Chapter 2
Immunology and Nanotechnology: Effects and Affects

Kaushita Banerjee and Harishkumar Madhyastha

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2.1 Introduction

A body’s immune system is functionalized to defend various infections and ailments from external source. Immunity can be tweaked as per the internal and external environ to match up with body’s necessities. Immunotherapeutic strategies have been a cost-effective process utilised since ages to augment a body’s immune sys-
tem and identify, target, and abolish toxic cells within the body, thus making it a universal testing strategy for elimination of toxic cellular components (Davis and Brodin 2018). A successful therapy is governed by various factors like the structural intricacy of pathogen, an appropriate delivery system, the route by which it is administered, ability to recognise and attack specific target cells, host immunity, etc. (Witztum and Lichtman 2014). Amongst the bodily preventive barriers, the biological one constitutes of cells, soluble factors, and organs that creates a protective surface restricting the invasion of foreign matter. The immune system includes a complex array of biochemical and cellular responses intricately interlinked with some specific pathways and sporadically can be disconcerted at diverse stages leading to immunosuppression or stimulation. Thus, it is crucial to scrutinize immune interactions with any new chemical or biological entity before it is explored industrially, biomedically or therapeutically. With recent developments in the field of nanotechnology, immunotherapy has traversed in targeting diverse challenging disorders including cancer and autoimmune diseases. Moreover, the progression of several adjuvanted or inactivated vaccines to boost immune response, has led to the boom of nano-based self-adjuvanted particles (Shah et al. 2014). Nano sized materials and have been custom-made to either target or avoid interactions with the immune system and fit into various biological and medical arenas by interacting with the innate and/or acquired immune system for successful and efficient prophylaxis. The immediate line of mechanistic nonspecific defence against any infection is conferred by the macrophages and neutrocytes of innate system followed by an immunological memory of the lymphocytic cells developed by adaptive immunity to track down the infection and recognize similar pathogenic counterparts in future (Jones 2005; Mogensen 2009). Both these immune systems function absolutely dynamically in destroying an antigenic molecule in a salubrious body. Hence, nano scaled particles are now being used to reorient and alter the specific immune responses for preventative and curative outcomes. Existing naturally or architecturally improved, these nanostructured materials include nanoparticles, nanoemulsions, nanotubules, liposomes, fullerenes, virus like particles, immune-stimulating complexes, etc. that provides a cutting-edge stratagem for substantial improvisations and modulations in the immune system to treat various diseases and thus embraces to develop newer immunomodulatory agents, that could effectually orchestrate or deliver immunologically active agents to specific target sites (Goldberg 2015; Dacoba et al. 2017). In this chapter, we enumerate the physical, chemical and biological properties of some nano-structured materials (vaccines, nanotubes, nanoemulsions, dendrimers, polymeric complexes, liposomes, virus like particles, etc.) on the immune response and the role of nanotechnology in modifying and tuning such properties for varied end applications. Immunostimulation and immunosuppression caused by nanomaterials and their mechanistic approach to interact with the immune cells without any unwanted immunotoxicity has also been highlighted. Therefore, our interest lies in exploring the “effects” of nanosized entities in immunological applications and also the potential challenges of how it “affects” the overall process of immune system.
2.1.1 Vaccines

In current times, many disease definite vaccines are in either in ready use or being developed rapidly. Newer progressions in immunological and molecular paradigm have led to the exploration of vaccine materials that are host and disease precise with immunological memory for better targeting and response over an extended period of time. A vaccine should effectually be able to trigger the T helper type-1 (Th-1) and T helper type-2 (Th-2) cells which further induces antigen-specific T and B lymphocytes for recognition and response to antigenic determinant (Guimaraes-Walker et al. 2008; Heffernan et al. 2011). Traditional vaccines used since twentieth century comprise of live, attenuated, killed, toxoid, conjugate, naked, lysates that are whole organism ones and also components like polysaccharides and bacterial toxins. Alternatively, new age vaccines focus on nucleotide differences and antigenic expression via sophisticated techniques like recombinant DNA technology and reverse transcription polymerase chain reaction, one among them being the DNA vaccine immunotherapy (Martin et al. 2008; Beckett et al. 2011). “An overall effective vaccine” balances and condenses the percentage transmission rate of a disease in an immunized/vaccinated population cluster in comparison to the unvaccinated ones under a given set of conditions (Haber et al. 1991; Halloran et al. 2010). Vaccine effectivity is reliant on the antigenic immunogenicity and can be improved by incorporating adjuvants that activate the humoral, cellular and mucosal immune responses against foreign antigens. Most nanoscale materials enhance the adjuvant potency by targeting its direct delivery to the immune system or increase the effect of innate immunity (Fifix et al. 2004; Chadwick et al. 2010) and system is depicted in Fig. 2.1. Some of the nanotechnological approaches like adjuvants and carriers that have been explored to improve the clinical effectivity of vaccine are reviewed here.

