Positively charged particles are more efficiently internalized into cells than neutral- or negatively charged nanoparticles because they bind more effectively to negatively charged groups on the cell surface. Jiang et al. examined the cellular internalization of plain polystyrene nanoparticles and amino-functionalized polystyrene nanoparticles in mesenchymal stem cells and found that amino-functionalized polystyrene was internalized more rapidly than pristine polystyrene [10]. In addition, they found that amino-functionalized polystyrene was internalized via clathrin-mediated endocytosis, whereas plain polystyrene was internalized mainly via a clathrin-independent endocytotic pathway. Therefore, the surface coating or surface charge of nanoparticles influences not only the degree of internalization but also the mechanism through which the nanoparticles are internalized.

Li et al. compared the inflammatory and fibrogenic effects of MW-CNTs functionalized to create different surface charges [11]. Whereas the pulmonary fibrogenic potential of anionic-functionalized MW-CNTs was lower than that of pristine MW-CNTs, strong cationic-functionalized MW-CNTs induced greater pulmonary fibrosis than that of pristine MW-CNTs via activation of the NLRP3 inflammasome. Furthermore, Qiu et al. compared the cytotoxicity of three gold nanoparticles each coated with a different polymer (i.e., cetyltrimethylammonium bromide, polystyrene sulfonate, or poly(diallyldimethylammonium chloride) [3]. Poly(diallyldimethylammonium chloride)-coated gold nanoparticles exhibited a much greater degree of cellular internalization but were not cytotoxic.

Together, these results show that surface charge and functional groups play an important role in the toxicity of nanoparticles. Since a wide variety of nanoparticles with different functional groups have now been developed, we will be able to further investigate the effects of size and surface charge on the systemic biological effects of nanoparticles.

3 Shape

Although the influences of particle size, surface charge, and material composition on the biological effects and cellular uptake of nanoparticles have been extensively studied, the effects of particle geometry are much less understood. Chan's group have shown that fewer rod-shaped gold nanoparticles enter cells compared with spherical gold nanoparticles because of the longer membrane wrapping time required for the rod-shaped nanoparticles [12, 13]. Agarwal et al. have shown that large or intermediate-sized nanodisks are internalized more efficiently compared with nanorods or small nanodisks and also that the mechanisms of uptake were shape and cell type specific [14]. These results suggest that cells

can trigger unique uptake pathways in response to nanoscale geometry (both shape and size) and, therefore, that cells have different shape-dependent internalization efficiencies.

The results presented here and in the previous section show that synergism between size, surface chemistry, and shape must be taken into consideration when developing nanoparticles for biomedical applications.

4 Regulation of the Surface Properties of Nanoparticles for the Development of Nanomedicines

Foreign particles are removed from the body by phagocytes such as macrophages. For the medical application of nanoparticles, especially as part of passive targeted drug delivery systems, it will be important to improve the retention of nanoparticles in the blood. That is, systemically administered nanoparticles should not be cleared rapidly from the body and should instead remain in the circulation to allow the drug sufficient time to accumulate at the target site at a sufficiently high concentration. One way to prevent the clearance of nanoparticles from the circulation is to conjugate them with polyethylene glycol (PEG) or another water-soluble polymeric modifier. Covalent conjugation of PEG to the nanoparticle surface (through a process called pegylation) results in a longer plasma half-life and alters the tissue distribution of the conjugates compared with the native form because they avoid uptake by macrophages and renal clearance [15–18]. Furthermore, the prolonged circulation lifetime of the conjugates induces the enhanced permeability and retention effect, which results in increased delivery of conjugates to tumor tissue.

However, since the pegylation of nanoparticles may also prevent the delivery of drugs to targeted cells or the uptake of the nanoparticle into targeted cells, Rodriquez et al. have suggested an alternative approach to prolong the circulation lifetime of nanoparticles that uses CD47, which is a membrane protein and marker of self that is expressed on all cell membranes and prevents macrophage phagocytosis. Rodriquez et al. reported that nanoparticles conjugated to peptides designed from CD47 are not cleared by macrophages and are therefore retained longer in the circulation, resulting in enhanced dye and drug delivery to tumors [19]. In the future, other such homeostatic self-factors might similarly be used to prevent the clearance of nanoparticles by phagocytes, improve the targeting of specific tissues, or enhance the delivery of therapeutics and imaging agents.

