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Review Article

The Impact of Nanoparticles on the Immune System: Application of Nanoparticles

Duarte Jonatas*

Department of Materials Science & Engineering, University of Washington, Seattle, USA

ABSTRACT

Since the early days marking the first use of nanomedicine in the early 80s, there has been a meaningful change in the scientific field involving the Fabrication, characterization, and application of nanomaterials to treat many diseases, including cancers and genetic disorders. As unique and attractive properties of this novel class of materials unraveled, significant advances and discoveries were made over time. Addressing several challenges posed by conventional therapy, which were the only available treatment option for ailing patients, nanomedicine provided enhanced benefits, including reduced dosing, improved pharmacokinetics, and superior targeting efficiency. Several such formulations have successfully made their way to clinics and have shown promise in prolonging terminally ill patient populations' survival rates. However, the complex immune system and its various components, including various proteins and surface receptors, have made nanomaterials' journey from bench top to the bedside a treacherous one. The innate and adaptive immune system interactions with nanomaterials are still under investigation and full of mysteries. This review highlights the various aspects of therapeutic nanocarriers and their current understanding of their immune systems' interactions.

INTRODUCTION

Large surface area, high aspect ratio, small size, and unique physical and chemical properties in NPs enable their potential applications in many biomedicine fields, such as drug and gene delivery, imaging, photodynamic therapy, and tissue engineering. The small size of nanoparticles offers them the ability to overcome various biological barriers to transport and deliver therapeutic agents to the target tissue. NPs may overcome drug resistance when functionalized with targeting moiety. The Nano photosensitizers used in photodynamic therapy (PDT) show higher solubility than normal photosensitizer playing an important role in the treatment of cancer. Additionally, the increased resolution and sensitivity give nanostructure-based diagnostics an advantage over classical methods. Compared to traditional molecular medicine, NPs show advantages, such as intermixing, diffusion, sensoric response, and ultrafast kinetics make nanomedicine a local process at the nanoscale [1]. At the same time, NPs will enter and interact with human body during these processes. As an important protective system to defend organisms from foreign matters and danger signals inside the body, the immune system plays a critical role in keeping homeostasis in human body. The immune system exerts its function through innate immunity and adaptive immunity. Innate immunity is the first line of defense against microbial invasion, which interacts with the foreign materials and cleans the pathogen or pathogen-infected cells, which is nonspecific to pathogen. The function of innate immunity was realized by the phagocytic cells, which phagocytose pathogen and release cytokine to clear pathogen. If the pathogen cannot be effectively cleared by innate immunity, the adaptive immunity, as the second line of defense in human body, will be activated. During these processes, some phagocytic cells act as antigen-presenting cells (APCs) and present specific antigens to specialized cells which are responsible for adaptive immunity, such as T cells and B cells. By this antigen-presenting process, pathogen (antigen) could be recognized by T cells and B cells and stimulates the adaptive immune response, which is specific to pathogen. The strong ability to eliminate pathogens makes the immune system important in most disease treatment. However, abnormal intensity of immune response, including immunosuppression and immunostimulation, will lead to disease. Immunosuppression can be caused by impairment of any component of the immune system, which results in a decreased immune function and thereby leads to pathogen which cannot be effectively cleared and infection or tumor will occur. Immunostimulation could enhance the ability to resist pathogen, but it may result in a strong adverse response such as autoimmune disease if it was hypersensitive.