2.1.1.1 Virus Like Particle (VLP) Adjuvants for Vaccines

These virus-like particles ranging from 15 to 100 nm are highly diverse adjuvants and carrier systems comprising of either naturally found viral protein subunits formed by bioconjugation of viral capsid with antigens/ligands or synthetically engineered multidimensional scaffolds with surface presentation of antigens on them. Additionally, integrating ligands and mediators might as well make a vaccine more efficacious immunologically. Studies showed that VLP’s incorporated with CpG oligodeoxynucleotides and protein Melan-A (melanoma antigen recognized by T cells-1) tend to activate tumour necrosis factor-α (TNF-α) and interleukin-2 (IL-2) inducing T_CM cells (central memory T cells) and T_C cells (cytolytic T lymphocytes) (Ghasparian et al. 2011). Their nano-size, uniform and symmetrical structure and stable conformation enables the favourable uptake of antigens by the antigen producing cells (APC’s). The smaller the particle, the better is its penetration through the tissues and rapid its circulation in the lymphatic system leading to...
proficient triggering of acquired immune response as compared to large VLP’s (Reddy et al. 2007; Manolova et al. 2008). Dendritic cell specific ICAM3-grabbing non-integrin monoclonal antibodies coated virus like particles also often illustrate better uptake and processing of extracellular proteins via the histocompatibility complex class II pathway stimulating the dendritic cell initiation and antigen targeting on both histocompatibility complex class molecules (Schirmbeck et al. 1996). Besides, it also briefs the CD4+ and CD8+ T-lymphocytes for antigen destruction (Kaba et al. 2012) mechanism. Two of the well-known VPL based vaccines, hepatitis B and human papillomavirus virus vaccines have been the oldest and first generation VLPs that was amassed by recombinant protein engineering in mass scale (No et al. 2011). Nevertheless, these had certain limitations with patients having
immunocompromised immune systems and geriatric population. Also, drawbacks of adjuvanted vaccines take in the probable risks of rare and severe immune response in individuals after a time duration. Therefore, it is crucial to investigate further on these lines for to modify vaccination efficacy (Martínez-Sernández and Figueiras 2013). Nano sized VLPs thus offer improved and varied initiation of humoral and cellular responses for safeguarding against chronic influenzas and HIV contagions and attesting its importance to public health.

Chemically developed lipopeptide based synthetic VLPs are much more attractive option in assembling the nanoparticle and stabilization of antigen structures (Boato et al. 2007) to boost neutralizing antibodies against severe chronic infections like HIV-1. Synthetic VLPs have frequently been plied to demonstrate envelope glycoprotein GP120 based protein epitope mimetics (PEMs) (Riedel et al. 2011) which are recognised as new primes for vaccine research.

Since these synthetically derived VLPs do not require recombinant technology or monomeric peptide expressions from viral producer cells, these can easily incorporate MHC molecule bound T cell epitopes and palmitoyl-cysteine lipopeptide to activate Toll like receptor-2 (Ghasparian et al. 2011). The induction of immune response becomes much easier if the structural orientation, the antigenic design and presentation is done using the nanoparticle-based vaccine approaches that provide swift responses to the non-accessible and preserved neutralizing epitopes than the readily accessible ones (Mascola and Montefiori 2010; McBurney and Ross 2009) in order to control enormous rates of genetic alteration and variation during infection. Therefore, implementing nanosized viral particle-based adjuvants is the need of the hour for better projection of cell mediated immune responses, cytotoxic T-lymphocyte antigenic determinants and antibodies to restraint an array of opportunistic viral infections (Sanou et al. 2012).

