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Recent advances using gold nanoparticles as a promising multimodal tool for tissue engineering and regenerative medicine

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ABSTRACT

Gold nanoparticles (AuNPs) have arisen a lot of interest in the clinical realms of nanomedicine. Despite the large advances made in cancer research using AuNPs, their use in tissue engineering and regenerative medicine (TERM) is still in its infancy. Herein, it is discussed the properties, functionalization, and emerging use of AuNPs as a multifunctional and multimodal platform for drug delivery, phototherapy, diagnostic and cell imaging purposes. Moreover, the recent reports related to the ability of AuNPs to enhance stem cell differentiation for bone tissue engineering, to enhance the mechanical and adhesive properties of scaffolds and surface topography to guide cell behaviors are addressed.

1. Introduction

Tissue Engineering and Regenerative Medicine (TERM), a multidisciplinary field including engineering, biology, and medicine, has been promising to develop viable therapeutic alternatives to organ and tissue transplantation. TERM thus holds great attention to tackle the clinical tasks by repairing, replacing or regenerating damaged tissues with functional engineered counterparts [1–3].

The human organs and tissues are composed of cells that can grow, proliferate and differentiate into desired cell type onto the 3D scaffold materials. In TERM, the use of stem cells such as mesenchymal stem cells and adipose-derived stem cells to differentiate into different cell lineages such as chondrocytes (cartilage cells), osteoblasts (bone cells), adipocytes (fat cells) have been considered as a great choice and continue to be significantly used [4]. However, to date, the limitations encountered for the regeneration of artificial tissues (bone, cartilage, skin, cardiac/skeletal muscle, nerve) are mainly due to poor mechanical and cell adhesive properties of scaffold, inefficient cell growth and differentiation at the defect site, as well as unstable growth factors to stimulate cell growth [5,6].

TERM has the willing to develop a system that will be able to enhance the regeneration of the tissue, by it means a system that will deliver growth factors and improve mechanical properties of scaffold, providing to the cells a suitable environment to differentiate. Within this challenge in mind, researchers attempt to introduce new scientific and technology concepts to revolutionize this clinical realm. To date, nanotechnology has emerged as a promising tool and has made a major impact in modern science [7,8]. In mid-1990's, scientists start to actively exploit the remarkable features of nanotechnology for various biological and medical applications and since the advances in nanotechnology for medicine continue to grow with the development of novel biomedical strategies [9,10]. With the aim to improve the present progress in TERM, a tremendous number of studies have successfully exploited polymeric and inorganic nanoparticles (NPs) [11–14]. Among those, gold nanoparticles (AuNPs) are one of the most promising and explored tools in nanomedicine. AuNPs have been widely used as therapeutic agents (drug delivery system [15], photothermal therapy [16]), diagnosis agents [17] and imaging agents [18,19]. Their nanoscale size, which meets the dimension of biological compounds, their easy preparation, high surface area, easy functionalization make them particularly interesting to accomplish the duties related to TERM. Besides, they present remarkable physicochemical properties, which are different from those of the corresponding bulk materials, and make them unique compared to classical NPs such as liposomes, polymeric NPs, and protein-based NPs. These physicochemical properties derive from the localized surface plasmon resonance (LSPR), a collective oscillation of the conduction electrons that typically occurs in the visible to near-infrared (NIR) region spectrum and can be easily detected by NIR-UV-visible spectrometry or even by eye [20]. Therefore,

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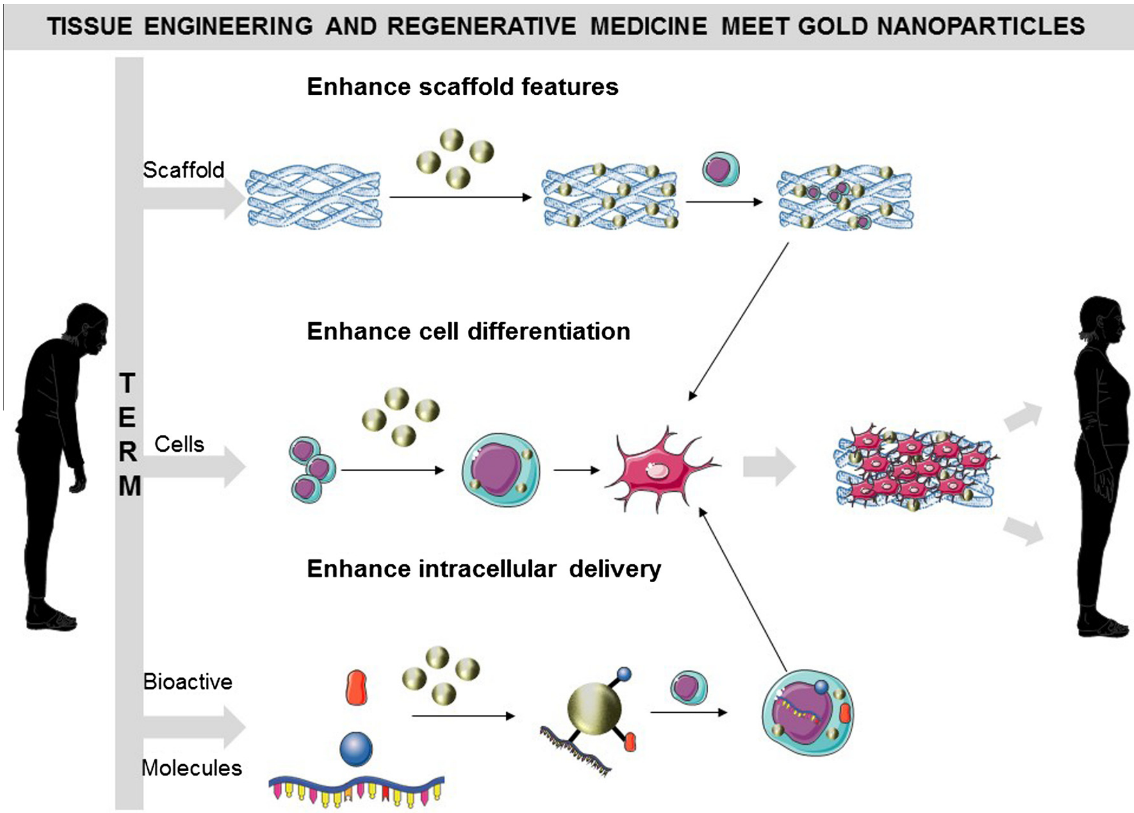