Many groups have examined the use of carbon nanoparticle-based active targeted drug delivery systems for the treatment of cancer. Antibody-, folate-, arginine–glycine–aspartic acid peptide-, or epidermal growth factor-modified SW-CNTs have all been

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successfully used to actively target cancer cells [20–22]. The challenge in this approach is the identification of cancer cell-specific targets because conventional protein targets are often expressed by both normal and cancer cells. Therefore, the use of an integrated "omics" approach that utilizes proteomics, genomics, and metabolomics will be necessary to further identify potential cancer cell-specific targets.

5 Protein Corona

The adsorption of proteins on the surface of nanoparticles is an important factor that influences the biological effects of nanoparticles. When nanoparticles enter a biological fluid such as blood, they are rapidly coated with proteins and other biomolecules. For example, when nanoparticles are mixed with plasma, a protein corona is formed within 30 s [23]. The overall protein composition of the corona does not markedly change over time, although the concentration of a specific protein in the corona may change [23]. Which proteins bind to which nanoparticles depends on the physical properties of the nanoparticle; therefore, the size and surface properties of nanoparticles are important factors in determining the composition of the protein corona [24].

The binding of proteins to the surface of a nanoparticle changes the surface charge and alters the biological effects and rate of cellular uptake of the nanoparticle. Lesniak et al. showed that silica nanoparticles are more efficiently internalized into cells via a stronger adhesion to the cell membrane in the absence of serum compared with in the presence of serum when a protein corona is present on the nanoparticle surface [25]. Furthermore, Ge et al. have suggested that the binding of blood proteins to CNTs reduces CNT cytotoxicity [26].

The protein corona is also a major step in facilitating the phagocytosis of nanoparticles by macrophages. Deng et al. showed that negatively charged gold nanoparticles bind to fibrinogen causing it to unfold, which promotes the interaction of fibrinogen with Mac-1, an integrin receptor that is expressed on macrophages, in vitro [27]. The binding and activation of Mac-1 then induce the macrophage inflammatory response. In addition to proteins, nanoparticles can also be coated with lipids. The binding of lipids to MW-CNTs has been shown to influence the cellular uptake and toxicity of MW-CNTs [28–31].

Peng et al. have reported the successful use of the protein corona to regulate the biodistribution of nanoparticles [32]. By preforming a stable albumin corona around nanoparticles, they were able to inhibit plasma protein adsorption, prolong circulation lifetime, and reduce toxicity. This method is a simple yet potentially useful approach for optimizing nanoparticle drug delivery.

Many reports have described interactions between nanoparticles and extracellular proteins; however, nanoparticles also bind to intracellular proteins after being internalized into cells. Wang et al. showed that gold nanoparticles directly bind RNA polymerase, thereby suppressing RNA transcription in erythroid cells [33]. Furthermore, Falaschetti et al. have shown that several types of metal oxide nanoparticles bind to 20S proteasome subunits and increase 20S proteasome activity [34]. Proteasomes regulate intracellular protein degradation, and dysregulation of proteasome activity induces disorders such as cancer and neurodegenerative disease, suggesting that nanoparticles may provide a novel nanomedicine strategy against cancer and neurodegenerative disease. It will therefore be necessary to examine in more detail the effects of the nanoparticle protein corona on the cytosol.

6 Activation of Complement

It has been reported that the nanoparticle protein corona induces undesirable effects in vivo such as complement activation and blood clotting. Complement binds to foreign substances such as microbes and artificial materials that have entered the body to facilitate their clearance by macrophages. However, after engulfment, the nanoparticle protein corona may trigger unwanted inflammatory responses. Therefore, complement activation must be avoided to minimize the clearance of nanoparticles and induction of inflammatory responses.

Many studies have examined the relationship between nanoparticle size and degree of complement activation. For example, pegylated lipid nanocapsules with a diameter of 20, 50, or 100 nm have been shown to activate complement in a size-dependent manner [35, 36].

In contrast, some groups have also examined strategies to utilize the activation of complement by nanoparticles as a potential target for immunotherapeutics [37, 38]. Since the complement system plays an essential role in both adaptive and innate immunity, Reddy et al. designed a nanoparticle that strongly activates complement and successfully produces humoral and cellular immunity in mice [37]. Pluronic-stabilized polypropylene sulfide nanoparticles with a diameter of 25 nm were more efficiently translocated to lymphatic capillaries and their draining lymph nodes and accumulated in lymph node-residing dendritic cells than were larger particles (100 nm). Furthermore, the nanoparticles activated the complement cascade, which generated a danger signal in situ and possibly activated dendritic cells, and induced antigen-specific antibody responses and cellular immunity. In the future, it may be possible to harness these effects to produce novel vaccines for infectious diseases or cancer.

