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The Role of Nanomaterials in the Treatment of Diseases and Their Effects on the Immune System

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Abstract

Nanotechnology has been widely exploited in recent years in various applications. Different sectors of medicine and treatment have also focused on the use of nanoproducts. One of the areas of interest in the treatment measures is the interaction between nanomaterials and immune system components. Engineered nanomaterials can stimulate the inhibition or enhancement of immune responses and prevent the detection ability of the immune system. Changes in immune function, in addition to the benefits, may also lead to some damage. Therefore, adequate assessment of the novel nanomaterials seems to be necessary before practical use in treatment. However, there is little information on the toxicological and biological effects of nanomaterials, especially on the potential ways of contacting and handling nanomaterials in the body and the body response to these materials. Extensive variation and different properties of nanomaterials have made it much more difficult to access their toxicological effects to the present. The present study aims to raise knowledge about the potential benefits and risks of using the nanomaterials on the immune system to design and safely employ these compounds in therapeutic purposes.

Introduction

Nanomaterials have structures smaller than 100 nm with physicochemical properties capable of affecting biological processes [1]. The nanomaterials can be synthesised from a wide range of materials, the most common of which being silicates, non-oxide ceramics and metal oxides. Nanomaterials have many features and capabilities with unique structural characteristics such as desirable size, greater solubility, easier to pass through cellular barriers and more reactivity [2]. The application of nanotechnology has created new hopes in solving today's human problems. In recent decades, the nanotechnology has been introduced as a factor affecting different industries, and the use of nanomaterials has expanded rapidly in various fields. The pharmaceutical and medical industries have also benefited by the use of nanotechnology such that it has led to the introduction of new applied products into the market [3], [4].

Nanotechnology has been used in the fields of prevention, diagnosis and treatment of various

diseases. However, the interaction of nanomaterials and the immune system remains somewhat unknown. Previous studies have shown that the nanomaterials can cause excitation or suppression of immune responses through binding to blood proteins. Adsorption of these proteins bound to nanomaterials is recognised by various immune cells. Also, they affect the interaction of nanoparticles (NPs) with other blood components [5], [6]. Nanomaterials contribute to the activity of the adjuvant by increasing antigen presentation to the immune system as well as the enhancement of the innate immune responses. Determining the degree of biocompatibility of nanomaterials with the immune system is largely fulfilled by their surface chemistry. Today, the nanotechnology is widely used to improve targeted immune responses to the prevention and treatment of infectious and non-infectious diseases. Localised nano immunotherapy through the reduction of systemic toxicity improves the immunostimulatory molecules [7]. The applications of nanotechnology in medicine and immunology are extensive. This study has reviewed some applications of nanomaterials in medicine, the use of nanomaterials in the treatment of autoimmune diseases, the effect of nanomaterials on immune responses, the use of nanomaterials in vaccine design and the effects of nanomaterials on the body and the immune system.

The nanomaterials and their application in medicine

Despite the medical advances in recent years, some diseases such as AIDS [8], [9], cancer [10], [11], infectious diseases [12], diabetes [13], chronic pain [14], [15] and autoimmune diseases [16], [17], have not been treated. Since nanoparticles are the foundation of nanotechnology, their use in the medical branch has opened new perspectives in therapy [18]. Accordingly, the properties of nanoparticles should first be evaluated; and if approved, they will be then used for therapeutic purposes. Nanomedicine deals with the ever-increasing advances in theories, devices and nanoscale apparatuses as well as with nanostructures specific for the diagnosis, prevention, or treatment of diseases. The use of nanomaterials in medical interventions has led to direct contact of the nanomaterials with the human body [19]. The nanomedicine can be accomplished by detecting, restoring and regenerating damaged tissues at the molecular levels. Another research topic in the nanomedicine is the extensive design and the use of various research tools to produce drugs with a targeted release in the body. In this drug delivery method, the drug is directed to the target cells and delivered to the desired site [20].

Considering the antimicrobial properties of different types of nanoparticles, such as nanosilver, nano titanium and copper nanoparticles, one of their important applications is to control a variety of pathogens. Also, recent results have shown that gold nanoparticles and also magnetic nanomaterials due to their unique properties can be recruited in various areas of treatment and nanomedicine [21], [22], [23]. Researchers, through the exploitation of the outer surface of nanomaterials, have established nanoscale interactions between materials and biological systems to dramatically enhance their performance and create new structures [24]. The use of intelligent devices in medicine with the least damage to surrounding tissues is another application of the nanomaterials. Another application of nanomaterials in the medical field is the production of compatible components in sensor systems that can diagnose and prevent diseases. Environmental sensors are designed on a very fine chip to complete the experiments that communicate with the outside of the patient's body reveal the internal body conditions such as heart attack, tumour, or localised infections [25], [26]. Magnetic resonance imaging (MRI) is an advanced and non-invasive technique for the early diagnosis of many diseases, including cancer [27]. Several diseases can be currently diagnosed with a drop of blood-based on laser systems in the infrared, visible, and ultraviolet frequency ranges. New approaches for producing DNA-based nanoscale tools also show the advancement of nanotechnology in life sciences and medicine [28], [29]. The use of these new therapies makes many diseases detectable and treatable at the onset. However, despite all the advantages of nanoparticles (such as identifying the disease location and drug delivery), they should escape somehow from the immune system, which is recognised as an invader. The defence system able to destroy nanoparticles is a major barrier to using nanotechnology in medicine. The applied nanoparticles are systematically trapped within minutes and then removed from the body. Cell membrane-coated nanoparticles can stay intact for several hours without any damage in the body. Among these particles, protein nanoparticles are of interest because of numerous benefits such as easy access to their resources, renewable resources, reasonable cost, biocompatibility, biodegradability, the presence of multiple functional groups to carry high doses of the drug, and the ability to link simultaneously targeting groups to target nanoparticles to certain cells or tissues [30], [31], [32].

