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Immune Response to Nanomaterials: Implications for Medicine and Literature Review

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Abstract Nanomaterials, substances below 100 nm, are increasingly used in medical diagnosis and treatment every day. The use of such materials has helped deliver drugs across the blood–brain barrier, alleviate allergy symptoms, specifically target cancer or HIV cells, and more. However, the tunable characteristics of such materials have not been perfected. The different materials, sizes, shapes, and structures have different responses on the body. This paper will investigate the successful treatments made with nanoparticles and some general health effects. A review of the literature revealed an inflammatory response and an increased production of reactive oxidative species (ROS) to be common immune responses to nanomaterial use. The mechanisms by which the inflammatory response and ROS production occur will also be discussed.

Keywords Nanomaterials · Reactive oxygen species · Nuclear factor-κB · NF-κB pathway · Advances · Allergy · Immunology · Immune response

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Introduction

Nanomaterials consist of small-scale substances, below the size of 100 nm [1], that are engineered to offer unique mechanical, optical, electrical, and magnetic properties [2]. Nanoparticles can be prepared from a variety of substances, ranging from metals to basic elements to polymeric compounds. These materials include diverse structures such as nanoparticles, nanotubes, and quantum dots [3] to various core elements such as gold, titanium, silver, silica and even organic-based materials [4]. Tunable characteristics, low dosages, and targeted sites have lead to the increasingly growing use of nanotechnology in medicine. Nanoparticles have been used in a variety of applications including drug delivery, magnetic resonance imaging (MRI), cancer treatment, gene therapy, biosensors, separation science, and various topics in allergy immunology [5].

The most exemplary example of nanomaterial use in therapy is in cancer treatment. Liposome-encapsulated magnetic nanoparticles were successfully demonstrated to carry cathepsin protease inhibitor to a mammary tumor in a mouse and reduce the tumor size, as well as simultaneously provide a strong contrasting agent for sensitive MRI images [6]. Magnetoferritin nanoparticles have been used, without the use of any targeting ligands or contrast agents, to target and visualize tumor cells that overexpress transferrin receptor 1 (TfR1) with a sensitivity of 98 % and specificity of 95 % [7•]. Nanoparticles, still in their early stages, have successfully delivered loads to targeted sites. Sol–gel nanoparticles were used to carry small inhibitory RNA (siRNA) in a study that targeted either Fidgetin-like 2 or Kif 19 as potential modulators of wound healing [8].

However, further research is needed to measure and record all side effects of biocompatibility, cellular penetration, and site-specific targeting. Studies have shown toxic effects from these carriers, as expected of any foreign particulate. Use of nanomaterials has shown chemical

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imbalance, cellular damage, changes in gene expression, immune response, metabolic changes, and apoptosis. Both chronic and acute toxicity can lead to extensive intracellular damage as well as other potential risks to human health, depending on the material and tissue. What is striking is that most of the studies presented reveal that most nanomaterials initiate some form of inflammation and/or ROS production. This review will further explore studies where inflammation directly resulted from testing different nanoparticles and the most likely mechanisms for this potentially lethal side effect.

Nanomedicine: Advances in Allergy & Immunology

Nanoparticles can serve as ideal carriers to detect allergies and alleviate some of their symptoms. Allergies are associated with an unbalanced Th1 and Th2 immune response, with increased levels of cytokines, IL-4, 5, and 13, and immunoglobulin E (IgE) [9]. The use of magnetic core-shell nanoparticles as a microchip for allergy diagnosis has increased capture kinetics by a 1,000-fold by quantifying IgE) [10•]. Particles can be used not only for detection but also treatment. Chitosan, a biodegradable material, has been reported to deliver Der f-CS intranasally to BALB/c mice, alleviating airway hyper-reactivity, lung inflammation, and lung mucus production. The nano-vaccine also decreased cytokine and IL-4 [11].

The efficiency of particles relies on the plethora of modification methods and functionalities. This allows particles to be novel materials in treating diseases and disorders that were and still are deemed incurable. For example, quantum rods (QRs) functionalized to incorporate siRNA, QR-si510 HIV-1 siRNA nanoplex, have been shown to suppress HIV-1 viral replication for an extended period of time [12]. HIV is especially hard to target in the central nervous system due to the blood–brain barrier [13]. However, modification of quantum rods to carry drugs, such as Saquinavir, has successfully resulted in a decrease in HIV-1 replication in infected peripheral blood mononuclear cells. This means that there was significant uptake of QR-Tf-Saquinavir by brain microvascular endothelial cells via receptor-mediated transport [14].

