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Advances in Surface Engineering Strategies for Enhancing Nanomaterial Biocompatibility

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Abstract. Nanomaterials exhibit tremendous potential in biomedical applications due to their unique physicochemical properties. However, their interactions with biological systems, particularly biocompatibility issues, present significant challenges that hinder their clinical implementation. This review explores recent advancements in surface modification techniques aimed at improving the biocompatibility of nanomaterials. The article examines a range of surface engineering strategies, including polymer coatings, lipid layer modifications, protein and peptide engineering, zwitterionic and small-molecule coatings, bioinspired approaches, and emerging surface treatment technologies. The review emphasizes the mechanisms of these techniques and their impacts on biocompatibility parameters such as cytotoxicity, hemocompatibility, immunogenicity, and in vivo circulation time. Finally, the review addresses the current challenges faced in surface modification and outlines future research directions to guide the design of safer and more effective biomedical nanomaterials.

Keywords: Nanomaterials, biocompatibility, surface treatment, polymers, biomimetics

1. Introduction

Nanomaterials are defined as materials with at least one dimension smaller than 100 nanometers. Their exceptionally high surface-to-volume ratio, combined with unique physical, chemical, and optical properties, has spurred extensive research across various fields, particularly biomedicine. In the context of global healthcare challenges - such as aging populations, rising chronic disease prevalence, and the growing demand for precision medicine - nanomaterials hold great potential to revolutionize modern medical practices. In biomedical applications, nanomaterials are extensively used in drug delivery, bioimaging, disease diagnosis, tissue engineering, and treatments. For instance, nanoparticles can function effectively as drug carriers, improving drug targeting and bioavailability [1]. Quantum dots, with their superior optical properties, are frequently used in bioimaging and sensing [2]. Additionally, nanofibers and nanotubes hold significant promise for applications in tissue engineering and regenerative medicine due to their favorable structural and mechanical properties.

Biocompatibility, defined as the capacity of a material to perform with an appropriate host response in a given biological context, is a crucial determinant for the clinical translation of nanomaterials. Despite the numerous advantages of nanomaterials, their interaction with biological

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systems and associated safety concerns represent substantial barriers to clinical translation. The interactions between nanomaterials and biological systems are highly complex and may trigger a range of adverse reactions, including cytotoxicity, genotoxicity, immunogenicity, and potential long-term toxicity [3]. Clinically, biocompatibility directly impacts patient safety and treatment effectiveness; incompatible materials can result in therapeutic failure or serious complications. For example, studies have shown that certain carbon nanotubes may have potential carcinogenicity [4], while graphene-based nanomaterials may induce complex inflammatory responses [5]. Therefore, enhancing the biocompatibility of nanomaterials to ensure their safety and effectiveness in biological systems is a major focus of research in nanomedicine.

Surface modification has emerged as a crucial strategy to address biocompatibility concerns. By carefully adjusting surface properties, such as composition, charge, hydrophobicity, and functional group presentation, surface engineering significantly modulates nanomaterial interactions within biological environments. The surface of nanomaterials is the first interface that directly contacts the biological environment, and its properties directly influence how cells and tissues respond to these materials. This review comprehensively analyzes recent advancements in surface modification techniques, focusing specifically on strategies designed to enhance nanomaterial biocompatibility. Through a critical evaluation of current methodologies and their biological implications, this paper aims to deliver valuable insights to support the informed design and development of safe, effective, and clinically viable biomedical nanomaterials.

2. Advanced surface treatment technologies to enhance the biocompatibility of nanomaterials

2.1. The significance of nanomaterials

Nanomaterials are classified based on the number of dimensions in which their size is confined: zero-dimensional (e.g., nanoparticles, quantum dots), one-dimensional (e.g., nanowires, nanotubes), two-dimensional (e.g., nanosheets, nanofilms), and three-dimensional nanostructured materials. Examples include zero-dimensional fullerenes and metal nanoparticles, one-dimensional carbon nanotubes and nanofibers, two-dimensional graphene and nanocoating, and three-dimensional nanoporous structures and composites. This dimensional classification facilitates the understanding of the structural diversity of nanomaterials and their associated applications.

