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Immunomodulatory potential of nanomaterials: Interaction with the immune system

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Immunomodulation is an attractive approach to overcome the limitations of traditional therapeutic regimes against diseases. Immunomodulation-based therapies are emerging as promising alternative strategy that involves the defense mechanisms of the host to recognize and selectively eliminate diseases. Recent developments in nanotechnology have forged a revolution as development of nano-emulsions, nanotubes, and nanoparticles have provided promising strategies as novel immune-modulatorsto enhance efficacy at target sites. Moreover, interaction between nanoparticles and the immune system may cause unanticipated adverse reactions such as hypersensitivity, inflammation and necrosis. Therefore, to ensure a successful and safe clinical application of immune-modulatory nanoparticles, it is necessary to gain in-depth knowledge and a clear understanding of the multifaceted nature of the interactions between nanoparticles and immune system. Since elevated immunological responses are detrimental in elimination of exogenous or endogenous antigens, there are many bottlenecks that prevent the complete regulation of the immune system. Therefore, using nanostructures as transport vehicles to deliver immunological compounds to specific target sitesto overcome severe limitations. Different nanostructures are being exploited to develop novel adjuvants, innovative vaccines,and drugs to alter the immune system for various infectious and non-infectious diseases. The review focuses on various nanoparticle and their interplay with the immune system.

Keywords: Immunomodulation, Immunosuppressant, Nano-vaccines, Nano-adjuvants

Introduction

Nano-sized biomolecules such as proteins, oligonucleotides, and polysaccharides act as antigens, allergens, or pathogen-associated molecular patterns (PAMPs) play important role in the immune response. The enhancement of the immune response by nanoparticles can be achieved through innate immune potentiation or by the enhanced delivery of antigens. Virus-like particles activate the innate immune response via Toll-like receptors and the repetitive display of antigens, whereas, nanogels and cationic liposomes are examples of vaccine carriers. Innovative strategies to produce and develop integrated novel nanoparticle packages enable the explorationof a widerepertoire of active ingredients thus vanishing limiting factors of using nanoparticles that are not suitable in terms of pharmacokinetics or biocompatible. In addition, the surface coating chemistry of nanoparticles and immunogenic cargo carrying capacity is being continuously exploited to develop better adjuvants, nanoparticle-mediated, combination, and mono-therapies including traditional radio and chemotherapy. Innovative engineering to design nanoparticles as artificial antigen-presenting cells holding immunostimulatory competence to exploit nanostructured architecture for sustained anti-tumor activity.

Nanoparticles are an excellent system in the development and delivery of vaccines at the same time boost the immune responses[1]. Nanoparticles such as virus-like particles (VLP), and MF 59 have been applied successfully for decades while others are still at the early stage of the development phase. The present study reviews the role of nanotechnology and its applications in designing vaccines and immunosuppressive agents, it also provides better conceptualization and clarity to hack the immune system to produce desired immune responses against various diseases using nanostructured material.

Nanotechnology in Vaccination

The conventional vaccines have been modified but still, the low immunogenic response of these vaccines,

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toxicity, multiple cycles of vaccine administration, and instability are the hurdles to achieving complete immunity against diseases. Nanotechnology has played a very significant role in vaccine development and increased cellular and humoral immune responses. The nano-based vaccines not only increase the immunological responses and stability of antigens but also target their delivery and slow release (Table 1). Nano-size materials such as virus-like particles (VLPs), liposomes, polymeric, inorganic nanoparticles, and emulsions have the potential to act as stabilizing and delivery agents for vaccine antigens. These nano-based vaccines facilitate the uptake and recognition of antigens by Antigen-Presenting Cells (APCs). Further, modification of the surface properties of these vaccines allows the delivery of antigens to specific receptors on the cell surface, thus stimulating selective and specific immune responses.

