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Immunological and Anti-inflammatory Properties of Nanoparticles: A Review

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Abstract:-The physicochemical characteristics of nanoparticles, including size, charge, hydrophobicity, and shape, dictate how they interact with different immune system components. The objective of creating nanoparticles is to directly target the immune system or evade the immune identification. However, determining their unintentional effects on the immune system and comprehending the mechanisms behind these unintentional effects are crucial to determine the safety profile of a nanoparticle. Although the literature has addressed the immunostimulatory qualities previously, the immunosuppressive and anti-inflammatory properties have received less attention. This review's objective is to close this gap. The present article discuss about targeted immunosuppression brought about by either immunosuppressive or anti-inflammatory medication delivery via nanoparticles or by nanoparticle engineering. Further the inherent unintentional immunosuppressive characteristics of nanoparticles will be discussed along with the potential advantages or disadvantages of such attributes

Keywords*:* Immunosuppressive; Anti-inflammatory; Nanoparticles; Immunostimulatory

1. Introduction

A increasing amount of research indicates that immunotoxicity, which is the immune system's dysregulated function, plays a role in the initiation and progression of a number of diseases, including autoimmune diseases and cancer (Merk et al., 2001; Descotes, 2004; 2012; Dobrovolskaia and Kozlov, 2005; Dietert, 2011). However, this relatively new science of toxicity did not become a significant interface between pharmacology and innovative drug creation until recently. Immunosuppression and immunostimulation are the two categories into which immunotoxic effects will be divided for the purposes of this introduction. Every one of these groups has been connected to certain negative outcomes documented in diseases affecting humans. Historically, the primary focus has been on immunosuppression; immunostimulation phase of therapeutic care. Products made with nanotechnology are complicated because they frequently incorporate macromolecules, tiny molecules, and nanoparticles. Because of this, it is acknowledged that an essential part of evaluating the safety of nanomaterials is to keep an eye on both their immunosuppression and stimulation (Dobrovolskaia et al., 2009). In contrast to medications developed from biotechnology, immunostimulation has received greater interest in nanotechnology than immunosuppression. Nanoparticles can be designed to avoid such interactions or to explicitly target the immune system. In addition to being immunoreactive themselves, they may alter immunological responses to small and macromolecular medicines (Alving et al., 1996; Perkins et al., 1997; Watanabe et al., 2008; Libutti et al., 2010; Van Beers et al., 2012). Nanoparticles and the immune system may interact in ways that are advantageous or detrimental. While nanoparticles' immunostimulatory qualitieshas just lately received more attention as new medications produced through biotechnology have entered the have previously been examined (Dobrovolskaia and McNeil, 2007; Pantic, 2011; Boraschi et al., 2012; Elsabahy and Wooley, 2013), although their anti-inflammatory and immunosuppressive qualities have received less focus. In this essay, we will examine the evidence that shows that nanoparticles have both intentional and inadvertent anti-inflammatory and

immunosuppressive effects. When immune responses are anticipated to be inhibited in order to alleviate immunological-mediated diseases, this is known as intended immunosuppression (e.g. to treat inflammatory and autoimmune disorders or to prevent transplant rejections and allergy reactions). Unintended immunosuppression is the term for an unintentional, helpful, or harmful reduction in immune function. When it helps prevent autoimmune and inflammatory diseases, unintentional immunosuppression can be advantageous. On the other hand, if it causes disorders like myelosuppression, thymic suppression, and decreased immune responses to infections, it can be detrimental and cancer. This review will address the mechanism of action as well as the immunosuppressive and anti-inflammatory characteristics linked to both nanoparticles themselves and to the medications that are conjugated with or encapsulated in them.