Characterization of Nanomaterials and Delivery Methods

The effects of nanomaterials on cells may vary with different conditions of the materials, depending on particle size, shape, charge, composition, structure, size distribution, aggregation rates, surface chemistry, and porosity [15]. The smaller the size of the nanoparticles, the larger the surface volume to mass ratio, and thus the more enhanced the surface properties [16]. Nanoparticles have different physical, chemical and biological properties from their molecular or bulk counterparts due to their increased surface area [17]. For example, bulk gold samples are practically inert; however, gold nanoparticles have been proven to be highly active for several reactions, including low-temperature oxidation of CO and partial oxidation of hydrocarbons [18]. A large surface area, a common characteristic of all nanomaterials, is what provides functionality and a site for surface coating with polymers or biorecognition molecules for increased compatibility [19]. However, this trait is a double-edged sword as nanoparticle toxicity is largely due to particle size and surface area [20]. The functionality will depend on the particle type and material as well as the interactions between the particles and the targeted cell type. Particles must overcome barriers such as enzymatic degradation, phagocytic cells, changes in blood and hydrostatic pressure, and ionic efflux pumps [21].

Nanomaterials can be administered via nasal, oral, intraocular, pulmonary, and other routes [22]. It is important to note the uptake mechanism through some of these major pathways that will be utilized for medical treatment and drug delivery, as well as the interactions of the particles with the particular cells. Oral and intravenous injections of particles are the most likely methods of drug administration. The gut is constantly exposed to macro-, micro-, and nanoparticles. Ferritin, a naturally occurring iron oxide-based 12-nm nanoparticle with a protein shell is ingested via meat- and plant-based foods [23]. It has been shown to be endocytosed by epithelial cells in the gut as a source of iron [24]. The most common uptake for micro- and nanoparticles in the gastrointestinal tract is via the M-cell-rich layer of Peyer's Patches [25]. M-cells are epithelial cells that favor transcytosis of macromolecules and particles and are important immune-inductive sites [26–28]. The surface charge of the particles seems crucial to bypass the adhesivity and viscoelasticity of gastrointestinal mucus. Jason et al. have shown that anionic polystyrene diffuse a magnitude of 20–30 times faster than cationic particles. Des Rieux et al. have also shown increased efficiency uptake of sub-micron-sized aminated particles over caboxylated particles in epithelial cells [25]. As expected, hydrophobic particles are more easily taken up than hydrophilic particles [29].

Once the nanoparticles enter the blood stream, their size is important in determining blood circulation time and destination. The particles pass through the barriers and filters of the body, just as does any other macromolecule, regardless of size, shape, dose, or material, and accumulate in certain organs. Balasubramaniana et al. found the number of 10-nm gold particles found in the liver after 24 h was the highest, followed by blood, spleen, kidney, lungs, brain, reproductive organs, thymus, and heart. Larger particles of 50, 100,

and 250 nm were solely distributed to liver, spleen, and blood. The same study found gold particles to upregulate and downregulate gene expression in the liver and spleen of rats. These genes were responsible for lipid metabolism, defense response, detoxification, cell cycle, and circadian rhythm, and more [30]. The same accumulation of particles in the liver and spleen has been seen with 10- to 20-nm carbon nanotubes [31], 11-nm iron oxide [32], and 13-nm quantum dots (CdSe/ZnS) [33]. This is explained by a phagocyte-rich reticuloenthothelial system (RES) where nanoparticles bind to antibodies [34].

It is difficult to appease all cellular properties and receptors without initiating some unintended effects. The specific properties of nanoparticles are the cause of the unintended side effects. For example, the cytotoxicity of positively charged Au nanoparticles on HeLa cells was shown to be dependent on hydrophobicity, with a direct relationship between hydrophobicity and ROS production [35]. The external environment is just as crucial to the function and behavior as is the intrinsic properties. The behavior of particles changes with slight adjustments in pH, viscosity, magnetization, etc. For example, physiological fluid can change iso-electric points of particles and result in altered agglomeration rates. Romoser et al. observed silver nanoparticles to settle quickly compared to titanium dioxide, quantum dots, and Fullerol, resulting in heightened NF-kB/ERK response when the particles were exposed to primary HDF cells [36].