7 Activation of Coagulation

Some reports have suggested that nanoparticles activate the coagulant cascade. The blood coagulation system can be initiated via two pathways: the extrinsic cascade pathway, which is triggered by the release of tissue factor from a site of injury, or the intrinsic cascade pathway, which is triggered either by the activation of coagulation factors that have been brought into contact with a negatively charged substance or by the accumulation of activated platelets in the collagen layer under the vascular endothelium. Generally, the activation of platelets is associated with clot formation. The results of in vitro testing suggest that SW-CNTs and rutile titanium dioxide nanorods activate platelets and accelerate thrombus formation [39–41]. Burke et al. have also reported that some MW-CNTs directly activate platelets in vitro and that intravenous injection of some MW-CNTs reduces platelet count [42].

Our previous study showed that an excessive concentration of silica nanoparticles induced severe hepatotoxicity, lethal toxicity, and abnormal activation of the coagulation system in mice [43]. In addition, pretreatment with the anticoagulant heparin prior to the administration of silica nanoparticles reduced the induction of lethal toxicity and hepatotoxicity, suggesting that silica nanoparticle-mediated abnormal activation of the coagulant system was the main contributing factor to the lethal toxicity of silica nanoparticles.

We also examined the effects of silica nanoparticles on the coagulation system after intranasal exposure [44]. Hematological examination and coagulation tests showed that platelet count was decreased and activated partial thromboplastin time was prolonged in mice treated with silica nanoparticles, indicating that silica nanoparticles activate the coagulation cascade after intranasal exposure. In addition, in vitro activation tests showed that silica nanoparticles activate coagulation factor XII in a size-dependent manner, unlike micro-sized silica particles, suggesting that silica nanoparticles induce abnormal activation of the intrinsic cascade via activation of factor XII or platelets in the blood. Since a major factor in blood coagulation is the activation of coagulation factor XII via contact with hydrophilic activating particles, the abnormal activation of the coagulation system may be prevented by modifying the surface of silica nanoparticles to alter how they interact with coagulation factor XII.

8 Activation of Immune Responses

When foreign substances enter the body, the immune system recognizes them as foreign and initiates immune responses. In particular, macrophages, which are professional phagocytic cells,

recognize and engulf nanoparticles as part of the body's defense mechanism. There are many reports showing the inflammatory effects of nanoparticles. It is known that nanoparticles are mainly recognized and phagocytosed by macrophages once they enter the bloodstream. We previously demonstrated that silica nanoparticles induce a strong inflammatory effect compared with micro-sized silica particles [45]. We compared the inflammatory effects of silica particles of various diameters (30–1000 nm) both in vitro and in vivo. Silica nanoparticles with a diameter of 30–70 nm induced greater cytokine production in macrophages than did larger silica nanoparticles in vitro. Furthermore, intraperitoneal injection of smaller silica nanoparticles induced stronger inflammatory responses as well as greater cytokine production than did larger silica nanoparticles. We also found that nSP70-mediated tumor necrosis factor alpha production was dependent on reactive oxygen species production and the activation of mitogen-activated protein kinases and that addition of a functional -COOH group to the surface of the silica nanoparticles suppressed silica nanoparticle-induced inflammatory responses.

9 Nanoparticle-Induced Immunosuppression

Urban air pollution is a major environmental problem in industrialized and developing countries. Indeed, increased levels of air pollution are associated with a wide range of health effects such as altered inflammatory responses in the respiratory system and cardiopulmonary disease [46, 47]. Urban air pollution is also associated with increased susceptibility to lung infection [48]. Similarly, exposure to nanoparticles has been shown to impair bacterial clearance from the lungs in mice. Shvedova et al. have shown that pharyngeal aspiration of SW-CNTs leads to increased susceptibility to infection by *Listeria monocytogenes* in mice due to decreased alveolar macrophage phagocytosis of bacteria and decreased phagocyte nitric oxide production [49]. Furthermore, Kim et al. have shown that inhalation or instillation of copper nanoparticles leads to increased susceptibility to infection by *Klebsiella pneumoniae* [50].