The biocompatibility of nanomaterials is influenced by a complex array of factors, including size, shape, surface charge, chemical properties, hydrophobicity, and material composition [3]. For example, nanoparticle size significantly affects cellular uptake efficiency and toxicity. Smaller nanoparticles typically exhibit enhanced cellular internalization but may also pose increased cytotoxic risks [4]. The surface charge of nanomaterials further modulates their interaction with the negatively charged cell membrane. Positively charged nanoparticles, in particular, tend to interact strongly with cell membranes, enhancing cellular uptake but potentially increasing cytotoxicity.

Although nanomaterials demonstrate immense potential within the biomedical domain, their biocompatibility remains encumbered by significant challenges, including cytotoxicity, genotoxicity, immunogenicity, and long-term toxicity [3]. For instance, in vitro studies have indicated that multi-walled carbon nanotubes exhibit cytotoxicity comparable to tattoo ink in specific cell lines, and in vivo studies indicate that intraperitoneal injection of these nanotubes in p5+/- mice can induce mesothelioma [4]. Moreover, graphene-based nanomaterials may trigger inflammatory responses through interactions with immune cells and inflammatory mediators [5]. Therefore, mitigating these challenges is imperative for ensuring the safe and effective clinical translation of nanomaterials [6].

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2.2. Polymer-based surface modification

Polymer-based surface modification techniques represent one of the most prevalent methods for enhancing the biocompatibility of nanomaterials. Among these, polyethylene glycol (PEG) modification (PEGylation) is particularly prevalent. PEG, a hydrophilic polymer, forms a hydration layer on the surface of nanomaterials, effectively reducing protein adsorption and preventing particle aggregation. This modification not only improves the stability of nanomaterials in biological fluids but also prolongs their circulation time, thereby achieving the so-called "stealth" effect. Numerous studies have substantiated that PEGylated iron oxide and silica nanoparticles significantly improved biocompatibility, even at high concentrations. Additionally, PEGylation enhances the hemocompatibility of materials such as chromium-doped zinc gallate and diatomaceous earth-based nanoparticles [7].

In addition to PEG, other biocompatible polymers, such as chitosan, alginates, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP), have also been extensively employed for surface modification. These polymers confer spatial stability and improve nanomaterial interactions with biological systems. For instance, chitosan, a naturally occurring cationic oligosaccharide, interacts electrostatically with negatively charged cell membranes, thereby facilitating cellular uptake. Studies have shown that chitosan-coated iron oxide and silver nanoparticles exhibit reduced toxicity compared to their unmodified counterparts. Alginates, natural polysaccharides derived from seaweed, are frequently utilized to produce hydrogel-based nanoparticles for drug delivery and tissue engineering applications [8].

Heparin-like polysaccharides (HEP) can offer spatial protection to nanoparticles, preventing protein adsorption and macrophage uptake. More significantly, certain polysaccharides can selectively target specific cell types through interactions with carbohydrate receptors present on the cell surface.

2.3. Lipid-based coatings

Lipids, as the fundamental constituents of biological membranes, are inherently suitable for creating lipid-based coatings for nanomaterials that significantly enhance biocompatibility. Natural phospholipids commonly form uniform lipid bilayers on nanoparticle surfaces, effectively reducing protein adsorption and improving the stability of nanoparticles in biological fluids.

Liposomes, nanoscale vesicles that mimic the structural properties of biological membranes, have gained widespread use as drug delivery systems [1]. Due to their biomimetic structure, liposomes possess excellent biocompatibility and can encapsulate both hydrophilic and hydrophobic drugs, enabling controlled release and targeted delivery.

In recent years, an innovative biomimetic strategy has emerged involving the coating of nanoparticles with natural cell membranes, such as those from red blood cells (RBCM-NPs) and white blood cells. This approach significantly enhances biocompatibility by transferring native cell membrane characteristics like extended circulation time, reduced immune recognition, and improved targeting of specific tissues. For instance, RBCM-NPs can effectively evade clearance by the immune system, while nanoparticles coated with white blood cell membranes exhibit enhanced targeting of inflammation sites.

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2.4. Protein and peptide surface engineering

Given their crucial biological roles, proteins and peptides are widely employed for engineering the surfaces of nanomaterials, improving both biocompatibility and targeting precision. Proteins like serum albumin can adsorb onto nanoparticle surfaces, stabilizing charge distribution and forming a protective hydration layer that inhibits nonspecific protein adsorption, thus significantly enhancing nanoparticle stability in biological environments.