***Correspondence to:** Duarte Jonatas, Department of Materials Science & Engineering, University of Washington, Seattle, USA; E-mail: jonatasdu@edu.com

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NPS CANDIDATES USED IN NANOMEDICINE

Nanotechnology has a great potential in medicine applications such as medical diagnostics [60] and therapy. As an inorganic fluorophore, quantum dots (QDs) have photo stability which makes them ideal candidates for imaging tools in vivo. Recent study showed a technique to track lymph flow in real time using quantum dots optical imaging in mice. In addition, super paramagnetic iron oxide NPs (SPION) was also applied to trace neurodegenerative diseases by magnetic resonance imaging. Some carbon-based NPs are also applied in clinical use. Carbon nanotubes (CNTs) have unique physical properties such as electrical, thermal, and spectroscopic properties, which make them an advantage in detection and therapy of diseases. It was reported that CNTs could prolong survival of tumor bearing animals. Graphene has good biocompatibility, bio functionalization, and its unique mechanical, electronic, and optical properties for imaging and cancer phototherapy. And it was demonstrated that graphene oxide (GO) have antibacterial properties, making them candidates as antibacterial agent [2].

POLYMERIC NANOPARTICLES

Many biodegradable polymers have been used as drug delivery agents and have increased therapeutic efficiency with minimal off-target toxicities. Several specialty polymers like poly, and poly have got considerable attention due to their biocompatibility with and controlled release properties of chemotherapeutic agents. Other polymers derived from naturally occurring sources like sodium alginate and chitosan have also been employed as drug delivery agents. Lipid or protein-based soft nanoparticles comprises another important class of soft nanomaterials.

Apart from the commercially available polymers mentioned above, a host of synthetic biodegradable polymers has been synthesized and can efficiently deliver therapeutics at the desired site. For such transport to the disease site, two types of targeting mechanisms are generally followed: (a) Passive or size-dependent transport and (b) Active or ligand-mediated transport. Microenvironment-sensitive chemical units have also been immobilized onto both soft and hard nanoparticles to sense biochemical triggers like hypoxia, pH, enzyme concentration, and temperature. These stimuli-sensitive polymers form self-assembled structures at the physiologically prevailing conditions but can sense the specific trigger distinctive to the cancer microenvironment. Such sensory input is translated to the collapse of self-organized structures leading to drug release. Significant advancements have been achieved in the area of stimuli-responsive polymeric nanoparticles for cancer therapy [3]. Inspired by these works, we have reported the synthesis and use of several pH-responsive block copolymers comprising hydrophilic PEG and hydrophobic polycarbonates for delivery of newly discovered molecular inhibitors, such as hedgehog, ERK inhibitor or conventional chemotherapeutic agents such as Gemcitabine. Physical encapsulation or chemical conjugation of these molecular species within stimuli-sensing nanoparticles improved their therapeutic profile by protecting the drugs against rapid metabolic clearance and suppressing their off-target toxicity. Although physical encapsulation of drug molecules inside polymeric nanocapsules is a popular and facile strategy for designing controlled-release drug delivery systems, chemical conjugation to polymeric scaffolds has also been widely employed by researchers for designing polymer-drug conjugates. Conjugation of drugs is achieved via chemical coupling of drugs to the polymer backbone via simple amide or ester bond linkage, which, when subject to certain conditions prevailing in the cancer tissues, leads to their cleavage subsequent release of the drug. This approach protects the drug against enzymatic degradation, prolongs its circulation time, and ensures efficient payload delivery to the targeted tumor tissue [4].

Soft nanoparticles have been equipped with targeting ligands, immobilization of which on nanoparticle surface is also a popular strategy to design "ligand targeted therapeutics." Several ligands, including peptides, polysaccharides, proteins, aptamers, and small molecules, have been used for targeting the tumor tissue. The rationale behind employing targeting ligands is to harness their binding affinity to specific receptors on the cell surface, thereby increasing the therapeutic efficiency and accumulation of the NPs on a specific population of cells. As this is mostly a surface phenomenon, it is frequently more advantageous to employ multiple ligands instead of a single one to increase cellular uptake via a multivalent effect. Multivalency is concerned; dendrimers and hyper branched polymers have been developed and are included within the family of soft nanomaterials.