### 2.1.1.2 Nanoparticle-Based Carriers for Vaccines

Another way of increasing the vaccine efficacy is the use of nanoparticle carriers as such or in combination with other immuno-mediators or human dendritic cell specific antibodies for enhanced antigen delivery and presentation (Look et al. 2010). Among them, is a biocompatible and biodegradable copolymer; poly (lactic-co-glycolic acid, PLG) used as a condensed carrier for hepatitis B surface antigen that aids quick absorption and endocytic organelle localization of vaccine antigens in dendritic cells as well as produces high concentrations of antibodies definite antigens (Bharali et al. 2008). PLGs also serve as good matrices supporting sheathing, co-delivery of active drugs in animal models (Mundargi et al. 2008). Other VLP carriers include nanogels, cationic liposomes, pullulan derivatives and several polymeric nanocapsules and nanospheres. Studies on the use of PLG hydrogels in mice models have revealed these carriers to simultaneously attain hypodermal delivery of hepatitis B antigens and sustained release of colony stimulating factor-2, an essential cytokine for segregating and maturing the dendritic cells (Chou et al. 2010). Such carriers efficiently cause the maturation and migration of the alpha component
of integrins to the draining lymphatic vessels induces hepatitis B antigen-specific antibody even at low antigen titre values. It is relevant to state here that these biodegradable virus like particle carriers are successful candidates for vaccine delivery daises as they not only integrate immunogenic antigens for immunocompromised systems but also balances the nascent structure and steady continual release of the biological antigenic intermediaries over a time frame (Mundargi et al. 2008). Another kind is the self-assembling peptide nanoparticle (SAPNs) vaccine carriers utilized for recurring antigen display. Customized through recombination techniques, SAPNs inculcate in them distinct properties of certain pathogens and VLPs and show improved immunogenic responses to antigens. Due to the icosahedral structure with coiled-coil repeated pattern of hydrophobic and charged amino acid residues, SAPN are a repetitive scaffolding motif that lead to antigenic display, cellular stimulation, increased production of high concentration-high affinity antibodies against phylogenetic antigenic determinants (Raman et al. 2006). SAPNs when tailored with the coiled protein trimer epitopes of severe acute respiratory syndrome coronavirus produces virus specific deactivating antibodies post vaccination (Negahdaripour et al. 2017). Upon immunization of chicken with SAPNs and merger of an immunogenic protein epitope into the extracellular domain of matrix protein-2 of influenza A virus showed better exhibition of antigen determinant oligomers in their nascent spatial arrangement and led to the reduced shedding H5N2 virus subtype in chickens (Li et al. 2018). Further, inserting both B and T cell epitopes of Plasmodium species sporozoite surface proteins and modifying it into the SAPNs led to the expression of high titre antibodies and memory T cells (producing interferon-γ) and offered a protection to the mice against the surface protein of malarial parasite Plasmodium berghei (Seth et al. 2017).

2.1.2 Nanoemulsions

Typically, two phase immiscible colloids with a dispersed and a dispersion phase, stabilized together using a surfactant modifier defined as nanoemulsions. Emulsions can be either oil in water or water in oil type. These systems are kinetically and to a large extent thermodynamically stable upon dilution. Emulsions can be termed as ‘nano’ or ‘micro’ depending on their component assemblage and the overall stability it confers to a system (Tayeb and Sainsbury 2018). The use of adjuvants dated back to 1990s when alum was the only ideal adjuvant used for most of the human use vaccine because of its safety and effectivity. It was only after this when emulsion adjuvants for vaccines re-emerged with the manufacture of MF59. A mixture of squalene oil with polyoxyethylene sorbitan monooleate and sorbitan ester as surfactants, MF59 adjuvanted vaccines have been successfully administered for influenza virus (Domnich et al. 2017). This adjuvanted vaccine works by improving cellular uptake of antigens and heightening the release of chemokines along with site accumulation of different white blood cells upon injection which further upregulates and matures the C-C motif chemokine receptor-7 expressed in semi-mature/
mature dendritic cells to then migrate to the draining lymphatic nodules (Calabro et al. 2011; Lin et al. 2020). In comparison to aluminium salts-based adjuvants, MF59 are potentially superior in inducing both humoral and TH-1 cell mediated immunity and providing antiviral immune responses even at very small doses of viral antigen unlike aluminium adjuvants that confer inconsistent antiviral immune response (Cioncada et al. 2017; Shah et al. 2019). Initial clinical investigation on MF59 vaccine as potent applicants for herpes simplex virus, human immunodeficiency virus, cytomegalovirus, hepatitis B and C virus, human papillomavirus etc. are currently being explored (Patel et al. 2019). Though being one of the most promising and effective adjuvanted vaccine, MF59 suffers a major drawback of being unstable and temperature sensitive in nature. Reactivity upsurge, muscular inflammation and pain at the injection site also limits its use (Schultze et al. 2008). W805EC, a Glycine max oil based nanoemulsion mucosal adjuvant has been investigated in animals and human model to exhibit enhanced mucosal, humoral and cellular immunity upon intranasal delivery. Its mechanism of action involves retaining the emulsion droplet structure which then binds to the negatively charged proteins. W805EC’s micro size and positive zeta potential favour its smooth diffusion to the mucosa and cellular binding/uptake to the plasmalemma causing the initiation of innate and acquired immune response (Stanberry et al. 2012; Myc et al. 2013; Kim et al. 2014). In addition, the epithelial cells of mucosal membrane of the nasal cavity secretes cytokine that then activates the endocytic receptor DEC 205 to the lymph nodes. Nanoemulsion adjuvants also act as cell death inducers by releasing ‘calreticulin’, an immunological cell death signal and enable phagocytosis of antigen-loaded dendritic cells in tissues (Makidon et al. 2012; Bielinska et al. 2014). Emulsions inherently have the capacity to impede microbes and exhibit adjuvanted action and thus are used as multifaceted pharmacological agents for vaccinia, syncytial and influenza viruses, etc., are considerably less toxic with no antagonistic effects on the various models tested upon (Kaurav et al. 2018; Morcol et al. 2019).