Nanomaterials and Health Effects

Many studies have shown various toxicological effects, depending on the organ and the material of the particle. Some effects are common to all particles. Particles were earlier reported to detect and alleviate symptoms of allergies including inflammation by affecting cytokine and IgE levels. However, depending on the material, size, and ligands, particles themselves can induce the immune response or lead to other health effects. Here, we will divide the effects based on the particle material.

In vitro studies have shown silver nanoparticles (Ag NPs) to cause elevated ROS levels [37], lipid peroxidation [38], and a reduction in GSH [39]. A reduction in mitochondrial function of A549 cells exposed to Ag NPs for 24 h was observed in a dose-dependent manner [40].

Silica is a very common component of nanoparticles today because of industrial use in cosmetics, printer toners, drugs, and food [41••]. Chronic inhalation of crystalline silica can result in silicosis, a generally progressive fibrotic lung disease [42]. Acute exposure of particles has also been shown to have damaging effects. Acute oral exposure to polystyrene nanoparticles can disrupt iron transport and nutrient absorption [43]. Yamashita has shown that 70-nm silica particles and titanium oxide (TiO2) particles restricted the growth of fetuses in pregnant mice in high dosages [44].

Gold is a very common material in biomedical studies. As mentioned before, its inert properties are ideal as a transport mechanism. Most toxicity associated with gold particles is due to attached ligands and not the core material itself, whether in high doses or long periods of exposure [45]. If attached ligands are the source of the problem, then surface modification is a simple solution. Poly(ethylene glycol) (PEG) is a functional group that is known to reduce cytotoxicity [46]. PEG is characterized as amphiphilic [47] and non-immunogenic [48], and reduces opsonization by proteins [49] and improves overall biocompatibility [50]. The PEG layer on the surface of NP is critical to blood interactions and RES organ biodistribution. PEGylated gold NPs interact more with blood proteins and cells, resulting in longer blood circulation times [50] and a 10-fold increase in tumor uptake and accumulation [51]. PEGylated single-walled nanotubes have shown longer blood-circulation half-life and low hepatic uptake in vivo, which is vital for use in drug-delivery systems [52].

Carbon nanotubes (CNTs) can be visualized as sheets of graphene rolled into a cylinder. The long length and small diameter provide CNTs the characteristic of a large aspect ratio, high tensile strength, and high electron conductance, ideal for biosensing and drug delivery [53]. Single-walled carbon nanotubes administered intratracheally have been shown to deteriorate allergen-related airway inflammation with mucus hyperplasia in mice [54]. Allergic inflammation is very important in human asthma [55]. The inflammation is a result of increased proinflammatory cytokines such as IL-1β and IL-6 [56]. High levels of reactive oxygen species (ROS) and decreased metabolic activity were observed in A549 lung epithelial cells and Jurkat T lymphocytes after acute exposure to high doses of multi-walled carbon nanotubes (up to 30 μg/ml) [57]. Single- and multi-walled carbon nanotubes have increased allergic effects with egg albumin when administered intranasally in mice [58].

Although metals are more prolific in the field, a push has been made recently to produce equivalent natural polymers such as chitosan, alginate, polymethacrylic acid [59], polystyrene [60], and poly-glycidyl methacrylate [61]. Theoretically, these organic-based particles should have fewer effects at the cellular level than the metal counterparts, although this organic-based field is still developing. However, cytotoxicity and genotoxicity studies have revealed these particles to cause similar effects as their metal counterparts. Cationic polystyrene nanospheres were found capable of inducing cellular ROS production, GSH depletion, and oxidative stress [62]. Glycidyl methacrylate has also been shown to cause DNA damage in the human lymphocytes in concentrations of up to 5 mM [63].

It is known that in vitro conditions are not realistic and produce different results from in vivo results in other studies. This is also true for nanoparticles. Specific studies have found carbon nanotubes to be toxic in vitro [64], whereas other studies have found no significant toxicity in vivo [65]. Fullerenes show different toxicology results with in vivo versus in vitro experiments in rats [66].