Dendrimers are a class of materials that are branched at the edges and possess a unique 3-dimensional structure. These are usually classified as macromolecules or branched polymers and have been useful as novel drug delivery agents. The core-shell structure of dendrimers that gives them macromolecular properties has often been used for 'host-guest' type interactions for sensing of various ions or biomolecules and entrapment of drugs and dyes. Synthesis of the perfect dendrimer is often cumbersome, and therefore more easily realizable dendritic scaffolds have been developed [5]. Termed as 'hyperbranched polymers,' these nanoscale unimolecular species demonstrate spherical presentations of dendrimers; however, they do not require a stepwise synthesis to realize a multivalent and branched topology.

As with polymeric nanoparticles, various active and passive targeting strategies have been applied to dendritic systems to render them highly effective in delivering therapeutics to the tumor core with minimal off-target toxicity. Particularly with non-polar chemotherapeutic agents, dendrimers and hyperbranched polymers provide a useful scaffold to aid in solubility and formulation stability of chemotherapy without compromising their therapeutic efficiency. Conjugation of specific antigens for specific delivery using monoclonal antibodies has also been explored as applications of dendrimers and hyperbranched polymers for vaccine research.

NANOPARTICLE MEDIATED IMMUNOTOXICITY

Since the advent of nanomedicine, there has been a surge in the use of various nanomaterials described in the previous sections for a whole range of therapeutic applications. Although several features of nanoparticles in terms of high payload, low dosage, and targeting capacity make them attractive candidates for use in cancer treatment, an essential aspect of clinical consideration remains the Immunotoxicity of these NPs.

When used for *in vivo* application, especially for systemic delivery of therapeutics, NPs, and biological agents' interface play a fundamental role in nanomaterials' fate in effective delivery, clearance, and accumulation [6].

The immune system's primary function is to protect the body against foreign particles considered threats. The broad classification of the immune system is innate and adaptive. Innate immunity generates a non-specific inflammatory response when in contact with foreign

bioactive agents like bacterial and viral strains. This system's mechanism of action is through various receptors functioning as pathogen recognition agents followed by the acquired immunity system's activation through antigen-presenting cells (APCs). In contrast, the adaptive immune system is responsible for generating antibodies in response to the antigens and follows a complicated pathway. Immune systems recognize nanoparticles via their surface properties and compositional features. Therefore, these features can act as handles to mediate interactions of nanoparticles with the immune system.

The first contact of NPs with biofluids exposes them to various proteins to form a crown effect commonly referred to as protein corona particle [7]. Although other biomolecules like DNA, RNA, and ribose sugars also interact with NPs, they have been underrepresented in literature and ensuing scientific investigations. Interactions of the NPs with the plasma proteins and other biomolecules alter their fate as various biochemical changes alter the bioactivity of NPs.

Phagocytes, which comprise an essential part of the immune system, are the first to interact with any foreign bodies, including nanoparticles. The two types of interactions this brings about are immunosuppression or immunostimulation. While immunosuppression renders the host organism susceptible to various infections due to the immune system's incompetency to combat any invasion, immunostimulation is responsible for a host of disorders, including inflammation.

Undesirable interactions between the immune system and nanoparticles have often been reported due to immunostimulation or immunosuppression, which might cause inflammatory or autoimmune disorders, thereby increasing the chances of the receptor's body incurring an infection [8]. Immune recognition can be bypassed via several methods, of which using a polymeric substance to create a hydrophilic environment is amongst the most popular. However, this cannot negate antibody production. On the other hand, to elicit the desired immune-response, antigen-presenting cells are directly stimulated, or antigen is delivered to the desired cellular compartment via targeting methods.

IMPACT OF NANOPARTICLES IN VITRO AND IN VIVO ON THE IMMUNE RESPONSE

Uptake by the innate immune system transfers NPs within a recognizable size range to these areas, where the lymphatic system directs them. **In vivo,** murine models show adverse effects in these areas and suppress natural killer (NK) cells. These models have also shown a variety of interactions with T and B cells in these areas. Models involving negatively charged SiO_2 showed suppression of these cells, inhibiting NK cell activity, suppressing proinflammatory cytokine production, resulting in a lack of inflammatory responses. Silver nanoparticles (AgNPs) are bound to various tissues, resulting in reactive oxygen species (ROS) induction, inflammation, and tissue damage [9]. The toxic effect of AgNPs on the proliferation and cytokine expression by human lymphocyte cells and peripheral blood mononuclear cells (PBMCs) has also been investigated[69]. The immunosuppression induced by these AgNPs caused broad organ damage in these areas and harmed organisms. The accumulation of NPs can also harm organs like the liver, spleen, and lymph nodes.