Fig. 1. Scheme representing the importance of introducing AuNPs in TERM realm. TERM combines three elements: scaffold, cells and bioactive molecules for engineered or repaired tissue. The addition of AuNPs in each element aims to enhance scaffold features (mechanical, adhesive), cell differentiation and intracellular delivery of bioactive molecules in order to bring an ideal microenvironment for the regeneration of the damaged tissue.

the mission of AuNPs in TERM is to act as a multimodal tool in order to enhance scaffold properties, cell differentiation and intracellular growth factor delivery (Fig. 1), while monitoring in real-time cellular events.

Despite the large advances made in cancer research using AuNPs, their use in TERM is still in its infancy. However, their potential in this area is away analogous to cancer theranostic approaches. Hence, the asset of exploiting AuNPs as a promising multimodal tool for TERM will be discussed while supporting some new trends in the cancer field. Firstly, it is reported the preliminary strategies for tuning the properties of AuNP's, by means of synthesis, functionalization and cell-AuNPs interactions, which are requested for the preparation of a biocompatible nanomaterial. Then, the recent works using AuNPs as an individual or multifunctional tool for drug delivery, diagnosis and imaging in TERM, specifically related to stem cell research is overviewed. Finally, the recent advances using AuNPs to enhance stem cell differentiation for bone tissue engineering, and to improve mechanical and adhesive properties, and favored nanostructures of scaffolds to guide cell behavior will be addressed.

2. Preparation and properties of AuNPs

2.1. Synthesis routes

The synthesis routes of AuNPs have been widely developed in order to control their shape and size, thus leading to diverse properties and multimodal applications. To date, numerous methods have been reported for preparing a wide variety of shapes (Fig. 2) such as nanospheres [21,22], nanorods [23,24], nanoplates [25], nanodumbells [26], nanostars [27,28] and nanocages [29]. Wet-chemical synthesis of AuNPs is the most common method and is carried out of presence of a stabilizer, which can bind to the atom exposed at the AuNPs surface. This capping agent allows stabilization and prevents uncontrolled growth and aggregation of the NPs. For more details regarding the processes to control AuNPs synthesis, we highly encourage to read the following reviews [30,31]. Here, we will briefly describe the «classical» methods to prepare spherical AuNPs. Typically, the AuNPs synthesis approach implies both the use of a reducing agent that serves to reduce Au^{3+} to Au atoms and a stabilizer (capping agent) to maintain colloidal stability. The synthesis of spherical NPs have been developed by Turkevish [32] in 1951 and since has been employed in a multitude of studies. NPs with a size of 20 nm were prepared with citric acid that acts both as the reducing and stabilizing agents. Later [33], the size-controlled NPs were developed by varying the ratio gold salt and sodium citrate. On the other hand, the preparation of anisotropic NPs such gold nanorods (AuNRs) requires the use of a template, mostly surfactant, and the most established and efficient process to prepare high yield is based on the seed-growth method [34,35]. Firstly, gold seed are prepared by reduction of chloroauric acid salt ($HAuCl_4$) solution by sodium borohydride in a cetyltrimethyl ammonium bromide (CTAB) aqueous solution. Subsequently, the seed is added to a gold "growth" solution in presence of CTAB, silver nitrate and ascorbic acid (weak reducing agent).

As aforementioned, the synthesis of AuNPs implies the reduction of gold ions and the use of a charged chemical that maintains the colloidal stability of the NPs via repulsive force. However, AuNPs exhibit low stability and biocompatibility in biological environment. Therefore, the concept of "green synthesis", using biocompatible compounds, has been considered as an alternative