Short peptides, including aptamers and cell-penetrating peptides, can be conjugated to nanoparticle surfaces to provide precise targeting and improved biocompatibility. Aptamers, short nucleic acid or peptide sequences with high specificity and affinity for target receptors, facilitate the targeted delivery of nanoparticles. Cell-penetrating peptides, on the other hand, facilitate the translocation of nanoparticles across the cell membrane, thereby improving cellular uptake efficiency [7].

Furthermore, biomimetic peptides derived from proteins in bones and teeth have been employed to simulate the biomineralization process, promoting the repair and regeneration of bone tissues. This approach, by mimicking the natural biological processes, allows for the design of nanomaterials with enhanced tissue regeneration properties.

2.5. Zwitterionic and small molecule coatings

Zwitterionic ligands, which simultaneously contain positive and negative charges, effectively regulate nanoparticle surface charge density and solubility. These properties notably prevent protein corona formation, thereby significantly reducing nanoparticle sensitivity to ionic fluctuations and ensuring robust stability and biocompatibility in complex biological environments.

Thiol-alkyl acid ligands exhibit a strong affinity for metal surfaces, forming robust protective layers through thiol-metal interactions, thereby enhancing the stability and biocompatibility of nanoparticles in biological fluids. Furthermore, the carboxyl groups on these ligands offer additional functionalization opportunities, enabling the design of multifunctional nanomaterials.

Other small molecule modifications are commonly employed to precisely adjust nanoparticle surface hydrophobicity and charge, influencing their biological behavior [7]. These modifications play an essential role in minimizing non-specific interactions with biological components and improving the overall biocompatibility of the materials.

2.6. Biomimetic approaches in surface modification

Inspired by the structure and function of natural biological systems, biomimetic design is an essential strategy for developing nanomaterials with exceptional biocompatibility. One such biomimetic approach involves the use of polydopamine (PDA), a synthetic polymer whose molecular structure closely resembles the amino acid DOPA found in mussel adhesive proteins. PDA-based coatings have been utilized to fabricate hydrogels with antibacterial properties and adhesion capabilities, making them highly suitable for wound healing applications.

Biomineralization, the process through which organisms naturally form inorganic minerals, has been harnessed in nanomaterial fabrication to achieve biocompatible and tissue-regenerative materials. For example, by simulating bone mineralization, hydroxyapatite nanomaterials have been created for use in bone tissue engineering, enhancing their biocompatibility and regenerative potential.

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3. Emerging trends and advanced surface treatment technologies

In addition to traditional surface modification techniques, emerging technologies offer novel approaches to enhance the biocompatibility of nanomaterials further. Techniques such as chemical vapor deposition (CVD), electrochemical deposition, dip-coating, and spray-coating allow for precise control over the thickness and uniformity of coatings. For example, CVD is commonly employed for coating scaffolds and catheters, ensuring uniformity and high precision in coating applications [9]. Microfluidics-assisted coating and in situ protein coating technologies represent promising advances, enabling more precise control over the coating process and improving the biocompatibility of complex coatings [10]. Microfluidic technology allows for the precise mixing of coating materials and nanoparticles, thereby minimizing damage to the biological materials [11]. In situ protein coating technologies enable proteins like PEG-maleimide to self-adsorb onto nanoparticles, reducing immunogenicity and avoiding the need for complex surface modification steps [11].

Layer-by-layer assembly techniques also hold great promise for constructing nanomaterials with customized surface properties. They offer additional flexibility and control over the final material's biological interaction [12].

4. Comparison between surface treatment and biocompatibility

The literature review highlights significant advancements made in enhancing the biocompatibility of nanomaterials through various surface treatment technologies. For example, PEGylation has effectively reduced the cytotoxicity of nanoparticles, extended their circulation time in the bloodstream, and diminished nonspecific protein adsorption. Lipid coatings, particularly those derived from natural cell membranes, enhance nanoparticle biocompatibility and confer improved targeting capabilities. Protein and peptide surface engineering allows for precise cellular targeting, thereby enhancing cellular uptake. Zwitterionic coatings and small molecule modifications regulate surface charge and hydrophobicity, minimizing protein corona formation and improving nanoparticle stability. Biomimetic methods, such as the use of polydopamine and biomineralization, provide new approaches for developing nanomaterials with inherent biocompatibility. Emerging surface treatment technologies, such as microfluidics-assisted coating and in situ protein coating, demonstrate substantial potential for precise control over nanoparticle surface properties, further improving biocompatibility [10].