Although the precise mechanism of the increase in the risk of pulmonary infection has not yet been clarified, Kodali et al. have suggested a "ligand hijacking" theory [51]. Certain nanoparticles are known to bind to class A macrophage scavenger receptor (SR-A), a transmembrane glycoprotein whose natural ligands include bacterial cell wall components [52]. Kodali et al. have suggested that the endocytic internalization of SR-A following nanoparticle binding reduces the amount of cell surface SR-A available to interact with bacterial cell wall components, leaving macrophages unable to engulf bacteria. More studies are needed to clarify the mechanisms of this phenomenon.

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Tsai et al. have shown that gold nanoparticles inhibit the Toll-like receptor (TLR)-mediated innate immune function activated by macrophages [53]. They have shown that gold nanoparticles accumulate in lysosomes after engulfment by macrophages and that they bind to high-mobility group box-1 in the lysosomal compartment, which is the general DNA sensor involved in the regulation of TLR9 signaling. This binding then leads to attenuation of TLR9 function. In addition, Sumbayev et al. have shown that gold nanoparticles neutralize extracellular interleukin (IL)-1β, leading to suppression of IL-1β-meditated inflammation [54].

The immunosuppressive effects of nanoparticles on dendritic cells (DCs) have also been shown. Tkach et al. have demonstrated that DC functions are modulated by SW-CNTs after pulmonary exposure [55], although the precise mechanism of this modulation remains unclear. They also showed that negatively charged graphene oxide suppresses the capacity of DCs to present antigens to T cells by decreasing the intracellular levels of immunoproteasome subunit LMP7, which is required for antigen processing, although non-charged "spherical" C_{60} fullerenes and negatively charged "spherical" C_{60}-TRIS fullerenes do not have this effect [56].

Together, these results suggest that the safety of nanoparticles is related not only to the inflammatory and immune system-activating effects of the nanoparticles but also their immunosuppressive effects. These data indicate potential opportunities for the utilization of nanoparticles as immunosuppressive therapeutics for the treatment of autoimmune disorders where it is desirable to inhibit antigen-specific immune responses.

10 Biodegradation of Nanoparticles

To understand the toxicity of nanoparticles, we must first fully understand how nanoparticles are metabolized, biodegraded, and excluded after being internalized into cells. There are many reports regarding the exclusion of nanoparticles from cells, although the precise mechanisms remain unclear. For example, Yanes et al. have shown that mesoporous silica nanoparticles are excluded from cells mainly via lysosomal exocytosis and that the cell-killing effect of anti-cancer-drug-loaded silica nanoparticles is enhanced by decreasing the rate of exocytosis [57]. These results suggest that it is necessary to consider the rate of exclusion of nanoparticles from cells when designing a nanomedicine.

Until recently, nanoparticles were thought to undergo little decomposition in vivo. However, recent studies have shown that CNTs are decomposed by natural enzymatic catalysis. Kagan et al. have shown that myeloperoxidase (MPO), an enzyme abundant in neutrophils, plays an important role in the oxidative biodegradation of SW-CNTs and that SW-CNTs degraded by MPO in vitro

do not induce inflammatory and oxidative stress responses after pharyngeal aspiration in mice [58]. Consistent with these results, clearance of SW-CNTs from the lungs is decreased in MPO-deficient mice after pharyngeal aspiration, and the inflammatory responses in MPO-deficient mice are much more robust compared with those in wild-type mice [59].

An alternative mechanism for the degradation of CNTs in vivo has been suggested because neutrophils live for only a short time in the body. Kagan et al. have shown that superoxide/nitric oxide → peroxynitrite-driven oxidative pathways of activated macrophages are involved in the "digestion" of SW-CNTs and clearance of nanoparticles from the lungs [60].

Collectively, these studies suggest new ways to control the biopersistence of CNTs through genetic or pharmacological manipulations.

11 Conclusion

A range of toxicological studies have been conducted using various functionalized nanoparticles, cell lines, incubation conditions, agglomerations and aggregations, doses, and observation endpoints. It is therefore difficult to obtain systematic information about the interrelationships among the physicochemical properties and biological effects of nanoparticles. More rational methodologies must be developed to allow interpretation of the overarching information contained in the experimental data. Furthermore, since there is usually a difference between in vitro and in vivo results, an in vitro experimental system that mimics conditions in vivo is needed. Information collected by using this system would be useful for gaining a better understanding of the potential health risks of nanoparticles to humans. A detailed understanding of the toxicological properties of nanoparticles and balanced evaluations of risk–benefit ratios will be required before we can begin to develop safe and efficacious nanomedicines for routine clinical use.

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