2.1.3 Liposomes

Regardless of the availability of a number of nano adjuvants and carriers being used to deliver vaccines, traditionally, liposomes serve as excellent vaccine carriers for targeted delivery. Liposomes favour the encapsulation of a diverse group of antigens, polar and nonpolar drugs and exhibits increased immunogenicity. These are comparatively safe on the body without the emergence of any adverse immune reactions. Some of the commercially marketed liposomal carriers are mainly of PEGylation type, such as Doxil®, Ambisome®, Myocet®, etc. (Marasini et al. 2017; Joshi et al. 2019). The positive charge on lipid structure and its overall spatial arrangement enables liposomes to competently absorb and preserve antigens to nanostructures, retain it at the site of administration, augment better immunogenicity with stimulation of innate and T helper type cell responses that lead to the triggering of antigen presenting cells (Henriksen Lacey et al. 2010; Tandrup Schmidt
et al. 2016; Marasini et al. 2017). Improved systemic adjuvant action, antibody mediated immunity for various applications and reduced toxicity at multiple sites of monophosphoryl lipid A and Toll-like receptors in the body are some of the characteristics of cationic liposomes (Bal et al. 2011). Reports on amended constancy and immunity against tuberculosis causing *Mycobacterium* has been elucidated (Mohammed et al. 2010). Liposomal adjuvants such as virosomes, archeosomes, etc. have also been seen to have immunostimulatory effect on several cellular mediators. In conglomeration with vesicles of cell membrane, these assist the appropriate targeted antigen delivery as vehicles (Yu et al. 2019). Mechanistically, the size of the liposomal entities decides their method uptake *viz.*, smaller sizes mimic the viral uptake whereas bacterial uptake pathway is followed with increase in size (Zahednezhad et al. 2019). Hydrodynamic size, two-dimensional surface electric charge, physiochemical features makes liposomes suitable for its use as a whole vaccine soon that could surpass the current cationic lipid particulate vaccines such as quaternary amines, imidazole, cholesterol and amidine-based compounds for treatment of several infectious diseases.