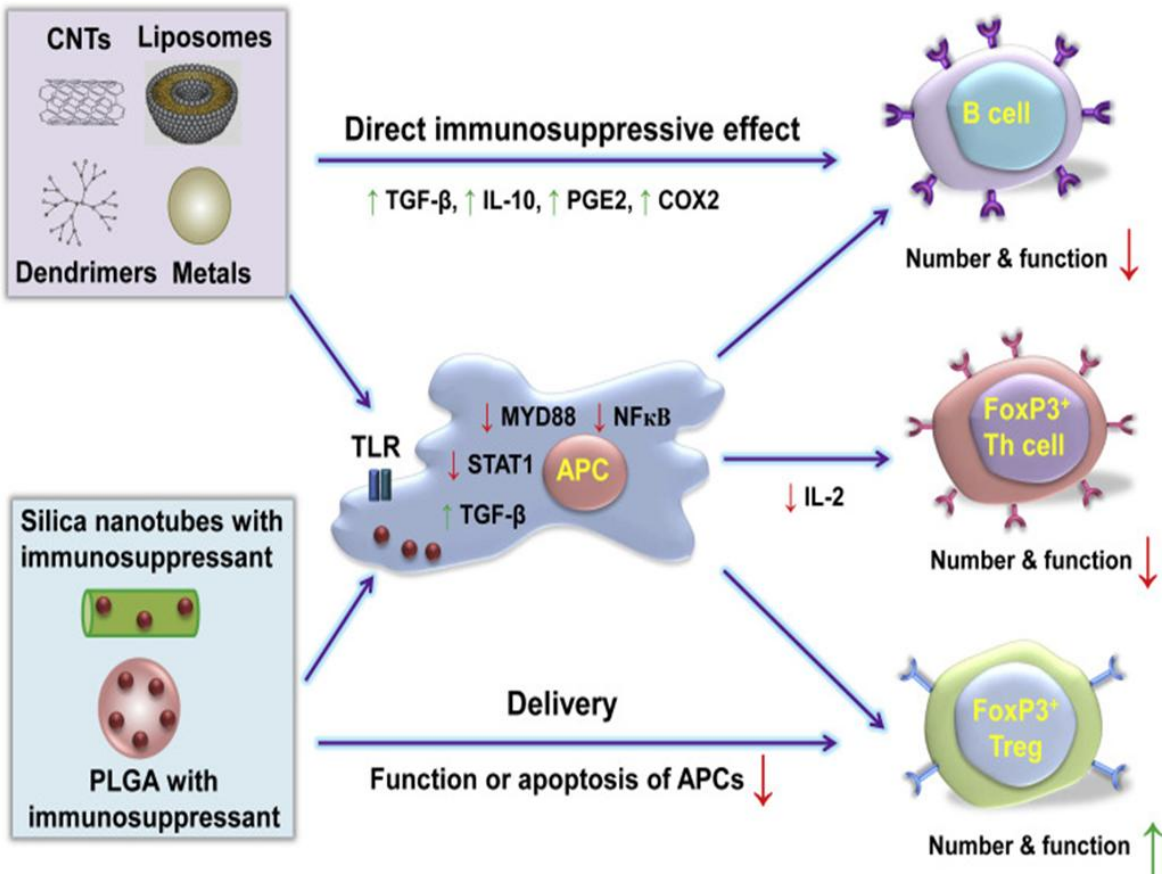

Figure : 1 Immunosuppressive and anti-inflammatory properties can be achieved by either using nanoparticles as carriers for immunosuppressive and anti-inflammatory drugs (indirect mechanism of action), or by optimizing nanoparticle properties to allow particles to suppress the immune system (direct mechanism of action). Immunosuppression and anti-inflammatory properties of nanomaterials can be either therapeutically beneficial or detrimental. Shown are examples of immunosuppressive and anti-inflammatory nanoparticles and their mechanisms of action.

