loaded with various growth factors [14,15]. At week 14 post implantation in rabbits, the lower layer allowed bone growth and the upper layer lead to a cartilage tissue, but thinner and more fibrous than in the surrounding healthy tissues. As an improvement of this first version, the authors demonstrated in vitro that MSCs could be added to the upper layer in synergy with osteogenic cells in the bottom layer [16,17].

Following a similar strategy involving a crosslinked polymer matrix improved with entrapped particles, Hong et al. used collagen coated poly(lactic acid) (PLA) microspheres dispersed in a gel consisting of

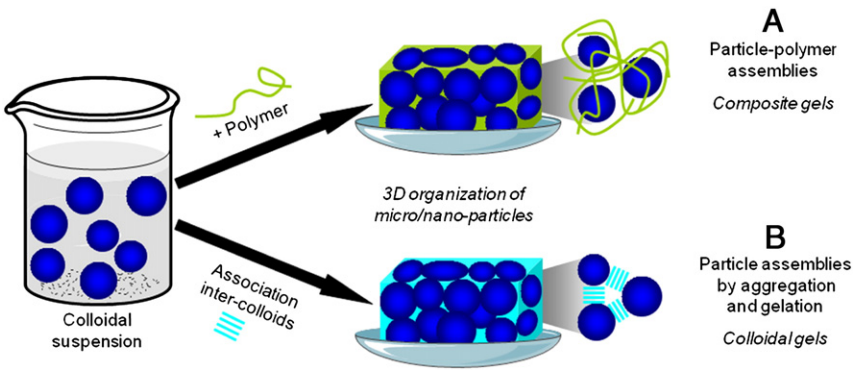

Fig. 1. Schematic representation of particle assembly types presented in this paper: (A) Particle-polymer assemblies (composite gels) (B) particle assemblies by aggregation and gelation (colloidal gels).