### 2.1.4 Immunostimulatory Complexes (ISCOMs)

Lipophilic antigenic adjuvanted nanocarriers used for vaccine delivery, ISCOMs are a conglomeration of phosphatides, aglycone carbohydrate moieties, cholesterol and antigens forming open sphere like structural lattices of the size of viruses which allows their incorporation into the cell membrane and enables dendritic cell mediated antigenic endocytosis (Barr and Mitchell 1996). ISCOMs can suitably be used for oral, intranasal, parenteral delivery of antigenic epitopes to induce immune response of mucosal sites (Rhee 2020) and their connotation with intracellular lipid bilayers enables their entrapment within the cytosol present in antigen producing cells. Both antibody and cytokine-mediated immunity against a range of antigenic determinants as well as T helper type-1 and 2 pathways are actuated by these immune-stimulatory carriers (Cibulski et al. 2016). Besides the presentation of major histopathology complex-I (MHC-I) protein on antigen processing cell surfaces with its exposure to the transmembrane glycoprotein CD8, ISCOMs also assist the cross presentation of external antigens in the endogenous pathway, proving their exclusivity which is not seen in most other nanocarriers (Cibulski et al. 2016; Morelli and Maraskovsky 2017). The mechanism trails around with the transportation of antigen from the endosome into the cytosolic matrix of the antigen producing cells resulting in its proteasomal deprivation and demonstration to the T lymphocytes through MHC-I pathway. This process is initiated and progressed *via* the C-type multi-lectins expressed on the dendritic cell exterior and bound to the carbohydrate moiety of saponins. This characteristic of ISCOMs is advantageous in the targeted delivery of vaccines at mucosal sites (Corthésy and Bioley 2018). Research on vaccine delivery by these immune-stimulating complex adjuvants to oral and nasopharyngeal sites have also gained importance (Mowat et al. 1999; Hu...
et al. 2001). Studies to boost the mucosal and systemic adjuvant function of B-cell targeted fusion protein cholera toxin A-1in has shown that ISCOMs preserve this fusion protein and avert its enzymatic disruption in the digestive tract (Helgeby et al. 2006; Harandi and Lycke 2017). In fact, the correlation of cholera toxin A-1 protein with ISCOMs leads to highly immunogenic entity which on administering in nano quantities are well tolerated in the systemic mucosal routes (Mowat et al. 1999). McEntee et al. (2015) demonstrated high CD4+ T lymphocyte-immunoglobulin A/G immune responses in mice models upon administration with the ISCOM-cholera toxin A-1 amalgam and also highlighted their substantial stability upon freeze drying and lyophilization (McEntee et al. 2015). Recently designed ISCOMATRIX™ therapeutic adjuvants have improved antigenic and immunomodulatory properties in comparison to ISCOMs and have much wider applications. Devoid of an antigen, ISCOMATRIX™ vaccines contain a semi-purifiable Quil A extract which has an additional therapeutic and prophylactic impact on a diverse group of bacterial, viral, cancer antigens (Skwarczynski and Toth 2016). These exhibits humoral as well as cellular immunity and can modulate both the immune response systems by both the major histocompatibility complex pathways. By directing the distinctive cytotoxic T-cells, T-helper cells and immunoglobulins towards the mucosa, these antigen devoid adjuvants have been used to treat a variety of infectious diseases. Likewise, another cationic variant of ISCOMATRIX, the PLUSCOMs are much more competent in conferring effectual antigenic exhibition and amplified T-cell immune response against very small doses of antigens as compared to the conventional ISCOMs (Pham et al. 2009). However, ISCOMs require a lipophilic antigen because of the open spherical structure they possess, thus limiting their use in the other antigen types (Sun et al. 2009). ISCOMs could be an exhilarating method for mucosal vaccination in the times to come.

2.1.5 Polymeric Micelles, Dendrimers and Carbon Nanotubes

Strategically oriented nano assemblage of synthetic polymers, polymeric micelles are amphipathic in nature. Their less energy bonds help them dissociate easily and hence these are considered as a suitable candidates for varied applications. Studies depict that a 30S peptide micellar vaccine of these polymeric micelles can induce antigen-defined antibodies for pneumonia (Morein et al. 1983). With high levels of Immunoglobulin/A and hemagglutination inhibition titres, these micellar structures modified as per their hydrophilic and hydrophobic units can serve well for H5N1 avian flu (Prabakaran et al. 2010). Their substantial stability and alterable physico-chemical properties have made them suitable as nanocarriers in vaccine delivery. Dendrimer molecules are structurally alike the micelles are covalently linked, making them much tougher and indissociable. These homogenously branched polymers are highly compatible for a number of industrial and biomedical applications. A derived dendrimer, known as the multiple antigenic peptide (MAP) are currently in use as nanocarriers for vaccine delivery and have shown promising results with the
intramuscular malarial vaccines (Kim et al. 2018). Carbon embedded nanosized tubes also are effective in initiating immune response. Carbon nanotubes have branched carbon atoms linked together to form a closed structure permitting them to be excellent immunogenic carriers for antigen-antibody response.