Table 1 — Showing certain types of nano-based vaccines[13]

Nano-based vaccines	Size range	Mechanisms
Virus-like particles	15-30 nm	Repetitive antigen display, structural or molecular mimicry of the virus, particle size-dependent tissue penetration and trafficking to lymphatics and TLR activation
MF59	150-200 nm	Neutrophil, monocyte, and DC recruitment, antigen uptake, the induction of humoral and TH1-type immune responses
W805EC	200-400 nm	Antigen uptake by and activation of epithelial cells and DCs, TLR2 and TLR4 activation, local cytokine production, mucosal antibody responses, and TH1, TH2 and TH17 cell responses
PLGA	100-200 nm	Encapsulation for sustained local antigens and co-mediator release
Nanogel	30-40 nm	Antigen entrapment in a hydrated nanogel matrix for slow release, delivery to APCs, and introduction of tumour-specific cells and antibody responses
Cationic liposomes	200-1000 nm	Encapsulation and targeted antigen delivery or uptake by APCs, and recruitment of monocytes to the injected site

Virus-like particles (VLP) based vaccines

The diverse VLP have unique nanometersizes (20-150 nm), symmetrical shapes, and stable structure[2]. VLP can be used as a vaccination not only against infectious diseases but also for cancer. Recently it has been reported that the problems like chronic inflammation diseases like Alzheimer's disease, high blood pressure, and rheumatoid arthritiscan be treated[3]. VLPs are broadly classified into two main classes, *viz*. VLP that have viral surface proteinsubunits and artificial VLPs made by chemical synthesis[4-5]. The VLPs can be conjugated with antigenic peptides or ligands without modification. The efficacy can be enhanced by linking with toll-like receptor (TLR), CpG oligonucleotides, and peptide epitomes as they can activate cytotoxic T lymphocytes (CTLs) and multifunctional central memory T cells and secretes interferon- γ (IFNγ), interleukin 2 (IL-2) and tumor necrosis factors (TNF). Such VLPs are taken up by antigen-processing cells (APCs)[6].

Vaccine carrier based on nanoparticles

Vaccine carriers of different types have been used in vaccination such as hydrogel polymers or "nanogel", poly (Lactide-glycolide) nanoparticles, cationic liposomes, and cholesterol bearing hydrophobized pullulan (CHP)[7-10]. The use of Biodegradable polymer nanoparticles is safe and biocompatible.

Cationic riposomes

The antigens are encapsulated by Cationic liposomes (diameter of 200 to 1000 nm) and are released into immune cells. It forms stable complexes with negatively charged therapeutic agents like siRNA and mediates its delivery in vitro in mammalian cells. Polyethylene glycol (PEG) coated cationic liposomes have been developed for gene silencing using systemic delivery of nucleic acids.

Nano-Emulsion

Emulsions are a mixture of water in oil and nanoemulsions are isotropic solutions containing two

immiscible liquids having nanometric sizes which are thermodynamically unstable systems. MF59, influenza vaccine, is composed of a mixture of squalene oil and polymorphic 80 (Tween80) and sorbitantriolate (span 85), is injected intramuscularly and increases the antigen uptake, accumulates monocytes as well as release inflammatory cytokines at the injection site. Another example is W805EC contains soybean oil, injected intramuscularly in animals and humans causing strong humoral, mucosal, and cellular immune responses. Due to their size and high potential coefficient, these can penetrate the mucosal layer and binds to the cellular membranes besides these advantages nanoemulsions have no toxicity effect on humans and animals.

Self-assemble peptide nanoparticles (SAPNs)

SAPNs are synthesized using algorithmic structural proteins with repeating units and can express in *E. coli* Almost 180 peptides are held together and can induce the immune system to produce antibodies. The vaccine for severe acute respiratory syndrome coronavirus (SARS-CoV-2) and Avian Influenza Virus[11,12].

Additional nanoparticles

In nature, there are many nanostructures that can be used in vaccines and immunology such as calcium phosphate or hydroxyapatite nanoparticles and plasmids. A novel strategy is based on designing vaccines to target B-cells and bind with TLR ligands. Another strategy is the use of outer membrane vesicles (OMVs) based vaccines in which the antigenic stable chimeric fusion protein of HA (H1-types haemagglutinin (HA) of influenza A virus and the receptor binding domain (RBD) of MERS-CoV. Nanoparticles can also suppress the immune responses against certain types of allergies, transplant rejection, and autoimmunity diseases[16-20]. Fullerene (C60) is an immunosuppressor, made up of carbon and is commonly used for electronics, polymer composites, and paints. However, co-incubation with mast cells can reduce IgE-mediated signal response, and degranulation as well as induce ROS (reactive oxygen species) production. When it is turned into cylinders it forms carbon nanotubes (CNTs) of 10 nm in diameter and some micrometers in length.

