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Review

Surface modification and local orientations of surface molecules in nanotherapeutics

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ABSTRACT

Nanotechnology has emerged as a powerful tool for various therapeutic applications, solving many difficulties in both diagnosis and treatment. However, many obstacles in complex biological systems have impeded the successful application of therapeutic nanoparticles, and fine-tuning nanoparticle properties have become extremely important in developing highly effective nanomedicines. To this end, particles have been engineered in various ways, with a special emphasis on surface modifications. The nanoparticle surface contacts the biological environment, and is a crucial determinant of the response. Thus, surface coating, surface charge, conjugated molecules, shape, and topography have enormous impacts on the total behavior of nanoparticles, including their biodistribution, stability, target localization, cellular interaction, uptake, drug release, and toxicity. Hence, engineering of the particle surface would provide wider dimensions of control for the specific and precise functions in the development of smart nanomedicines. Moreover, local orientation of nanoparticles in vivo and orientations of surface molecules are critical for their efficacy. Herein, we analyze surface functionalities, focusing on their mechanisms and respective advantages, and summarize results of surface engineering and renovating applications of nanoparticles.

Contents

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1. Introduction

The emergence of nanotechnology in medical science has improved drug delivery systems in terms of solubility, membrane permeability, drug targeting, and controlled release [1,2]. Over the last few decades, development of therapeutic nanocarriers has become an important area of research, as they can improve the delivery of active molecules to the target site and overcome biological barriers [1,3]. In complex biological systems, nanomedicines have faced obstacles such as rapid clearance, lack of proper interaction, nonspecific targeting, inability to enter targeted cells and the core of tissues, and uncontrolled drug release [4,5]. Several investigations have found that nanoparticle surfaces greatly impact their performance [6,7]. Because nanoparticle surfaces come in contact with biological systems, surface characteristics determine how the nanoparticles will behave in vivo and the overall effectiveness of the particles, including stability, cellular interaction, uptake, drug delivery, and toxicity [4,6,8,9]. Therefore, engineering of the particle surface provides another dimension of control for specifically tailoring the functions and developing smart nanoparticles.

Nanoparticle surfaces have been engineered in various ways for specific functions depending on the intended therapeutic use. Surface modifications such as attachment of bioactive and penetrating molecules, use of stimulus–responsive materials, surface coating, and modification of surface charge, texture, and shape allow nanoparticles to serve as smart devices that interact selectively with targeted cells, enter the core of tissues, and release drugs at a controlled rate, escaping from body clearance [4,10]. Surface modification with hydrophilic biocompatible polymers increases the circulation time and delays the removal of nanoparticles by the mononuclear phagocyte system (MPS), preventing rapid clearance prior to reaching the targeted tissue and delivering drugs [11,12]. The surface charge of nanoparticles has been modified according to the charge of the target cells or tissues to increase cellular interaction and internalization [13]. Conjugating active molecules on the surface of nanoparticles converts them into “guided vehicles” that exhibit cell-specific targeted interactions and penetrate to the core of the target tissue [1,14,15]. Attachment of specific penetrating peptides to nanoparticles is also effective for enhancing cellular uptake [16]. Nanoparticle surfaces have been decorated with stimulus–responsive materials to release drugs in response to various stimuli [17]. Importantly, the orientation and alignment of surface molecules affect their functions and the overall efficiency of nanomedicines [15,16]. In addition, modification of surface roughness and nanoparticle shapes significantly affect cellular interactions and drug release [18], and nanoparticle toxicity is related to surface properties, as variation in surface characteristics has significantly lowered the level of toxicity [19,20]. Combining these properties has allowed development of intelligent nanoparticles to meet delivery and therapeutic objectives [21].

Surface engineering thus has become a major tool to address the particular challenges of nanotherapeutics. Studies have shown how surface engineered nanoparticles can efficiently overcome the limitations of other delivery systems [22]. Nowadays, proper surface functionalization has become a prerequisite for effective application of nanoparticles [23]. In this review, we focus on different surface characteristics of nanoparticles and discuss conventional and newer functionalities that have been discovered to increase the efficiency of nanoparticles. We further review the effect of surface molecule and nanoparticle orientations on function.