2.2 Modulation of Immune System by Nanoscale Materials

Mutual conglomeration of Nanotechnology and Immunology have shown promising effects in therapy and treatment of diverse array of ailments. The interaction of nanomaterial with the immune system sometimes can persuade either a beneficial or detrimental outcome on the immune system. This immune based stimulation or suppression is dependent on a number of factors like the antigenic structural conformation, process end products, the stability and reactivity of the material. As a result, this immunomodulation affects the immunogenicity, adjuvanticity, inflammatory and recognition mechanisms of the immune system, diminution in the cellular components with decreased stimulus, incapacity to deal with infection and other malignancies, allergies, etc. (Dacoba et al. 2017). Some of the immunostimulatory and immunosuppressive effects of nanomaterial-based therapeutics are conversed here. And schematic is represented in Fig. 2.2.

2.2.1 Immuno-Stimulation

The overexpression of the immune-stimulators by the activation of certain cell components can lead to a number of consequences cellular immunogenicity and cell sequestration. Therapeutic nanomaterials may generate a specific antigen-antibody response for recognition of both the nanoscale material and body’s own jots as seen in most of the biologically utilized prophylactics (Chamberlain and Mire-Sluis 2003). A research data on polyamidoamine dendrimers revealed covert antigenic response of 3, 5 and 7th amino group of dendrimers (Roberts et al. 1996). A parallel study on the cross reaction between the C60 and C70 fullerenes yielded specific polyclonal antibodies, but did not produce anti-nanogold particle specific antibodies (Chen et al. 1998). This disruption in the process of systemic antigenic exhibition could possibly be due to the varied surface properties and functional assemblages of these particles, reactivity to a number of moieties and their predisposition genetically. Adjuvanticity is another aspect of immune-stimulation. Most of the nanoparticles are used as effective vaccine adjuvants for an upsurge in immune response. One such example is the HIV2 viral vaccine that upon reaction with nanomethylacrylate particles exhibited much higher volumes of specific antibodies in mice in contrast to conventional aluminium based adjuvants (Saravanan et al. 2018). A substantial titre of Immunoglobulin G was produced by liposomal nanoparticles in purified rabies virus glycoprotein immunized mice (Értl 2019). Dykman et al.
(2004) demonstrated the agglomeration of gold nanoparticles with the whole-surface bound half-antigen conjugates shot up the specific immunoglobulin levels in immunized animals. Further clinical investigation on hypersensitivity reactions of nanocarriers and also the antigenic structure-activity association needs to be dealt with. Inflammation is a result of the interaction of nanoparticle-immune response thus modulates the cells of immune system. Inflammation is a preliminary detection phase where upon recognising a foreign entity, immediate activation of cytokines and chemokines comes into play, disrupting the foreign particle. Nevertheless, the exact molecular mechanism of by which the immune cells trigger an inflammatory response when in contact with different types nanomaterials is still inadequately perceived. A better understanding of the structural composition the surface charges, the conformational motifs might throw light on the mechanistic functioning of inflammatory reactions. Positively charged Liposomal carriers are much better inflammation reaction inducers than the negatively charged ones. Cationic liposomes combined with polyamidoamine dendrimers were responsible for increased secretion of IL-2, Type-II Interferon and cachexin upon interaction with the human WBCs (Hattori 2016). Also, an upgraded expression of CD80/86 and maturation of dendritic cells was reported when combined with bacterial DNA by Cui and workers (2005). Liposomes have proved to be beneficial in cancer therapy as they possess anti-tumour properties. Another integral part of inflammatory responses is the balance between Type 1and 2 immunity. T helper cells 1 and 2 is triggered by

Fig. 2.2 Nanomaterial instigated immunomodulation of the immune system
inflammation, which then stimulates the cell mediated and humoral immune response primarily shielding against anaphylactic or antibody dependent immune reactions (Bal et al. 2011; Marasini et al. 2017).

Amid the nanocarrier and adjuvants used for vaccination, nanoparticles can influence both the T-helper cell type responses depending on their relative sizes. Nanoemulsions, dendrosomes and smaller particles in the range of 100–400 nm exhibits only type-1 immune response (Manolova et al. 2008). Consequently, it is extremely vital to have a detailed scrutiny on how the material configuration and its activity could influence the immune response and prevent adverse cellular reactions. A more comprehensible approach on the mechanism of nanomaterial-modulation mechanism and its effect on the immune system will help attain efficient and improve designs for vaccines.