The nanomaterials and the treatment of autoimmune diseases

In the autoimmune diseases, the immune invasion to certain tissues endangers their structural

and functional compatibility [16], [17]. The nanomaterials have been engineered to modulate the antigen-presenting cells (APCs), as well as to downregulate innate immune signals that reinforce adaptive autoimmune responses [33]. In a study by Schweingruber et al., [34] on the pharmacological treatment of experimental autoimmune encephalomyelitis (EAE), glucocorticoid loaded liposomes were found effective at doses lower than conventional glucocorticoid therapy through affecting the macrophages. One of the main limitations of conventional specific antigen-based methods for the treatment of autoimmune diseases is the antigenic complexity of autoimmune diseases and the need to target the multiple characteristics of autoreactive T cells. The nanoparticles coated by peptide-loaded major histocompatibility complex (pMHC) increase CD4$^+$ regulatory T cells with lower acidity. These nanoparticles in the target tissue also inhibit polyclonal autoimmune responses through a targeted selection of autoantigen loaded APCs [35], [36], [37]. New compounds of nanoparticles, such as nanoparticles with multiple surfaces, will help to develop the future generation of nano-based drugs for the treatment of autoimmune diseases [38], [39].

The effect of nanomaterials on the immune responses

The innate immunity is, in fact, a non-specific, natural, non-clonal, germline-encoded and non-anticipatory system, while the adaptive immunity is a specific, clonal, somatic, and anticipatory system [40]. The nanoparticles properties such as size, hydrophobicity, surface charge and coating agents determine their level of interaction with the immune system [41]. Adsorption of molecules on the NPs in specific microenvironments makes them be recognised as foreign agents by the innate immune system, resulting in an inflammatory response. The NPs have no direct contact with innate immune cells, except with molecules ornamented on their surface. On the other hand, a large amount of NPs loaded in chemotherapies for antitumor therapy is taken by leukocytes. Therefore, there is a potential loss of innate immune response [42].

Delayed adaptive immunity occurs based on the type and extent of innate immune responses and can expand and enhance inflammatory responses. The adsorption of body molecules on the surface of NPs causes their deformation, folding and immunogenicity, resulting in the adaptive immune response. The induction of NPs interferes with the molecular mechanisms of dendritic cells (DCs), affects the peptides presented to T cells and thus modulates the adaptive immune responses [43], [44]. In a study by Gustafsson et al., [45] TiO$_2$ NPs injected intravenously to rats caused an early immune response in the lungs and resulted in a consequent increase in the IFN-γ, IL-4 and IL-10 levels after several days.

The application of nanomaterials in vaccine design

The success of human papillomavirus (HPV) and hepatitis B virus (HBV) based particles in humans have led to the development of various virus-like particles (VLPs) and virus-based nanoparticles VNPs vaccine. One of the concerns about the use of engineered nanoparticles is their potential toxicity in the human body. Some of the contributing factors to the toxic effects of some materials in the human body are the low rate of biodegradability, high surface area to volume ratio, the ability of biological membrane coatings, and high reactivity. Self-assembly ability of a large variety of viral capsid subunits in VLPs shows advances in the vaccine design. The VLPs have a regular and multifaceted structure that is not usually a component of the host proteins, so they form pathogen-associated molecular patterns (PAMPs), which create the mechanisms for assessing the innate immune [46], [47].

Also, most of the VLPs enclose nucleic acids during production, as they may stimulate specific Toll-like receptors (TLRs). The features of the VLPs can be used in the vaccine design because they facilitate their taking by the antigen presenting cells (APCs), producing long-term cytotoxic T lymphocyte (CTL) responses and antibody responses [48], [49]. The VLPs are better and safer than other subunit vaccines because of lacking any genetic material. Although the production of synthetic particles usually has undesirable immunogenicity and conditions for removing in the body, their production is easier and safer than the VLPs [50].

