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Review

Nanoparticle-based bioactive agent release systems for bone and cartilage tissue engineering

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ABSTRACT

The inability to deliver bioactive agents locally in a transient but sustained manner is one of the challenges on the development of bio-functionalized scaffolds for tissue engineering (TE) and regenerative medicine. The mode of release is especially relevant when the bioactive agent is a growth factor (GF), because the dose and the spatiotemporal release of such agents at the site of injury are crucial to achieve a successful outcome. Strategies that combine scaffolds and drug delivery systems have the potential to provide more effective tissue regeneration relative to current therapies. Nanoparticles (NPs) can protect the bioactive agents, control its profile, decrease the occurrence and severity of side effects and deliver the bioactive agent to the target cells maximizing its effect. Scaffolds containing NPs loaded with bioactive agents can be used for their local delivery, enabling site-specific pharmacological effects such as the induction of cell proliferation and differentiation, and, consequently, neo-tissue formation. This review aims to describe the concept of combining NPs with scaffolds, and the current efforts aiming to develop highly multi-functional bioactive agent release systems, with the emphasis on their application in TE of connective tissues.

1. Introduction

Nanostructured materials have been widely investigated in tissue engineering (TE) and regenerative medicine fields [1]. Tissue engineering and regenerative medicine research focuses mainly on the development of strategies to promote natural tissue repair and regeneration mechanisms [1]. The so-called triad of a TE strategy involves the following fundamental components: cells, biomaterial scaffolds and signaling biomolecules [2]. Commonly, a TE approach comprises the seeding of adequate cells over or into biodegradable and porous biomaterial scaffold, before its implantation, in order to repopulate a defect site and/or restore tissue function [3,4]. The cells' environment is composed of an extracellular matrix (ECM) and bioactive agents [5]. The most commonly used bioactive agents in the culturing medium or included on the biomaterials scaffold composition are the growth/differentiation factors (GFs). They are proteins that have crucial roles in stimulating cell proliferation, migration, differentiation and maturation of functional tissues precursors [6,7]. A successful regenerative outcome requires a sophisticated tuning of the GFs concentrations at the biomaterial scaffold, particularly at its boundary with the healthy tissue [8,9]. Thus, the modality of GFs presentation to the surrounding cells has been recognized as a key fundamental issue in many TE approaches. The potential of NPs systems for GFs' delivery has been perceived to protect GFs during tissue regrowth [6]. Moreover, it offers adequate control over GFs' release rate. The development of a highly functional release system can be achieved by the combination of NPs with biomaterial scaffolds. This review aims to present and discuss the concept of combining NPs with biomaterial scaffolds and describe the current efforts to develop multi-functional GFs release systems, with special emphasis on their application in TE and regenerative medicine approaches to repair or regenerate connective tissues.

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2. Nanoparticles as bioactive agents release systems

NPs have been one of the most promising devices for improving the delivery of bioactive agents and, consequently, increase their therapeutic efficacy [10,11]. Besides drug delivery, NPs have been also used in *in vitro* diagnostics, *in vivo* imaging and TE [1,6,12]. Although, NPs refer to particles with size ranging between 1 and 100 nm [10], NPs also include sub-micron particles with the size below 1000 nm [12,13].

2.1. Types of nanoparticles

Fig. 1 shows examples of NPs used as carriers of bioactive agents.

Liposomes are the first carrier system [15]. Liposomes are lipid vesicles formed when lipids are added to an aqueous solution. Lipids that form liposomes are amphipathic, such as phospholipids. Amphipathic lipids have a head end (hydrophilic) that attracts water and a tail end that repels water (hydrophobic) [16]. Liposomes can be produced using several methods [17,18], being the thin film method the first and common one. Moreover, it is possible to prepare liposomes varying in size, phospholipid composition and surface characteristics to suit the application for which they are intended [15].

Polymeric NPs are probably the largest category of nanosized materials used in the drug delivery field [19]. Synthetic polymers such as polylactides, poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), polyethylene glycol (PEG), and poly(DL-lactide-co-glycolide) (PLGA) have been widely used for the preparation of NPs. However, NPs made from natural-origin polymers such as albumin, alginate, chitosan, dextran and heparin have also been explored. They present many advantageous properties such as biodegradability, biocompatibility with physiological systems, natural abundance, and suitability for chemical modifications and blending with the synthetic polymers [11,14,20]. Depending on the preparation method, nanospheres or nanocapsules can be obtained. *Nanocapsules* are vesicular systems in which the bioactive agent is confined to a cavity surrounded by a polymer membrane; while nanospheres are matrix systems in which the bioactive agent is physically dispersed [20,21]. Other systems based on polymers include micelles and dendrimers. *Polymeric micelles* are based on amphiphilic block copolymers, which assemble to form a nanosized structure in aqueous media [22]. *Dendrimers* are highly branched, globular polymeric materials with nanometer-scale dimensions. They are defined by three components: a central core, an interior dendritic structure (the branches), and an exterior surface with functional surface groups [23,24].

