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Naturally and synthetic smart composite biomaterials for tissue regeneration☆

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ABSTRACT

The development of smart biomaterials for tissue regeneration has become the focus of intense research interest. More opportunities are available by the composite approach of combining the biomaterials in the form of biopolymers and/or bioceramics either synthetic or natural. Strategies to provide smart capabilities to the composite biomaterials primarily seek to achieve matrices that are instructive/inductive to cells, or that stimulate/trigger target cell responses that are crucial in the tissue regeneration processes. Here, we review in-depth, recent developments concerning smart composite biomaterials available for delivery systems of biofactors and cells and scaffolding matrices in tissue engineering. Smart composite designs are possible by modulating the bulk and surface properties that mimic the native tissues, either in chemical (extracellular matrix molecules) or in physical properties (e.g. stiffness), or by introducing external therapeutic molecules (drugs, proteins and genes) within the structure in a way that allows sustainable and controllable delivery, even time-dependent and sequential delivery of multiple biofactors. Responsiveness to internal or external stimuli, including pH, temperature, ionic strength, and magnetism, is another promising means to improve the multifunctionality in smart scaffolds with on-demand delivery potential. These approaches will provide the next-generation platforms for designing three-dimensional matrices and delivery systems for tissue regenerative applications.

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Abbreviations: BDNF, brain derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BSA, bovine serum albumin; CaP, calcium phosphate; CCBD, central cell binding domain; CNT, carbon nanotube; CPC, calcium phosphate cement; DGEA, Asp–Gly–Glu–Ala (amino acid sequence); DNA, deoxyribonucleic acid; DOX, doxorubicin; ECM, extracellular matrix; EGF, epidermal growth factor; FN, fibronectin; GDNF, glial cell line-derived neurotrophic factor; GAG, glycosaminoglycan; G-CSF, granulocyte colony stimulating factor; GF, growth factor; GFP, green fluorescent protein; HA, hydroxyapatite; HGF, hepatocyte growth factor; HEMA, 2-hydroxyethyl methacrylate; HPMC, hydroxypropylmethylcellulose; HUVEC, human umbilical vein endothelial cell; IGF, insulin-like growth factor; IKVAV, Ile–Lys–Val–Ala–Val (amino acid sequence); IPTS, (3-isocyanatopropyl)triethoxysilane; MSC, mesenchymal stem cells; MSN, mesoporous silica nanoparticles; NGF, nerve growth factor; MNP, magnetic nanoparticle; NT3, neutrophin-3; OCN, osteocalcin; OPN, osteopontin; PA, peptide amphiphile; PAA, poly(acryl amide); PCL, poly(ε-caprolactone); PDGF, platelet derived growth factor; PDMS, polydimethylsiloxane; PEG, poly(ehylene glycol); PEI, polyethylenimine; PEO, poly(ethylene oxide); PET, poly(ethylene terephthalate); PGMMA, poly(glycerolmonomethacrylate); PHPMA, poly[n-(2-hydroxypropyl)methacrylamide]; PHSRN, Pro–His–Ser–Arg–Asn (amino acid sequence); PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PLLA, poly(L-lactic acid); PMMA, poly(methyl methacrylate); pNIPAAm, poly(N-isopropyl acrylamide); PPG, poly(propylene glycol); PPO, poly(propylene oxide); PTX, paclitaxel; PVA, poly(vinyl alcohol); RGD, Arg–Gly–Asp (amino acid sequence); RNA, ribonucleic acid; siRNA, small interfering RNA; TCP, tricalcium phosphate; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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1. What is smart composite biomaterial?

With respect to biomaterials, the term 'smart' refers to the nature of the interactions between a given biomaterial and the surrounding cells and tissues. Attributes of smart biomaterials include their instructive/inductive or triggering/stimulating effects of the cells and tissues. These types of biomaterials, in contrast to the surgical apparatuses, sensors, and devices, which do not directly contact the host cells/tissues, can intimately associate with various host constituents for relatively prolonged periods, providing chemical and physical cues to the cells. The consequent biological actions can be important in driving tissue repair and regeneration. Thus, for biomaterials, 'smart' encompasses aspects that are relevant to the surrounding cells and tissues. The instructive and stimulating cues provided by biomaterials are, in fact, the essential considerations in biomaterial studies, designed to bolster drug delivering capacity and/or tissue engineering efficacy. Therefore, significant effort that seeks to modulate the surface and bulk properties or to provide external therapeutic molecules have been made in biomaterials such as drug delivery systems and three-dimensional (3D) scaffolds.

