Iron Oxide Nanoparticles

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Iron oxide nanoparticles (IONs) have shown promising potential as delivery vehicles and cellular markers for theranostic applications. Their high biocompatibility, superparamagnetic properties and exceptional surface-coating versatility have facilitated the development of IONs that adequately interact with biological environments. The strategical modification of ION architectures towards performing highly specialized functions has allowed the rational design of next-generation nanoparticles for biomedical applications.

Keywords: iron oxide nanoparticles ; cellular uptake ; endosomal escape ; transfection

1. Introduction

Iron oxide nanoparticles (IONs) have gained significant attention over the past decades for their promising performance in disease diagnostics and the delivery of therapeutics [1]. In particular, their exceptional magnetic properties have alleviated some of the most relevant shortcomings in the targeted delivery of nanovehicles for biomedical applications [2]. IONs can be precisely guided and accumulated in specific tissues with the application of external magnetic fields since, at nanoscale sizes, iron oxide exhibits superparamagnetic properties that stem from its inherent ferromagnetism [3]. In addition to their remarkable magnetic properties, the low toxicity profile of IONs has made them superior candidates for biomedical applications when compared to other metal oxide nanoparticles [4]. The broad versatility of modifications that can be performed on ION surfaces, in particular, has made them highly attractive since they can be readily tuned to interact with different cell lines and subcellular compartments, as well as deliver therapeutic cargo. These versatile surfaces, in particular, allow the strategical tuning of IONs, which is imperative to orient their behavior in extracellular and intracellular environments, and dictate their biological performance.

2. Tailoring iron oxide nanoparticles for biomedical applications

2.1 Enhancing ION cellular uptake

Due to the enormous versatility of the endocytic pathways, numerous surface modification alternatives arise for enhancing ION internalization. In particular, several strategies have emerged to promote the interplay between IONs and the plasma membrane (PM). Nanoparticle surface chemistry, especially surface charge, has been established to directly contribute to ION internalization through electrostatic interactions with the PM [5]. Cationic coatings (e.g., cationic polymers, lipids, cell-penetrating peptides or proteins) have shown the most promising potential due to their avid interactions with negatively charged components of the PM, which induce the recruitment of the endocytic machinery and lead to their internalization [5]. However, high positive charge densities can induce disruptive outcomes due to the strong interaction forces with the PM and, therefore, should be closely monitored during ION design [6]. Anionic coatings, although not as potent, have also shown superior uptake rates than neutral nanoparticles [7]. Alternatively, tethering ION surfaces with targeting agents that are recognized by specific PM receptors has been the most common approach for their targeted delivery to specialized tissues. These agents should be selected according to the expression profile of membrane receptors in the target tissue and their relative expression with respect to surrounding tissues, as these should be predominant for adequate selectivity. Nanoparticle recognition by these receptors not only guarantees tissue selectivity but also serves as a direct entry route into cells by receptor-mediated endocytosis.

2.2 Enhancing ION endosomal escape

Once internalized, IONs that are not intended for lysosomal treatments must escape endocytic vesicles to avoid degradation or recycling processes [8]. Several endosomal disruptive mechanisms can be targeted for ensuring adequate intracellular delivery of IONs. A common approach for inducing endosomal leakage is interfering with the characteristic luminal acidification processes of endosomes, which induces osmotic imbalances that result in endosomal swelling and rupture [9]. This process, termed the proton-sponge effect, is achieved by incorporating pH-responsive coatings that

achieve high protonation degrees upon acidification or cationic coatings that create an osmotic gradient. Alternatively, IONs assembled with fusogenic lipids or amphiphilic molecules can induce endosomal escape via fusion of the lipidic envelope with the endocytic membrane by inverting its structure and allowing the release of encapsulated cargoes into the cytosol [10]. Pore formation by translocation mechanisms on membrane vesicles can also occur by tethering IONs with cationic peptides or proteins derived from several viral, bacterial, vegetal, and animal sources [11]. Other approaches have included photosensitizers [12] or photothermal transduction agents [13] to induce the generation of reactive oxygen species (ROS) and singlet oxygen ($^1O_2$) that lead to membrane destabilization. These endosomal escape strategies have been termed photochemical internalization (PCI) and photothermal therapy (PTT), respectively.

2.3 Enhancing ION-mediated transfection

As many nanoparticle-based delivery systems, IONs have been commonly used for the delivery of gene therapy sequences and vectors. However, inefficiency while crossing the nuclear envelope is one of the principal reasons for low transfection efficiencies [14]. Cationic coatings have been commonly used for gene delivery due to their ability to interact with nucleotides, where complexation occurs through electrostatic interactions. Moreover, these coatings present similar features to nuclear localization signal (NLS) sequences, which exhibit a strong positive charge and mediate active nucleocytoplasmic transport through importin proteins [15]. This has motivated the search for adequate coatings of such characters, such as cationic peptides or proteins, cationic lipids, and dendrimers.

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