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Chapter 9

Biocompatibility of Nanomaterials

Yasuo Yoshioka, Kazuma Higashisaka, and Yasuo Tsutsumi

Abstract

Remarkable progress has been made in the field of nanotechnology in the past decade. Many new nanoparticles, which are defined as particles with at least one dimension between 1 and 100 nm, have been created, and new medical applications for these nanoparticles are now expected. To be able to create effective and safe nanomedicines, more information is needed about the effects and safety of nanoparticles in vivo because physical properties such as material composition, particle size, surface area, surface chemistry, surface charge, and agglomeration state all influence nanoparticle biocompatibility, particularly with regard to activation of the complement, coagulation, and immune systems. In this chapter, we introduce the most recent developments in our understanding of the biocompatibility of nanoparticles and discuss how our current understanding translates to the field of nanomedicine.

Key words Coagulation, Complement, Immune response, Nanomedicine, Protein corona, Safety, Surface property, Toxicity

1 Introduction

Recent progress in the field of nanotechnology means that it is now possible to produce a wide variety of nanoparticles, which are particles that have at least one dimension between 1 and 100 nm. Compared with larger particles of the same material, nanoparticles have a larger surface area per unit weight, which produces desirable properties such as enhanced electrical conductivity, tensile strength, and chemical reactivity. Nanoparticles are already being used in the electronics, food, cosmetics, and medical industries. In the medical industry, the application of nanotechnology (nanomedicine) is expected to provide novel diagnostic and imaging technologies, photothermal therapies, and vaccine and drug delivery systems for poorly soluble or unstable drugs. Unlike larger, micrometer-sized particles, nanoparticles are small enough to be absorbed through biological barriers and therefore can enter almost all of the body's compartments, including cells and intracellular organelles. Furthermore, the targeting of nanoparticles to specific pathological sites may reduce the incidence of side effects by increasing drug

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exposure at target sites while decreasing systemic exposure. Biodegradable lipid nanoparticles and biopolymer-based nanoparticles are already being used as drug delivery systems; however, applications using non-biodegradable nanoparticles are still in development and are yet to be authorized for the use in humans.

Our current knowledge of the factors that affect the safety of nanoparticles is insufficient for the development of safe and efficacious nanomedicines. Since nanoparticles can penetrate cells and tissues that are remote from the portal of entry to the body, we must further examine the potential risks to human health posed by nanoparticles. If nanoparticles are to be used successfully as next-generation medicines, it will also be essential to address the concerns expressed in the literature regarding nanoparticle toxicity by collecting as much information as possible on the pharmacological and toxicological profiles of nanoparticles. The toxicity of nanoparticles is related not only to the effects of the nanomaterial itself but also to the concentration and length of time the nanoparticle spends in the body's tissues. Therefore, in addition to analyses of toxicity, systematic and thorough analyses of the absorption, distribution, metabolism, and excretion profiles of nanoparticles are needed to determine which nanoparticles pose a risk to human health.

Biocompatibility is the ability of a material to produce an appropriate host response in a specific situation. The body responds to nanoparticles, as it does to any foreign substance that enters it, by initiating biological responses that result in clearance of the nanoparticles. If these biological responses are unwanted, they can result in toxicity and bio-incompatibility. A high degree of biocompatibility is achieved when a material interacts with the body without inducing unacceptable toxic, immunogenic, thrombogenic, or carcinogenic responses. The levels of these responses are determined in part by how the nanoparticle interacts with various biological substances such as immune cells, proteins, and lipids (Fig. 1). Parameters such as structure, size distribution, surface area, surface chemistry, surface charge, and agglomeration state, as well as sample purity, also contribute to the biocompatibility of