ROS Production

The different types of particles mentioned either caused inflammation or increased ROS production or both. Reactive oxidative species are O_2-derived free radicals, including superoxide anion (O_2^-), hydroxyl (HO), peroxyl (RO_2), and alkoxyl (RO) radicals, as well as hydrogen peroxide (H_2O_2) [67]. Most of these species are produced via the electron transport chain in the mitochondria [68]. Superoxides are produced primarily by the reduction of oxygen at complex I, II, and III but also by the enzyme glycerol-3-phosphate dehydrogenase [69]. NADPH oxidases (NOXs), nitric oxide synthase and peroxisomal constituents generate ROS [70]. NOX2 generates superoxide radicals in phagocytic cells as a defense against ingested microorganisms [71]. ROS production is widely used in cell signaling and regulation. Other effects include enhanced stress resistance, cell adhesion, cytokine release, cell proliferation growth arrest, and apoptosis [72, 73]. It has been shown that nanomaterials of various materials and sizes destroy mitochondrial function. For example, ZnO particles taken up by cells released Zn2+ ions, disrupting mitochondrial function via charge balance and triggered ROS generation [74]. Another study by Song et al. also showed ROS production when 10 μg/mL of ZnO particles were introduced to Ana-1 cells [75]. Oxidative stress on dendritic cells has been reported to have a powerful effect on Th1/Th2 imbalance of the immune response. This expresses the importance of oxidative stress on asthma pathogenesis [55]. Fullerenes have potential benefits via Nrf2 pathway activation [76].

The size of nanoparticles greatly increases their ability to produce reactive oxygen species (ROS) [77]. Nanoparticles have been shown to generate free radicals that can disrupt the blood–brain barrier via oxidative stress [78]. Nano-sized copper particles have been shown to alter the levels of intracellular ROS as well as NO production in IP15 and HK-2 cells, resulting in oxidative stress and leading to cell membrane damage and unintentional modification of proteins. Oxidative and nitrosative stress altered the antioxidant defense and resulted in kidney toxicity and cell death via a cascade effect [79]. Other experiments have shown that size-dependence is not statistically significant but chemical composition is. TiO2, Al2O3 nanoparticles, and carbon nanotubes were shown to generate oxidative stress in NRK-52E kidney cells and A549 lung cells after accumulating in the cytoplasm [80].

Treatment of the particles with an antioxidant could potentially reduce the toxic amount of ROS produced. Foldbjerg et al. also witnessed induced significant ROS after a 24-h exposure of A549 human lung carcinoma epithelial-like cell to Ag NP concentrations ranging from 2.5 to 15 μg/ml. However, when cells were pre-treated with 10 mM*N*-acetyl-L-cysteine (NAC) for 1 h, the ROS levels were significantly reduced, especially the high concentrations of Ag NP [40]. This reduction would potentially also reduce DNA damage.

NF-kB Pathway for Inflammation

Besides ROS production, another major toxicological effect of nanoparticles is inflammation of cells. Inflammation is a potentially serious side effect of nanomedicine. Many recent studies have elucidated that differing nanoparticles work to cause inflammation by activating the NF-κB pathway [5, 81, 82, 83••, 84–88].

Nuclear factor of κB (NF-κB) is a transcription factor that plays a variety of different roles; these roles include cell survival, differentiation, and proliferation. NF-κB is crucial to the growth and development of the immune system and problems with it can lead to severe consequences [88]. Alongside this, NF-κB is heavily involved in the innate immune response and is a crucial regulator of inflammation [89]. The NF-κB proteins which are present inside most cells are p50 NFκB1, p65/REL A, c-Rel, NFκB2/p52, and Rel B [90–93].

NF-κB is regulated by two main pathways: the canonical and noncanonical pathways [89]. The canonical pathway works by recognizing a ligand which leads to the activation of signaling cascades which lead to activation of Ικκβ, which is complexed together with Ικκα and Ικκγ (also known as NEMO). NF-κB exists in its resting state bound by IκB proteins which inactivate the NF-κB subunits [5, 81, 93, 94]. The activation of Ικκβ leads to the phosphorylation of IκB proteins which free up NF-κB to translocate to the nucleus, where it leads to upregulated translocation of many target genes [5, 81, 91–94].