Despite the disconnect between **in vitro** and **in vivo** models, RAW 264.7 cells are the most commonly used cellular model for immunotoxic assays. These cells show pronounced dose-dependent cytotoxicity. NPs are best dosed out by a surface area factor, not mass, since the surface area is the biologically most effective dose metric for acute nanoparticle toxicity. When proportionally applied to cell cultures, silicon NPs caused more significant cytotoxicity than controls to monocytes and macrophages. This toxicity was evidenced to be the product of ROS release and oxidative stress [10]. These NPs also contributed to most lymphocytes' death through apoptosis and necrosis, which causes direct cellular damage.

Despite the apparent disconnect between **in vitro** and **in vivo** models, results have been consistent. The leading cause of cytotoxic factors created by NPs is TLR activation, ROS production, and the triggering of direct pro apoptotic factors. Broad immunosuppression and accumulation can also lead to organ and cell damage. These issues can potentially be offset by immune modulatory practices that would breed tolerance within the immune system.

CONCLUSION

The immune response of NPs is like a double-edged sword in nanomedicine applications by bringing both benefits and harms. We should take advantage of the benefits from the immune modulating properties of NPs and, on the other hand, avoid the undesirable immune responses in order to minimize the systemic side effects. The factors affecting the immune response are complex, including particle composition, size, surface chemistry, plasma protein binding, and exposure route. Investigation of the relationship between properties of NPs and systemic immune response is crucial for their application in medicine and other areas. Although treatments of acute and long-term immune toxicities have been developed, current approaches of prediction, prevention, and treatment of Nano immunomodulation are still lacking, encouraging further in-depth studies.

REFERENCES

1. Tinkle S, McNeil SE, Mühlebach S, Bawa R, Borchard G, Barenholz YC, et al. Nanomedicines: addressing the scientific and regulatory gap. Ann N Y Acad Sci. 2014; 1313(1): 35–56.
2. Martin CJ, Allender CJ, Brain KR, Morrissey A, Birchall JC. Low temperature fabrication of biodegradable sugar glass microneedles for transdermal drug delivery applications. J Control Release. 2012; 158(1): 93–101.
3. Verbaan FJ, Bal SM, van den Berg DJ, Groenink WHH, Verpoorten H, Lüttge R, et al. Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin. J Control Release. 2007; 117(2): 238–245.
4. Akhtar N. Microneedles: an innovative approach to transdermal delivery-a review.ijpps.2014; 6(4): 1-8.
5. Lee K, Lee CY, Jung H. Dissolving microneedles for transdermal drug administration prepared by stepwise controlled drawing of maltose. Biomaterials. 2011; 32(11): 3134–3140.
6. Donnelly RF, Raj Singh TR, Woolfson AD. Microneedle-based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Delivery. 2010; 17(4): 187-207.
7. Hopcroft MA, Nix WD, Kenny TW. What is the Young's modulus of silicon. J Microele Systems. 2010; 19(2):229–238.
8. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2004; 56(5): 603–618.

9. Mcallister D v, Wang PM, Davis SP, Park JH, Canatella PJ, Allen MG, et al. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: Fabrication methods and transport studies. Proc Natl Acad Sci. 2003; 100(24): 13755-13760.

10. Li J, Liu B, Zhou Y, Chen Z, Jiang L, Yuan W, et al. Fabrication of a Ti porous microneedle array by metal injection molding for transdermal drug delivery. PLoS ONE. 2017; 12(2): e0172043.