The biocompatible and biodegradable microparticles are used in oral immunisation to induce local and systemic immune responses. One of the biodegradable materials is poly (lactic-co-glycolide) (PLGA) copolymers that can be manipulated by altering the polymer composition and molecular weight. PLG microspheres are commonly used as carriers of bacterial vaccines, and few are studied for viral vaccines [51]. Liposomes are composed of two layers of phospholipids that are associated with cholesterol to stabilise the artificial membrane [52]. Also, the liposomes are mostly unable to provoke potent immune responses that require the use of adjuvants. Immune stimulating complexes (ISCOMs) are spherical micelles with a diameter of about 40 nm consisting of a mixture of Quil A saponins as strong adjuvants, cholesterol and phospholipids. The use of

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ISCOMS for rotavirus and herpes simplex virus type 2 (HSV-2) vaccines is allowed in horses. Despite the advances in ISCOMS, their use is limited due to problems similar to those of the liposomes. Also, nanoemulsions (NEs) based vaccines are noninflammatory mucosal adjuvants that can be an appropriate candidate for use in the vaccine platform. Although the process of developing new vaccines continues to be improving, formulations that work well in laboratory animals are usually expensive in human clinical trials, and there is little hope for their applications [53], [54]. In this regard, human experiments need to anticipate an outbreak of the disease so that to be able to protect against them. Since vaccines are of the most effective strategies to improve health worldwide, ongoing efforts are needed to improve vaccine immunity and efficacy.

Nanotoxicology

Nanoscale materials have found new properties and function over non-nano equivalent materials because of their small size and large surface area. Studies have shown that those properties of nanoparticles that lead to changes in their physicochemical properties [55], [56] can also cause potential toxicity. The nanotechnology is developing rapidly and has undoubtedly both beneficial and harmful effects on humans and the environment. Therefore, it is very necessary to apply different methods for evaluating the toxicity of nanomaterials, particularly the presence of nanoparticles in airborne workplace pollutants that could affect the health of workers. In cellular models, dendritic cells, epithelial cells and macrophages are commonly used to evaluate the toxicological and immunological effects of engineered nanomaterials (ENM). The standardisation of the ENM immunotoxicity test and the effect of the ENM on the body should be further investigated [57]. During usage or production of the ENM, the body is usually exposed through the lungs. It has been evidenced that the nanoparticles stimulate more strongly than particles with a larger size and can induce inflammatory and toxic responses in the lungs. Calu-3 and A549, which are human epithelial cell lines, are widely used to investigate the response of immune cells exposed to the ENM. The exposure of the respiratory tract to zinc oxide nanoparticles stimulates eosinophils and thus upregulates the serum IgE levels. Also, exposure to nanoparticles can cause the proliferation of respiratory epithelial cells, cell hyperplasia, and pulmonary fibrosis [58], [59]. Most toxicology studies have been carried out on nanomaterials such as metals, metal oxides, carbon nanotubes, fullerenes, polymer nanoparticles, and quantum dots. Wang et al., [60] showed that the distribution status of multiwalled carbon nanotubes (MWCNTs) also affects the profibrogenic cellular responses and pulmonary fibrosis in addition to inducing pulmonary toxicity.

Schinwald et al., [61] reported that graphene-based nanoplatelets through the pharyngeal aspiration and direct intrapleural installation could enter the lung and the pleural space and cause inflammation. Based on different results, researchers have concluded that nanoplatelets emphasise the complexity of nanoparticle toxicology and are likely to pose a nanohazard about the toxicity of the structure. Studying titanium dioxide nanoparticles indicated that the release of these nanoparticles from membrane-bound organelles could interact with cellular signalling to activate cell activation. Rossi et al., [62] exposed asthmatic rats to titanium dioxide particles and observed that ovalbumin (OVA) induced allergic pulmonary inflammation was significantly suppressed, indicating significantly decreased levels of cytokines, chemokines, leukocytes and antibodies in allergic asthma. Various studies have also shown that the changes caused by the nanoparticles, for example, and surface coating can lead to alterations in toxicological properties.

According to several studies, the skin is an important route for the penetration of nanoparticles in both occupational and consumer areas [63]. Although zinc oxide and titanium dioxide nanoparticles, the members of metal oxide nanoparticles, are commonly used in personal care formulations as protective agents against UV light, they are unable to penetrate the stratum corneum [64]. In contradiction to the previous report, Gulson et al., [65] exhibited that low amounts of zinc from zinc oxide nanoparticles used in sunscreens can pass through the protective layers of the skin and are found in the blood and urine. Several studies have shown that the safety and toxicity of nanoparticles in both in vitro and in vivo conditions are important for clinical applications.

Conclusion

The use of nanoparticles, according to their unique immunological characteristics, which are determined by size, shape, charge, porosity and hydrophobicity, enables researchers to change the immune responses arbitrarily using new and unexpected approaches. In the future, the application of nanotechnology in immunology may affect novel strategies for preventing or treating human diseases. In this context, nanotechnology will continue to introduce remarkable insights into the nature of immune responses and will create increasingly new materials and products based on nanoparticles. Moreover, nanoparticles because of their desirable surface area to volume ratio are highly reactive, which leads to their harmful interaction with biological systems and the environment, thereby creating

toxicity. Moreover, the small size of nanomaterials will allow them to penetrate into deeper areas of biological systems that are inaccessible to larger particles. Due to different properties of the nanoparticles, their application for therapeutic purposes, especially the effect on the immune system, requires further attention and research.

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