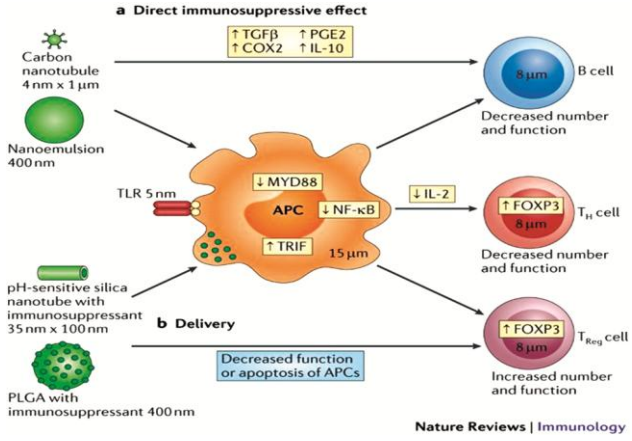

Fig. 1 — Nanoscale immunosuppression by nanomaterials[14-15]

Immunosuppression by nanotechnology

Nanotechnology can be used to systematically seize the detrimental immune response during certain allergies, autoimmunity, and graft rejection during organ transplant. The immunosuppressive effects of nanotherapeutics are discussed in the following sections Researchers have observed a direct effect of nanoscale on immunosuppressive including antigen-presenting cells (APCs) Nanoscale products might have a direct immunosuppressive effect (part a) on components of the immune response, including antigen-presenting cells (APCs), T cells. The upregulation of transforming growth factor-β (TGFβ), which results in enhances the production of cyclooxygenase 2 (COX2), prostaglandin E2 (PGE2), and interleukin-10 (IL-10), and reduces B cell and T cell activity (Fig. 1). With the delivery of immunosuppressants there occur a reduction in IL-2 with sirolimus, down-regulation of nuclear factor-κB (NF-κB) with steroids, and the up-regulation of fork head box P3 (FOXP3), which in turn results in increased regulatory T cell (Treg) activity (Table 2).

Table 2 — Immunosuppression of carbon nanotubes: Single-wall and multi-wall[15]

Nanoparticles	Size range	Mechanisms	Medical application	Current use
Fullerenes	0.5-1 nm	Suppression of mast cell and basophil degranulation	Allergy	In mice and *in vitro*
SWCNT	1-4 nm diameter; 1000-3000 nm length	Suppression of DC function	Inhalation exposure	In mice
MWCNT	10-20 nm diameter; 5000-15000 nm length	Suppression of T cell proliferation and function	Inhalation exposure	In mice

Conclusion

The prophylactic and therapeutic effects of specific immune responses have been engineered using nanotechnology. Soon researchers will customize immune responses in very innovative ways by using nanoparticles modified in shape, porosity, size, hydrophobicity, and charge. The outbreak of pandemic viruses and other pathogens requires the activation of innate and adaptive immune responses after a single dose of vaccine. The outbreak of COVID-19 and the development of vaccines through the intervention of nanotechnology demonstrate the potential of nano-based vaccines. Using antigens such as NOD-like receptors, TLR ligands, and other microbial pattern recognition systems could enhance the responses to antigens which normally do not produce this activity. A complete understanding of many immune diseases at the molecular level can overcome immune defects with the aid of nanoparticle-based vaccines and delivery methods. The application of nanotechnology in immunology will have far more impact on the development of new strategies for fighting against human disease in near future.

Conflict of interest

All authors declare no conflict of interest.

References

1 Smith DM, Simon JK & Baker JR Jr, Applications of nanotechnology for immunology. *Nat Rev Immunol,* 13 (2013) 592.

2 Elsayed H, Nabi G, McKinstry WJ, Khoo KK, Mak J, Salazar AM, Tenbusch M, Temchura V & Überla K. Intrastructural help: Harnessing T helper cells induced by licensed vaccines for improvement of HIV Env antibody responses to virus-like particle vaccines. *J Virol,* (2018) 92.

3 Jennings GT, Bachmann MF, Immunodrugs: Therapeutic VLP-based vaccines for chronic diseases. *Annu Rev Pharmacol Toxicol,* 49 (2009) 303.