The noncanonical pathway is controlled by particular members of the tumor necrosis factor (TNF) cytokine family; these members include BAFF, Lymphotoxin-β, and CD40 ligand. The defining aspect of the noncanonical pathway is that it is reliant on Ικκα and independent of Ικκγ (NEMO); activation of Ικκα by the TNF cytokine family leads to the generation of p52/RelB complexes as a result of the phosphorylation of p100. From here, transcription is regulated as in the classical pathway [5, 81, 94]. In general, cationic particles are more likely to induce inflammatory reactions than anionic and neutral species [95]. Anionic

generation-4.5 polyamidoamine (PAMAM) dendrimers did not cause human leukocytes to secrete cytokines53, but cationic liposomes induced secretion of cytokines such as TNF, IL-12, and IFNγ [96].

NF-κB has a direct role with many different diseases such as sepsis, HIV [97, 98], hypogammaglobulinemia [99], rhinosinusitis [100], rheumatoid arthritis, chronic lung disease [81, 82], systemic lupus erythematosis [101], and lupus nephritis [102••]. Toll-like receptors (TLRs) can activate immune-mediated glomerulonephritis and VEGF levels in human kidneys from lupus nephritis patients [102••]. BTK-dependent activation in hypogammaglobulinemia is related to NF-κB, essential for reprogramming the expression of genes that control B cell survival and proliferation [99]. Pteronyssinusi-induced apoptosis-related rhinosinusitis can occur [100]. The cytosolic domains of TLRs recruit adaptor proteins and initiate signaling pathways in response to ligand binding and the myeloid differentiation factor 88 (MyD88)-dependent pathway can lead to activation of the NF-κB [101].

Poly(acrylic acid)-coated gold nanoparticles (PAA-GNP) bind to different human plasma proteins including fibrinogen. Binding of PAA-GNP to fibrinogen leads to a conformational change which leads to fibrinogen binding to Mac-1 receptors on THP-1 cells, activating them. The activated MAC-1 receptors lead to degredation of IκB and allows for translocation of NF-κB to the nucleus, thereby activating it. The activated NF-κB leads to the up-regulation of pro-inflammatory genes and production of cytokines which leads to greater inflammation. The downstream results of binding of the MAC-1 receptor included increased production of IL-8 and TNF-α of which the latter is directly implicated in increasing NF-κB activity. Thus, PAA-GNP nanoparticles serve to increase inflammation by prompting activation of NF-κB through a conformational change in fibrinogen which leads to binding with the MAC-1 receptor [84–87].

Many nanoparticles lead to inflammation through activation of TNF-α including PAA-GNP, Zn, Au, Al, Ag, carbon-coated silver (CAg), and carbon black (CB). Nanoparticles such as ZnO lead to increased TNF-α which in turn activates NF-κB. ZnO works by activating the inflammatory pathways and increasing secretion of IL-6 and TNF-α, leading to the further stimulation of NF-κB [81]. Other nanoparticles, such as silver, carbon black, aluminum, and carbon-coated silver, all lead to increased levels of IL-6, TNF-α, and nuclear translocation of NF-κB. These different nanoparticles stimulate inflammation through NF-κB regulation and lead to the release of pro-inflammatory cytokines [103].

Conclusions

Nanoparticles present a novel approach towards future therapeutic options in a variety of different diseases. While their use is not yet prevalent, nanoparticle therapy has the potential to become a mainstream method of treatment. For that to occur, however, there are many issues that need to be resolved. Nanoparticles have been linked with inflammation and have been shown to be toxic in some cases [104]. The immune response generated by invasive particulates is a barrier that must be overcome by functionalizing the particles. Excessive ROS production initiated by nanoparticles uptake can have harmful, even lethal, effects. Understanding the pathways in which nanoparticles lead to inflammation can lead to new, safer methods for nanoparticle use. One current method by which they lead to inflammation is the NF-κB pathway, a key transcription factor in immune system responses. Further research can elucidate more detailed methods of NF-κB activation due to nanoparticle sensitivity. The field of nanotechnology is the future of biomedical studies and drug delivery mechanisms. Understanding the properties and interactions will cells will lead to ideal vaccination and treatment mechanisms and target specific degenerative diseases that are incurable today.

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- • Of importance
- •• Of major importance

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