Purposeful suppression of the immune system

In some cases, it may be advantageous to suppress immune system function: (i) graft rejection occurs when the immune system reacts to allogenic (foreign) antigens following organ and tissue transplantation; (ii) graft vs host disease occurs when leukocytes in transplanted tissue attack host cells as foreign antigens; (iii) autoimmunity occurs when the immune system loses tolerance to self-antigens; and (iv) allergies and atopic disorders are examples of situations where suppressing immune system function may be advantageous. However, there can be a lot of issues with the manufacture and administration of traditional immunosuppressive medications. The majority of these medications, including tacrolimus, cyclosporine, and rapamycin, have low bioavailability because they are hydrophobic. Moreover, they need solvents, which themselves have the

potential to have harmful side effects such immunotoxicities, neurotoxicities, and nephrotoxicities (Dye and Watkins, 1980; Varma et al., Van Zuylen et al., 2001; 1985). For instance, Cremophor-EL®, which is made of ethanol and polyethoxylated castor oil, has been linked to neuronal toxicity in some medications (Windebank et al., 1994; Scripture et al., 2006) and is known to induce complement activation-related pseudoallergy in sensitive people (Szebeni, 2005). Furthermore, it is thought that Cremophor-EL forms large micelles that have the potential to entrap small molecules that are administered in conjunction with drugs that are formulated with Cremophor. This could alter the biodistribution of the drugs, interfere with their efficacy, and cause off-target toxicities (Hawkins et al., 2008). The goal of reformulating immunosuppressive drugs utilizing nanotechnology platforms is to address these issues by enhancing solubility, enabling fine targeting, lowering dosages, minimizing side effects, and giving less intrusive alternative delivery methods. This section will go over some examples that show problems with conventional immunosuppressive medications and benefits from their nanotechnology-based reformulation. Based on how the immunosuppressive medications work, the available data will be covered in four areas.

Suppression of T-cells

One of the most popular targets for immunosuppressive interventions is T-lymphocytes. Interaction with antigen-presenting cells (APCs), such as dendritic cells (DC), that include co-stimulatory molecules and antigen-major histocompatibility complexes (MHC) on their surface, triggers the activation of these cells. The start of transcription and IL-2 synthesis (see Alexander et al., 2013b), a cytokine necessary for T-cell proliferation, is one effect of T-cell activation. Accordingly, T-cell activation can be stopped during antigen identification as well as signal transmission (Getts et al., 2011).

Widely used in transplant medicine for the treatment of autoimmune disorders are the fungal peptide cyclosporine A and the bacterial macrolide lactone tacrolimus, which were licensed by the US FDA in 1983 and 1994, respectively (Liu et al., 2007) In order to suppress transcription of genes producing cytokines and lower the rate of graft rejection, cyclosporine A and tacrolimus both interfere with the action of calcineurin, a factor essential for activation of the transcription factor, nuclear factor of activated T-cells (Abbas et al., 2012). These agents are usually packaged in vegetable oils (like Sandimmune® or Cipol®) or in gelatin capsules (like Neoral®) for traditional medicinal usage. Kidney damage, cardiotoxicity, and elevated blood pressure are common adverse effects of these medications (Bottiger et al., 1999; Liu et al., 2007). Dose monitoring of these medications is challenging due to their limited bioavailability, poor water solubility, and significant inter-patient variability in metabolism and excretion (Bottiger et al., 1999; Liu et al., 2007).