4 Queiroz AMV, Oliveira JWDF, Moreno CJ, Guérin DM & Silva MS, VLP-based vaccines as a suitable technology to target trypanosomatid diseases. *Vaccines,* 9 (2021) 220.

5 Noad R & Roy P, Virus-like particles as immunogens. *Trends Microbiol,* 11 (2003) 444.

6 Goldinger SM, Dummer R, Baumgaertner P, Mihic-Probst D, Schwarz K, Hammann-Haenni A, Willers J, Geldhof C, Prior JO & Kündig TM, Nano-particle vaccination combined with TLR-7 and-9 ligands triggers memory and effector CD 8+ T-cell responses in melanoma patients. *Eur J Immunol,* 42 (2012) 3049.

7 Johansen P, Men Y, Merkle HP & Gander B, Revisiting PLA/PLGA microspheres: An analysis of their potential in parenteral vaccination. *Eur J Pharm Biopharm*, 50 (2000) 129.

8 Ferreira SA, Gama FM & Vilanova M, Polymeric nanogels as vaccine delivery systems. *Nanomed. Nanotechnol. Biol. Med,* 9 (2013) 159.

9 Christensen D, Korsholm KS, Rosenkrands I, Lindenstrøm T, Andersen P & Agger EM, Cationic liposomes as vaccine adjuvants. *Expert Rev Vaccines,* 6 (2007) 785.

10 Uenaka A, Wada H, Isobe M, Saika T, Tsuji K, Sato E, Sato S, Noguchi Y, Kawabata R & Yasuda T, T cell immunomonitoring and tumor responses in patients immunized with a complex of cholesterol-bearing hydrophobized pullulan (CHP) and NY-ESO-1 protein. *Cancer Immun Arch,* 7 (2007) 7.

11 Raman S, Machaidze G, Lustig A, Aebi U & Burkhard P, Structure-based design of peptides that self-assemble into regular polyhedral nanoparticles. *Nanomed Nanotechnol Biol Med,* 2 (2006) 95.

12 Doll TA, Neef T, Duong N, Lanar DE, Ringler P, Müller SA & Burkhard P, Optimizing the design of protein nanoparticles as carriers for vaccine applications. *Nanomed Nanotechnol Biol Med,* 11 (2015) 1705.

13 Kushnir N, Streatfield SJ & Yusibov V, Virus-like particles as a highly efficient vaccine platform: diversity of targets and production systems and advances in clinical development. *Vaccine,* 31 (2012) 58.

14 Mobeen H, Safdar M, Fatima A, Afzal S, Zaman H & Mehdi Z, Emerging applications of nanotechnology in context to immunology: A comprehensive. *Front Bioeng Biotechnol*, (2022).

15 Kavosi A, HosseiniGhaleNoei S, Madani S, Khalighfard S, Khodayari S, Khodayari H, Mirzaei M, Kalhori MR, Yavarian M, Alizadeh AM, Falahati M. The toxicity and therapeutic effects of single-and multi-wall carbon nanotubes on mice breast cancer. *Sci Rep,* 8 (2018) 1.

16 Murugan NA, Chitra JP, Jeyaraman J & Rajendren SM, Multi-level scoring approach to discover multi-targeting potency of medicinal plant phytochemicals against protein targets in SARS-CoV-2 and human ACE-2 receptor. *Indian J Biochem Biophys,* 59 (2022) 1088.

17 Yagnik SV, Dangi K, Biswas L, Singh P & Verma AK, Nano-therapeutic efficacy of green synthesized gold nanoparticles (gAuNPs) and its antibacterial efficacy. *Indian J Biochem Biophys,* 59 (2022) 455.

18 Singh K, Chopra SD, Singh D & Singh N, Green synthesis and characterization of iron oxide nanoparticles using *Coriandrum sativum* L. leaf extract. *Indian J Biochem Biophys,* 59 (2022) 450.

19 Kumari V & Sangal A, Antimicrobial study of *Arjuna Terminalia* loaded PLGA nanoparticle. *Indian J Biochem Biophys,* 59 (2022) 291.

20 Gayathri R & Manju SL, A review on phyto-nanotechnology for therapy of alzheimer's disease. *Indian J Biochem Biophys,* 59 (2022) 867.