2. Surface modification for enhanced stability of nanoparticles

Surface properties play the most important role for nanoparticle stability in blood circulation. Conventional nanoparticles with unmodified surfaces are unstable and rapidly cleared by the MPS before reaching the target tissue. Nanoparticles are recognized by the immune system through opsonization, a process by which a particle becomes covered with opsonin proteins, making it more visible to the MPS (liver, spleen, lungs, and bone marrow), and thereby increasing clearance [24]. Different functional groups on nanoparticle surfaces are the primary determinants of stability [24,25]. Usually, the degree of hydrophobicity determines the extent of opsonin binding: a high level of hydrophilicity is associated with lower opsonin binding and higher stability of nanoparticles in blood circulation, whereas hydrophobic surfaces induce nanoparticle aggregation through hydrophobic interactions and minimize surface energy, which can trigger opsonization and rapid elimination [26].

The stability of nanoparticles in blood has been increased by surface modification. The surface has been coated with biocompatible hydrophilic polymers/surfactants or copolymers with hydrophilic properties. Hydrophilic polymers on the surface of the nanoparticles repel other molecules by steric effects. Thus, nanoparticles are not covered with opsonin proteins and are protected from rapid clearance [27]. Widely used surface-coating materials for prolonging the circulation time include polyethylene glycol (PEG), polyethylene oxide (PEO), polyvinylpyrrolidone (PVP), polyacrylic acid, dextran, poloxamer, poloxamine, and polysorbate (Tween-80). PEG is the most widely used material and has efficiently enhanced the stability of nanoparticles in many studies [26–28].

In addition to the density of the polymer on the nanoparticle surface, polymer conformation plays a significant role in determining stability [27]. PEG molecules with brush-like configurations on the surface of nanoparticles reduce phagocytosis and complement activation, whereas mushroom-like structures of PEG are potent complement activators and favor phagocytosis [11,29]. Polymer conformation is described using the Flory radius, F (Eq. (1)), which is determined by the number of monomers per polymer chain, n, and the length of one monomer, α, in Angstroms (α = 3.5 Å for PEG). Hence, F increases with increasing molecular weight of PEG. Polymers that are less densely grafted to the nanoparticle surface form mushroom-like structures wherein the mean distance between each grafting site is larger than the polymer size (Flory radius); thus, the individual polymer chains remain separated without interacting. When the mean distance is decreased and F is increased, each polymer chain overlaps, resulting in higher grafting density and polymer interaction. It forms a brush like conformation PEG, extending from the NP surface [30]. Brush-like PEG chains on the surface establish a hydrophilic lining that prevents attachment of molecules to the nanoparticles [31]. PEG densities below 9% on the surface of nanoparticles form a mushroom-like structure, and those above 9% form a more rigid, brush-like morphology [32]. Larger nanoparticles can be coated with smaller lengths of PEG (3400–10,000 monomers) because increases in hydrodynamic radius can shorten the half-life [33].

$$F = \alpha n 3/5 \quad (1)$$

Superparamagnetic iron oxide nanoparticles (4–5 nm) were coated with 20–30 dextran chains in a brush-like conformation, which reduced the rapid clearance of the nanoparticles from the bloodstream with a prolonged half-life ($t_{1/2}$) of 3–4 h [34]. Fig. 1 illustrates the effect of PEG density on serum exposure and macrophage uptake. Neutral functional groups on nanoparticle surfaces provide excellent protection from opsonization, whereas charged functional groups are responsible for active nanoparticle interaction with target cells [35,36]. A zwitterionic copolymer showed excellent shielding of nanoparticles in blood circulation and maximized their interactions with target tissue. Yuan et al. developed a zwitterionic polymer-based nanoparticle for enhanced drug delivery to tumors. The nanoparticles were neutrally charged at physiological conditions and thus showed a prolonged circulation time ($t_{1/2}$ ~ 24.05 h in a three-compartment pharmacokinetic model). After leaking into the tumor, the nanoparticles became positively charged in the acidic extracellular environment, and were efficiently taken up by tumor cells [35]. In our previous study, we modified silica nanoparticles with a PEG-conjugated polyethyleneimine copolymer, and studied the biodistribution profile by ICP-MS and