Some of these difficulties could be overcome by creating the (Canadas et al., 2004; Liu et al., 2007; Czogalla, 2009; Shin et al., 2010; Pople and Singh, 2012; Tammam et al., 2012) immunosuppressants into nanoparticles. As an illustration, cyclosporine's nephrotoxicity was considerably decreased in rats and in a rat model of ischemic kidney by liposomal and polymeric nanoparticle reformulation (Freise et al., 1994; Italia et al., 2007). Tacrolimus added to 75 nm lipid nanoparticles enhanced skin penetration and deposition while minimizing negative effects when compared to Protopic®'s conventional formulation (Pople and Singh, 2012). An additional instance of leveraging nanotechnology to enhance the transportation of T-cell-specific immunosuppressive medications is the research conducted by J. Azzi et al., wherein polylactide nanoparticles were employed to administer cyclosporine A ex vivo into DC (Azzi et al., 2010). The drug was delivered to the lymph nodes in vivo more easily when these drug-loaded DC were reinjected into the footpads of BALB/c mice (Azzi et al., 2010). It's interesting to note that DC was delivered to lymph nodes via nanoparticles, which shielded it from cyclosporine A's harmful effects and prevented T-cell growth. Another conventional immunosuppressive drug that inhibits T-cells in a different way than tacrolimus and cyclosporine A is rapamycin (Kahan, 2011). Mammalian target of rapamycin (mTOR) complex 1, which consists of serine/threonine protein kinase mTOR, is inhibited by rapamycin (Thomson et al., 2009). In numerous signaling pathways as well as in activities including protein synthesis, intracellular trafficking, mRNA turnover, and autophagy, mTOR serves as a crucial link. T-cell activation, proliferation, and migration are all suppressed by mTOR inhibition growth of cells positive for forkhead box P3 (FOXP3). Nevertheless, mTOR blockage affects a wide range of cells, including other immune cells, as it is not exclusive to T-cells. DC maturation, B-cell

activation, neutrophil chemotaxis, and APC absorption of antigen are all suppressed when mTOR is inhibited (Thomson et al., 2009). Patients using mTOR inhibitors have had side effects such as bone marrow suppression, renal toxicity, dose-dependent hyperlipidemias, and dermatological issues (Campistol et al., 2010; Kahan, 2011). The use of nanotechnology in the formulation of rapamycin has improved its safety profile, helped to overcome its low solubility, and increased its therapeutic efficacy (Woo et al., 2012; Chen et al., 2013; Shah et al., 2013). Transporting rapamycin via elastin-like polymeric nanoparticles have been linked to decreased injection site reactions and kidney toxicity, but in a mouse model of Sjogren syndrome—a systemic autoimmune disease that destroys exocrine glands, which produce saliva and tears—they showed therapeutic efficacy on par with, or even higher than, that of the free drug (Shah et al., 2013). After corneal transplantation, the procorneal region of the rabbits' eyes continued to receive rapamycin administered on chitosan/polylactic acid nanoparticles, which also enhanced the median allograft survival time (Yuan et al., 2008). T- and B-cells are inhibited by the traditional immunosuppressive medication mycophenolic acid (MPA). Clinically noted adverse effects frequently include nausea, vomiting, diarrhea, anemia, and leucopaenia. Extended skin grafts have been accomplished by MPA reformulation employing polylactic-co-glycolic acid (PLGA) nanoparticles or nanogel platforms reduced systemic toxicity through reduced dose-dependent survival (Shirali et al., 2011; Look et al., 2013; 2014). Furthermore, compared to conventional MPA, it has been shown that DC internalization of MPA-loaded nanoparticles leads to a greater reduction of IL-12 and IFN-γ levels. Furthermore, compared to conventional MPA, nanoparticle-formulated MPA increased the surface expression of programmed death ligand-1, a negative regulator of T-cells (Shirali et al., 2011; Look et al., 2013).