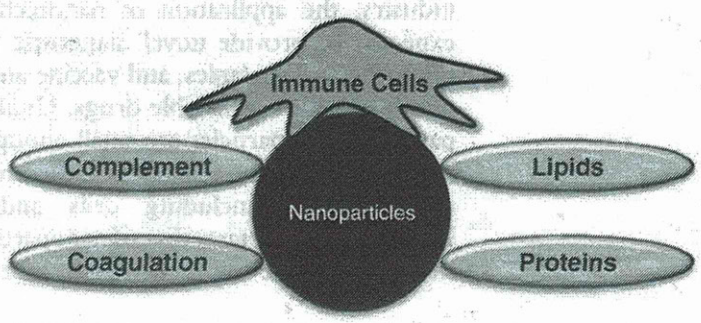

Fig. 1 Nanoparticles interact with various biological substances

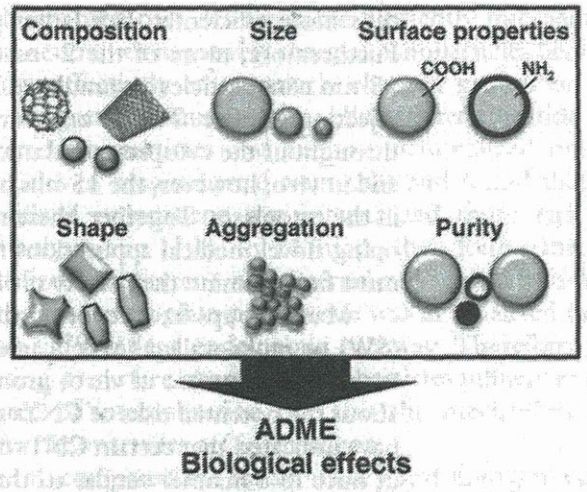

Fig. 2 Several parameters contribute to the biocompatibility of nanoparticles

nanoparticles (Fig. 2). Therefore, to understand the biocompatibility of a particular nanoparticle, we must first comprehensively understand the interrelationships among the physical properties of the nanoparticle and its interactions with biological substances.

2 Particle Size and Surface Charge

The biocompatibility of a nanoparticle is greatly influenced by its physicochemical properties [1, 2]. Therefore, to better understand the effects of nanoparticles in vivo, each type of nanoparticle must be evaluated individually. Particle size and surface charge are key parameters that affect the cellular uptake and biological interactions of nanoparticles. For example, Qiu et al. have shown that among gold nanorods with similar surface charges, shorter nanorods are internalized to a greater degree than longer nanorods, suggesting that the length of gold nanorods influences their cellular uptake [3]. In addition, we detected 70-nm silica nanoparticles (nSP70) in the maternal liver, placenta, and brain of pregnant mice and in the fetal liver, after intravenous injection, whereas we did not detect larger, micro-sized silica particles [2]. Furthermore, nSP70 induced miscarriage and fetal growth restriction in pregnant mice, whereas micro-sized silica particles did not. These results demonstrate the importance of evaluating the relationship between a nanoparticle's size and its reproductive toxicity.

Recently, ultra-small nanoparticles (diameter, <10 nm) have been investigated for their potential use as nanomedicines. Huang et al. compared the localization and penetration of gold nanoparticles (diameter, 2, 6, or 15 nm) in vitro and in vivo and showed that smaller gold nanoparticles internalized into cancer

cells more efficiently than larger gold nanoparticles in vitro [4]. Furthermore, more of the 2- or 6-nm nanoparticles than of the 15-nm nanoparticles accumulated in tumor tissue after intravenous injection in mice. The 2- or 6-nm nanoparticles were distributed throughout the cytoplasm and nucleus of cancer cells both in vitro and in vivo; however, the 15-nm nanoparticles were observed only in the cytoplasm. Together, these results suggest that before developing novel medical applications for ultra-small nanoparticles, we must first examine their safety profiles in vitro and in vivo.

Many groups have reported that certain types of single-walled (SW) or multi-walled (MW) carbon nanotubes (CNTs) are cytotoxic and genotoxic in vitro, prompting concern in the literature about the potential risks of CNTs to human health. Recent reports have indicated that certain CNTs induce mesothelioma-like lesions in mice in a manner similar to that observed in asbestos-induced mesothelioma. For example, Takagi et al. showed that intraperitoneally administered pristine MW-CNTs induced mesothelioma in a p53 (+/−) mouse carcinogenesis model, which was attributed to both biopersistence and geometric resemblance to asbestos of the MW-CNTs [5]. Poland et al. have also reported the asbestos-like pathogenic behavior of long, pristine MW-CNTs, which was associated with the needlelike fiber shape of the MW-CNTs, and established a structure–activity relationship based on the length of the MW-CNTs [6]. Furthermore, long, fibrous MW-CNTs were shown to produce inflammation and fibrosis in the peritoneal cavity at a level that is similar to, or greater than, that produced by long asbestos fibers; however, neither short asbestos fibers nor short, tangled MW-CNTs caused any significant inflammation [7], suggesting that length, diameter, and physicochemical properties are related only to the safety profile of pristine MW-CNTs.

Size-independent effects of nanoparticles have also been reported. Jiang et al. examined the effects of gold and silver nanoparticles coated with antibodies that bind to the ErbB family of protein kinases during signaling processes such as cell death [8]. Nanoparticles with diameters in the 2- to 100-nm range were all shown to affect basic cellular signaling processes, with those with diameters of 40 or 50 nm having the greatest effect, suggesting that when designing nanomedicines we must optimize the particle size depending on how the nanomedicine will be used.

Aggregation is a phenomenon associated with most nanoparticles; however, few studies have examined the influence of aggregation on cellular uptake and toxicity. One study by Albanese et al. has shown that aggregation influences the uptake patterns of different gold nanoparticles [9].

Being able to manipulate the surface chemistry of nanoparticles, such as by adding functional groups to reduce surface reactivity or enhance stability, will be indispensable in the future for the development of nanoparticles for the use as nanomedicines.