2.2.2 Immunosuppression

Suppression of immune response by the nanomaterials might be advantageous in preventing harmful aversions, autoimmune diseases, infections, etc. Nanomaterial mediated down-regulation of immune system could help reduce severe inflammatory disorders, a few of which has been emphasized here. Dendritic polymers merged with glucosamine molecules served as an inhibitory ‘go-between’ in induction of cytokines in human phagocytic and dendritic cells that were exposed to bacterial lipoglycans (Kim et al. 2018). Lipid based engineered nanoparticles favourably conglomerate with cell adhesion molecules on the inflammation induced endothelium, thus weakening inflammatory and hyperallergic reactions in the bronchioles by depriving the lymphocytic cells to attach the adhesion molecules, thereby decreasing the local inflammatory response at the site (Mitsui et al. 2016). Likewise, solid lipid nanoparticle and butyric acid cholesteryl ester conjugates diminished the binding of lymphocytes to inflamed endothelial cells making its place into colon cancer prophylaxis (Dianzani et al. 2006). Nanosized lactic-glycolic acid polymers embedded into celestone facilitated the reduction of inflammation in arthritic rat models (Kumar et al. 2017). Buckyball’s ability to absorb electrons onto their ellipsoidal surface, thus acting as scavenging moieties to reactive oxygen species enables them to diminish reactive species generation and immunoglobulin E arbitrated signalling (Mitsui et al. 2016). When single walled carbon nanotubes were exposed to mice with pharyngeal infection, amplified activation of dendritic cells followed by phagocytic cells of the alveolus and lymphocytes were triggered to reduce the inflammation in alveolus (Nahle et al. 2020). Fascinatingly, multi-dimensional nanotubes mediate the function of T lymphocytes can therefore modulate the T cell proliferation and suppress T cell antibodies. CNT also causes the upregulation of the expression of cyclooxygenase-2 and prostaglandin endoperoxide synthase enzymes in the mice spleen. These enzymes are modulators of cellular proliferation and cell death in tumours and other forms of cancer. Transforming growth factor also play a role in immunosuppression and controls its release in the phagocytes of
alveoli. Nanoemulsions can as well have immunosuppressive responses while delivering auto-antigens in the body. Wg5EC in combination with thyroglobulin, an auto-antigenic dimeric glycoprotein, exhibited abridged T helper cell-1 and 2 responses with upregulation of enzymes like scurfin and transforming growth factor-beta and improved T cell regulation. The nanoemulsion can therefore stimulate Toll like receptors-2 and 4 (that contains myeloid differentiation primary response gene-88 and Interferon-β containing adapters which induce pro-inflammatory cytokines), control targeted antigenic delivery and modulate the immune system (Bielinska et al. 2016). Extensive research conducted on nano sized material based immunostimulation has led to the invention of various bioengineered remediation that could be tailor made to suit a particular application. Uninvited immune suppressing effect, nevertheless needs detailed inspection to understand how a nanomaterial could mechanistically confine with the body’s immunity concurrently, while conferring protection against various malignancies and infections. Therefore, scrutinizing a material for its suitability, reactivity, stability, activity, toxicity is of utmost importance to help restrict immunosuppression and deliver better biological therapeutics.

2.3 Conclusion

The merger of immunology and nanotechnology in current times have proved to be a boon to immunotherapy based preventive healthcare arena and regenerative medicine. Nanotechnology derived prophylaxis has revealed propitious outcomes in the form of vaccines, nanocarriers, nanoemulsions, liposomes, immunostimulatory complexes, nanotubules, dendrimers, etc. for targeting specific aliments. Nanomaterials with varied dimensions, structural orientation, charge, porosity, reactivity and stability exhibit immuno-compatibility that helps in designing custom made immunological responses to target a particular disease/disease. Exploring the use of ligand molecules with nano-adjuvants and carriers have considerably modulated the immune cells to identify and trigger target specific receptors. For example, the absorption process of nanoparticles with different cytokines and chemokines, that is used as vaccine carriers (to activate innate and acquired immune systems) have rendered protection against many epidemics and viral diseases. Nowadays, antibody mediated immunological replacement therapy is finding its way where nanomaterial conglomerated immunoglobulin moieties could possibly modulate and manipulate the immune system. Also, immunomodulatory stratagems for pre-clinical experiments has led to the successful development and commercialization quite a handful of nano-preparations. Nanotechnology has also contributed significantly in managing advanced ailments like HIV, neuroendocrine tumours, tuberculosis, and many more. Hence it is crucial to understand the underlying immunological mechanisms to further improve the strategy and engineering of nano based formulations for better treatment exposition.
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