While the use of nanotechnology platforms in the reformulation of immunosuppressive drugs helps to minimize unwanted side effects, T-cell suppression can still be non-specific, making these enhanced formulations vulnerable to off-target toxicity. To further enhance T-cell suppression specificity, vaccines include nanoparticulates that create tolerance to a specific antigen have been created. By engineering nanoparticles to tune induction of the cytokine profile supporting specific T-cell subtypes, inhibit self-reactive T-lymphocytes, or exclusively increase regulatory T-cell (T-reg or FOXP3+ T-cells) subpopulations—which are essential in promoting self-tolerance and downregulating the immune response—better specificity of these nanoformulations has been achieved (Beissert et al., 2006), Below is a more detailed description of some examples of tolerogenic vaccinations based on nanoparticles that make use of these mechanisms. Polystyrene nanoparticles combined with the myelin antigen have been shown to be efficient in suppressing both the acute and relapse phases of multiple sclerosis in the mouse model of experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (Getts et al., 2012). T-cell anergy, abortive activations, and CD4+CD25+ T-cell activation were suggested as possible mechanisms causing the noted the degree of tolerance. It's interesting to note that polystyrene-myelin nanoparticles' ability to induce tolerance varied according to their size; smaller nanoparticles had a greater immunosuppressive effect than bigger ones. This effect, however, was only noticeable during the relapse and was not present during the acute period. The research revealed that the macrophage scavenger receptor, which is involved in the development of tolerance, does not recognize smaller nanoparticles. Additionally, a comprehensive comprehension of the distinctions between the acute phase and relapse remains to be established (Getts et al., 2012). To increase the production of FOXP3+ T-cells, PLGA nanoparticles coated with anti-CD4 antibody and loaded with leukemia inhibitory factor were employed. In a mouse model, these particles increased the totally mismatched graft's life duration from 7 to 12 days. of heart allografts with vascularization (Park et al., 2011). In a different study, iron oxide nanoparticles (IONPs) coated with peptides specific to diabetes were effective in reducing the mice's response to diabetic antigens when placed in the context of MHC (Tsai et al., 2010). Interestingly, the disease-induced autoregulatory cells that were increased with IONPs were both CD8+ and FOXP3−, but they also expressed CD44 and CD122, which are markers of memory cells. This study's key discovery is that the regulatory CD8+ cells suppressed the response to the pool of diabetes antigens by preferentially targeting auto-antigen-loaded APC. Another application for nanoparticles is the co-delivery of an antigen and a co-stimulatory moiety to DC. Previous research has demonstrated that 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), an aryl hydrocarbon receptor ligand, promotes T-reg production by the tolerogenic DC's induction (Quintana et al., 2010). In order to promote the development of T-regs confined to MOG35–55 antigen, Yeste et al. developed

gold nanoparticles covered with polyethylene glycol (PEG) bearing both ITE and myelin oligodendrocyte glycoprotein (MOG)35–55-specific T-cell epitope (Yeste et al., 2012). Finally, vaccines that induce tolerance to food allergens have been delivered using nanoparticles with success. Tolerance to this protein antigen was developed by oral administration of chitosan nanoparticles designed to transport DNA-encoding chicken ovalbumin (OVA). Adoptive transfer served as the confirmation of this tolerance development, which was mediated by CD4+CD25+ T-cells. A favorable shift in the cytokine profile for T-reg cell growth was also reported by the study (Goldmann et al., 2012).

Delivery of painkilling medications

The treatment of chronic inflammatory illnesses with corticosteroids has a long history (Schweingruber et al., 2011). Due to their quick removal from circulation, glucocorticoids must be administered often and at high doses in order to maintain effective blood concentrations. Consequently, it is not shocking that long-term corticosteroid use is linked to serious adverse effects. By using engineered nanomaterials as delivery vehicles, it is possible to extend the drug's circulation time, target it specifically, and control its release and retention of corticosteroids in the inflammatory tissue, thereby potentially resolving issues with the current anti-inflammatory standard-of-care (Mitragotri and Yoo, 2011). The examples that follow will show how effective nanoparticles are at delivering corticosteroids. For instance, the duration of medication circulation was extended by loading glucocorticoids onto liposomes This resulted in a lower number of injections and dose required to achieve comparable efficacy to the free drug in rat models of EAE (Schmidt et al., 2003; Linker et al., 2008) and rheumatoid arthritis (Metselaar et al., 2003; Anderson et al., 2010; Ulmansky et al., 2012). Moreover, the distribution of drugs was altered when glucocorticoids were added to liposomes. While glucocorticoids in their free form mostly worked through T-lymphocytes, their liposomal counterparts targeted macrophages, inducing an M2 phenotype that expressed anti-inflammatory cytokines (Schweingruber et al., 2011). Anti-inflammatory drugs have also been co-delivered using nanoparticles. For instance, to reduce inflammatory reactions, dexamethasone-loaded PLGA nanoparticles and siRNA targeting COX-2 were coupled (Park et al., 2012). PEGylation of the betamethasone phosphate-loaded polymeric nanoparticles extended the duration of particle circulation and higher anti-inflammatory action due to enhanced drug accumulation in the inflammatory tissues (Ishihara et al., 2009; Sakai et al., 2011).