2.2. Properties of nanoparticles

The properties of NPs have been widely studied and reviewed in the literature [1,21,25,26]. Composition, physical properties, surface chemistry and targeting ligands are among the parameters that can be manipulated to enhance the efficiency of the carriers (Fig. 2) [1].

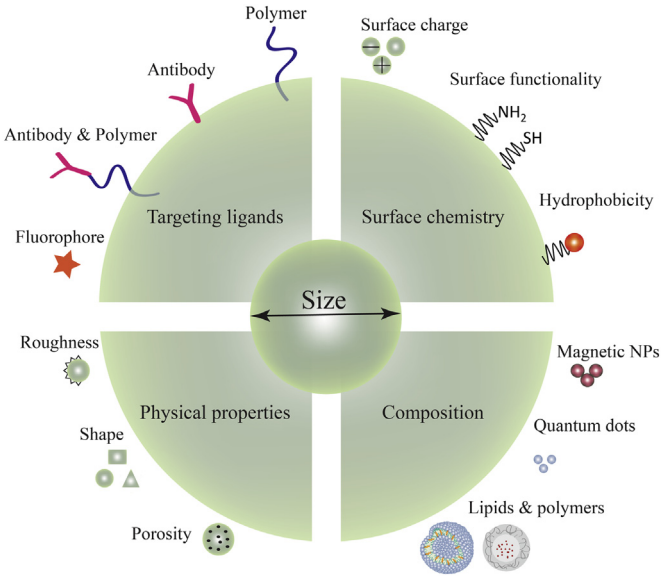

Fig. 2. Diagram representing the flexible tailoring of new NP formulations aiming for an intracellular delivery of therapeutic agents.

In fact, their nanoscale properties determine the diffusivity, biodistribution, biological fate, toxicity and the targeting ability [14]. The nanoscale dimension also increases the surface area to volume ratios, which increases the surface reactivity, drug loading ability, bioavailability and the release of loaded bioactive agents [13,19]. Moreover, they improve transport properties due to their ability to penetrate into tissues through capillaries and epithelial lining, and allow a more efficient delivery of therapeutic agents to target cells [14]. NPs can accumulate more than 10–200 times into tumor tissue than normal tissue due to the enhanced permeation and retention (EPR) effect [27–30]. EPR effect is a phenomenon that occurs in solid tumors, where macromolecules with molecular weight larger than 40–50 kDa or NPs are selectively retained in tumor tissues for longer time [30]. This effect occurs more in tumors than healthy tissues, because tumor blood vessels are characterized by poorly adherent endothelial cells with wide fenestrations and the lack of a smooth muscle cell layer. EPR effect is a "gold standard" for the anticancer drug design and for targeting sites of tissue inflammation [27–30]. Targeting to specific tissues is the most promising attribute of the NPs [14,31,32]. Therefore, to reach that capability, it is needed the covalent attachment of a defined ligand at the surface of the NP, which will specifically interact with antigens or receptors expressed at the surface of the target cells [33]. Another relevant property of NPs is the possibility of developing stimuli responsive release systems [34,35]. A variety of stimuli such as pH [36], temperature [37], ultrasonic waves [38], magnetic fields [39,40] and light [41] are currently being investigated to improve the release of bioactive agents.

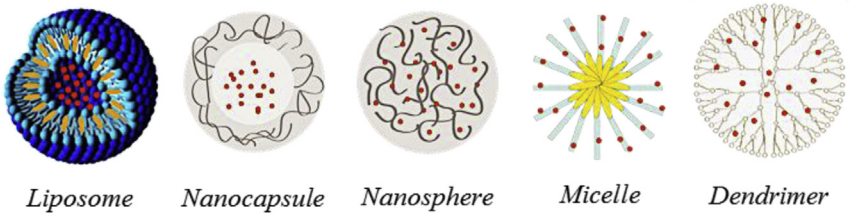

Fig. 1. Examples of NPs used in drug delivery. Adapted from Refs. [10,14].