Internal modulation mainly involves biomimetic modification of chemical, physical, and/or biological properties in ways that mimic the native tissue. If successful, the strategy can provide environmental cues to the surrounding cells that aid the cells in the recognition of the biomaterial surface and matrix, enhancing target functions such as adhesion, proliferation, migration, and tissue differentiation. Strategies for internal modulation include surface tailoring with biomimetic molecules such as peptides and adhesive proteins, tuning of the bulk chemistry to produce similarity to native extracellular matrices (ECMs), and adjusting physical properties (such as stiffness) to natural tissues, are possible strategies. Although this surface modulation can, in a sense, be considered as an external modulation, we categorized this as an important internal way of engineering biomaterials that ultimately have smart actions, fitting the biomimetic approach by chemistry modulation.

External modulation is typically germane to smart biomaterials with drug delivering potential. The external factors that are introduced to provide triggering and instructive cues to biologics involve chemical drugs, proteins, and nucleic acids. Typically, those biofactors are incorporated in many ways within biomaterials engineered in the form of porous foam scaffolds, hydrogels, fibers, and particulates. The mechanism of action typically involves membrane receptors or is through intracellular uptake within the cytosol or nucleus. Therefore, design of biomaterials with drug delivering functions must consider the biofactor of interest, site and type of action, and the location. An essential aspect of external modulation that is closely related with biomaterial design is the multiple delivery of biofactors, since this is crucial in scaffold design for tissue engineering. Furthermore, more controllable actions of the biofactors can be realized by delivering them in a manner that is responsive to external or internal stimuli. This responsiveness, in conjunction with shape memory properties, are being explored in the design of promising smart biomaterials that have multifunctionality, and can be categorized in the combinatorial modulation of internal chemistry and external therapeutic molecules.

In this review, we describe biomaterials with smart properties, particularly in the form of composites. In this context, composite refers to materials combined either between different polymers in natural or synthetic and/or those polymers with inorganics, and even sometimes to those combinatorial biomaterials with biological factors designed for such smart functions. The main target tissues in utilizing smart composite biomaterials can range from hard tissues, including bone and teeth, to soft tissues that require specific composite formulations. This composite approach is particularly promising and exciting, since the combined properties between materials largely overcome the limitations that come from a single phase material. This helps the biomaterial meet the requirements for the smart actions, such as physical and chemical mimetism to native tissues, controlled and sustainable delivery of biofactors including multiple delivery, stimuli-responsive delivery, and shape memory multifunctional effects.

2. Internal modulation for smart composite biomaterials

Native tissue ECMs comprise highly specialized composite structure at the molecular level, organized with macromolecules of differing chemistry and/or inorganic nanocrystallites. They retain certain physical and chemical properties required for tissue function. Exploiting biomaterials that are reminiscent of the ECM of the tissue of interest is always challenging. The resulting material will not be identical to the native ECM; thus, the properties will not exactly mirror those of the native system, yet, great strides have been made in biomaterial design, particularly due to developments in nanotechnology. Engineering synthetic biomimetic biomaterials has benefited from combining different types of materials such as natural/natural polymers, natural/synthetic polymers, and polymers/inorganics. This approach aims to create biomaterials that possessing physical and chemical properties equivalent to native tissues, which are hopefully reflected in the capability to perform relevant biological functions.

Recently, the physical cues of biomaterials, mainly physical stiffness, have gained great attention in dominating cellular responses and controlling fate. The concept is based on the material mimetism to native ECM elastic properties. Principally, physical properties such as elastic modulus and strength intimately reflect the different chemical compositions and their organization at the nano- or micro-scale. In this regard, the modulation of chemistry and organization is of particular importance. A wide range of compositional variables is possible by the composite approach that is tunable to the physical properties of the native tissues. Tailoring of physical properties is explained based on polymer–polymer or polymer–inorganic compositions targeting soft and hard tissue, respectively. Also, nanotechnological advances in organizing/structuring biomaterial composites have focused on self-assembled biomaterials with a smart functional moiety in the nanostructure as an approach to produce instructive smart composites. Another category in the internal modulation to biomimetism is surface engineering with ECM molecules, involving the full sequence recombinant proteins or engineered peptides (short or oligopeptides) with key domains, or in a fused form that has multiple actions. Strategies for the internal modulation of biomaterials that exploit smart composites with bulk or surface chemistry and physical traits that are mimetic to native tissues are schematically illustrated in Fig. 1.

2.1. Tuning physical properties to native tissues

Physical properties including stiffness (elastic modulus) reflect intimately the chemical composition and the organization of the

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