Anti-inflammatory medication distribution has also been well accomplished with dendrimers (Kolhe et al., 2003; Chauhan et al., 2004; Na et al., 2006; Chandrasekar et al., 2007; Cheng et al., 2007). Celastrol was incorporated into G4-OH polyamidoamine (PAMAM) dendrimers, which improved drug solubility and decreased drug toxicity (Boridy et al., 2012). It is crucial to remember that the drug's original qualities may alter if it is loaded into a nanocarrier. For instance, the celastrol-conjugated dendrimer did not lose its ability to decrease NO release generated by LPS, but it did lose its ability to prevent the release of pro-inflammatory cytokines (Boridy et al., 2012). PAMAM In a rat model of arthritis, dendrimers have also been utilized to provide indomethacin and methotrexate to reduce inflammation (Chandrasekar et al., 2007; Thomas et al., 2011). Since resting macrophages do not express the folate receptor β, functionalizing dendrimers with folate as a targeted ligand facilitated the delivery of anti-inflammatory medications to activated macrophages (Chandrasekar et al., 2007; Thomas et al., 2011).

anti-cytokine manifestation

Pro-inflammatory cytokine overexpression has the potential to harm healthy tissues. Anti-cytokine strategies have therefore been created for the therapeutic management of toxicities caused by cytokines. Two primary strategies were taken into consideration: (i) blocking the interaction between the cytokine and its receptor, and (ii) lowering the expression of the cytokine gene. The former was accomplished by neutralizing the cytokine or its corresponding receptor. Delivering the cytokine or receptor antagonist to the inflammatory tissue and keeping it there was the primary hurdle with this. Some of these difficulties have been overcome thanks to the targeted moieties' functionalization of the nanoparticle surface. One way to guarantee that nanoparticles reach the locations of active angiogenesis is to coat the surface of the particles with an Arg-Gly-Asp (RGD) peptide specific to αVβ3 integrin frequently follows an inflammatory response (Scheinman et al., 2011). Anti-

inflammatory drug injections into the joints are a traditional treatment for rheumatoid arthritis. Nevertheless, only molecules larger than 100 kDa are able to achieve good retention inside the joint, whereas smaller medicines quickly depart the joint (Whitmire et al., 2012). Engineered nanoparticles have been developed to tackle this issue. Moreover, research has demonstrated that nanoparticles can more effectively penetrate the synovium than microparticles (Horisawa et al., 2002). Although it has been demonstrated that copolymeric particles containing an IL-1 receptor antagonist (IL-1RA) stay in joints longer than IL-1RA itself, the effectiveness of this design has not been investigated in an in vivo disease model. [Whitmire and others, 2012]. Glucosamine coupled to anionic production 3.5 PAMAM dendrimers inhibited the release of pro-inflammatory cytokines in response to LPS via a mechanism involving rivalry for the MD2 component of the LPS receptor complex's LPS-binding pocket (Shaunak et al., 2004; Barata et al., 2011). SiRNA silencing expression of the cytokine gene itself or of elements of the signaling pathways leading to activation of cytokine gene expression can also greatly lower cytokine output (Scheinman et al., 2011). Nanocarriers may be able to help with issues related to off-target toxicities, poor stability in biological matrices, low efficacy, and lack of targeting that are common to therapeutic delivery of siRNA. For example, siRNA that inhibits TNF-α was delivered via cationic liposomes and chitosan nanoparticles. In the mouse model of collagen-induced arthritis, both formulations improved the illness score and dramatically reduced TNF-α release [Khoury and others, 2006; Howard and others, 2009]. PLGA nanoparticles coated with RGD were employed to shield STAT1 siRNA from being broken down by serum nucleases. RGD targeting boosted the delivery of nanoparticles into the lungs and enhanced siRNA uptake in the paw tissue of arthritic mice. While the sickness advanced in all control groups, the animals treated with RGD-PLGA-STAT1-siRNA nanoparticles recovered (Scheinman et al., 2011). Inducing the synthesis of anti-inflammatory cytokines is an additional strategy to reduce the amount of pro-inflammatory cytokines. For instance, in a mouse model of autoimmune diabetes, cationic polymeric nanoparticles loaded with DNA expressing the anti-inflammatory cytokine IL-10 avoided severe autoimmune destruction of the pancreas (Basarkar and Singh, 2009). Certain nanoparticles have the ability to activate cells' anti-inflammatory signaling. Dendrimers with a cyclotriphosphazene core, for example, phenoxymethyl-methylhydrazoneIn mice with experimental arthritis, branches and capped with azabisphosphonate reduced pro-inflammatory cytokine levels and stimulated production of anti-inflammatory cytokines (Hayder et al., 2011).