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Table 1. Surface modification strategies and their parameters [16-22]

Surface Modification Strategy	Nanomaterial	Impact on Biocompatibility Parameters
PEGylation	Fe_3O_4, SiO_2	Enhanced biocompatibility at high concentrations, prolonged circulation time, reduced protein adsorption
Chitosan Coating	Iron oxide, silver	Reduced cytotoxicity
Red Blood Cell Membrane Coating	PLGA	Prolonged in vivo circulation time
White Blood Cell Membrane Coating	-	Targeted inflammation sites
Zwitterionic Ligands	-	Reduced protein corona formation, improved solubility
Polydopamine Coating	-	Antibacterial, promotes wound healing
Biomineralization	-	Promotes bone tissue regeneration

5. Effectiveness and challenges of different surface treatment techniques

Different surface treatment methods enhance nanomaterial biocompatibility via distinct mechanisms. For instance, PEGylation creates a hydrophilic hydration layer that prevents nonspecific protein adsorption, reducing immune system recognition and clearance, thus extending nanoparticle circulation time in vivo. Lipid coatings, particularly cell membrane coatings, simulate the characteristics of biological membranes, allowing for improved interactions with biological systems, reduced immunogenicity, and potential targeted delivery. Protein and peptide surface engineering enables specific biological functionalities, such as receptor-targeted delivery, significantly enhancing therapeutic efficacy while minimizing off-target toxicity. Zwitterionic coatings and small molecule modifications regulate the surface characteristics, such as charge and hydrophobicity, to reduce protein corona formation and improve nanoparticle stability in complex biological environments. Biomimetic strategies, such as polydopamine-based coatings and biomineralization processes, provide innovative ways to design nanomaterials with innate biocompatibility, facilitating tissue regeneration.

The choice of surface treatment technology depends on various factors, including the nanomaterial type, the intended application, and the desired biological response. For example, PEGylation or cell membrane coatings are well-suited for drug delivery systems requiring prolonged circulation times, whereas protein—or peptide-based surface engineering may be more appropriate for targeted therapies targeting specific cell types.

Despite significant progress, several challenges and limitations persist. The long-term stability of some surface modifications remains inadequate in complex physiological conditions. Moreover, scaling laboratory-based surface treatment methods to large-scale production while maintaining cost-effectiveness presents an ongoing challenge. Some surface treatments may also inadvertently alter the properties of the nanomaterials themselves. For example, excessive ultrasonic processing used during surface modification of carbon nanotubes can lead to structural damage, negatively impacting their performance [13].

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The literature reveals discrepancies regarding the effectiveness and safety profiles of specific surface modification strategies. For example, the biocompatibility of gold nanoparticles can vary depending on their size, concentration, surface chemistry, and targeted cell types [14]. These variations indicate that the interactions between nanomaterials and biological systems are highly complex, requiring further investigation.

A universally accepted, standardized protocol for evaluating nanomaterial biocompatibility remains critical yet elusive [9]. However, the lack of a widely accepted standard has made it difficult to compare findings across different studies [15]. Furthermore, there may be discrepancies between in vitro biocompatibility assessments and in vivo results [15]. While in vitro studies provide preliminary toxicity screening, they cannot replicate the complexity of in vivo biological environments. Therefore, combining both in vitro and in vivo studies is necessary for a more comprehensive evaluation of the biocompatibility of nanomaterials.

6. Conclusion

Advanced surface treatment technologies have significantly improved the biocompatibility of nanomaterials, facilitating their development into safer and more effective biomedical tools. Polymer coatings, lipid layer modifications, protein and peptide engineering, zwitterionic and small molecule coatings, and biomimetic approaches offer substantial improvements, optimizing nanoparticle-biological interactions, minimizing cytotoxicity, extending circulation duration, and enhancing targeting accuracy.

Future research should address several critical areas to accelerate clinical translation and maximize therapeutic outcomes. Firstly, extensive investigation of the long-term biological effects of surface-treated nanomaterials is essential to ensure their safety in prolonged clinical applications. Second, there is a pressing need to develop more complex and precise surface modification methods is necessary to achieve finer control over the biological behavior of nanomaterials. Third, emerging technologies such as artificial intelligence and machine learning hold promise in nanomaterial design and biocompatibility prediction. Finally, overcoming regulatory hurdles and developing universally accepted standardized testing protocols is imperative to facilitate the clinical translation of advanced nanomaterials. Continued interdisciplinary collaboration and in-depth research are essential for realizing the full potential of nanomaterials in improving human health.

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