Anti-cell recruitment and anti-adhesive properties

Using the cell types attracted to the inflammatory area, inflammation and the resulting tissue damage can be reduced. It is possible to prevent the recruitment of inflammatory monocytes into the damaged tissue by using nanoparticles. For instance, in mice with streptozotocin-induced diabetes (Leuschner et al., 2011), lipid nanoparticles containing the chemokine receptor CCR2-specific siRNA (for receptor nomenclature see Alexander et al., 2013a) delayed graft rejection of pancreatic islet allografts. Leukocyte migration to the sites of inflammation is first facilitated by leukocyte adhesion to endothelial cells that comprise the blood vessel walls. Adhesion molecules and carbohydrate ligands on the surface of endothelial cells facilitate the first interaction between leukocytes and these cells. Leukocyte recruitment will be inhibited if this connection is broken to the inflammatory site. For this same objective, dendrimer-like nanoparticles were employed in multiple investigations (Rele et al., 2005; Dernedde et al., 2010). For example, leukocyte adhesion was blocked through L-selectin by β-lactose functionalized poly(ethylene oxide) dendrimer-like polymers (Rele et al., 2005). Furthermore, dendritic polyglycerol sulfates decreased levels of pro-inflammatory anaphylatoxins in addition to preventing leukocyte interaction with L- and P-selectins (Dernedde et al., 2010). In a mouse model of asthma, polymerized lipid nanoparticles with P-selectin inhibitors on their surface showed anti-inflammatory properties (John et al., 2003). The effectiveness of these inhibitors may be increased by reformulating traditional anti-adhesive medications onto nanotechnology platforms, as was the case in previous examples with anti-inflammatory drugs. The cholesteryl butyrate solid lipid nanoparticles, for example, were more potent neutrophil adhesion inhibitors compared to free sodium butyrate, to endothelial cells; it was proposed that this increased effectiveness came from the solid lipid nanoparticles' quick internalization into the cells (Dianzani et al., 2006).

Inadvertent immunosuppression

The identification of undesired immunosuppressive properties of engineered nanomaterials is a crucial step in determining their safety profile, as immune system inhibition can result in thymic suppression, myelosuppression, and a decrease in host resistance to infections and cancer. It is widely acknowledged that a nanoparticle's interactions with the immune system are determined by its physicochemical characteristics. In the context of adverse immunostimulation, such structure-activity relationships have been reported for a number of immune system components, including complement activation, platelet activation, and induction of leukocyte procoagulant activity (Dobrovolskaia et al., 2012; Ilinskaya et al., 2013). Research on the immunosuppressive characteristics of nanoparticles alone, however, is limited (Chen et al., 2004; Mitchell et al., 2009; Yamashita et al., Shen et al., 2011; 2012; 2009). This could be partially explained by problems with methodology and the absence of a systematic approach. Immunosuppression influences immune system function, and determining functional alterations requires long-term, systematic, multi-parameter in vivo research evaluating multiple elements of immunity. It is not an acute toxicity that can be easily studied in vitro. Numerous in vitro studies showcasing the immunosuppressive characteristics of examined nanomaterials concentrate on a restricted range of cellular functions, primarily cytokine production and surface marker expression. As a result, the information provided is insufficient to fully comprehend the immunosuppressive capacity of nanoparticles. For instance, immunosuppressive properties are not always present in nanoparticles that stimulate the production of the anti-inflammatory cytokine TGF-β. While TGF-β inhibits lymphocyte proliferation, in the event that It also promotes the growth of T helper 17 (Th17) cells, which cause inflammation in a range of autoimmune diseases (Abbas et al., 2012). These cells release specific cytokines, such as IL-6 and IL-1. Noting the type of cell generating TGF-β is particularly crucial because different cell types—Th3 cells, M2 macrophages, and T-regs—all express this cytokine and have different roles to play. Regretfully, no study detailing the induction of TGF-β by synthetic nanomaterials made an effort to pinpoint the specific cell type responsible for this cytokine's production. Some nanoparticles can stimulate one immune function while suppressing another, which adds even more complexity to the matter. For instance, silica oxide nanoparticles inhibited the innate immunological receptor toll-like receptor 9 (TLR9; see Alexander et al., 2013b for nomenclature), which stopped immune reactions to CpG oligonucleotides, but increased production of the pro-inflammatory cytokines TNF-α and IL-1β via TLR4-mediated LPS-induced production (Lucarelli et al., 2004). We hypothesize that the various reactions observed can be attributed to the many channels via which nanoparticles enter cells and the multitude of mechanisms via which they interfere with immune cell activity. While a number of mechanisms have been proposed to link specific structural characteristics of nanoparticles to their pro-inflammatory effects, the relationship between those qualities and their immunosuppressive effects is mainly unclear (Nel et al., 2006; Dobrovolskaia and McNeil, 2007). The research on the inadvertent immunosuppression and anti-inflammatory effects of nanoparticles will be reviewed here. When we say "unintended," we mean when immune responses are suppressed or inflammatory reactions are inhibited by nanoparticles intended for uses other than immune suppression. Some of these unexpected qualities may even be advantageous while others might be unfavorable. It's not always easy to distinguish between unwanted immunosuppression that is good and harmful. This frequently relies on the model under study and the evaluation of end points (such as cytokine secretion, cell adhesion, and cell survival). When utilizing one model and/or end point, the same nanoparticles may be advantageous; yet, when using a different model or end point, they may be detrimental. We shall refer to these "dual" qualities as modulatory until additional data allowing for a foundation of precise criteria for differentiation between advantageous and detrimental unintentional immunosuppression becomes available. Due to the obvious negative effects on the immune system's ability to operate, we shall classify myelosuppression and toxicity to immune system cells as unfavorable. We also emphasize the necessity of a methodical approach in the assessment of manmade nanoparticles' immunosuppressive qualities.

Modulatory impacts

Neutralizing nanoparticles

As PAMAM dendrimers were being investigated as possible indomethacin carriers, the dendrimers' anti-inflammatory qualities were unintentionally found (Chauhan et al., 2009). In vitro experiments evaluating NO

generation and COX inhibition, as well as in vivo investigations using three distinct models—rats with adjuvant-induced arthritis, carrageenan-induced oedema, and cotton pellet test—confirmed these capabilities. Surprisingly, surface functionalization and production (i.e., particle size) were more important for PAMAM dendrimers' anti-inflammatory qualities than the core. In contrast, 1,2-diaminoethane and 1,12-diaminododecane core dendrimers of the same generation and surface functionality were identical, and only big dendrimers ended with amines and hydroxyls were able to reduce inflammation (Chauhan et al., 2009). Moreover, the generation's anti-inflammatory Concentration determined the number of amine-terminated dendrimers (Chauhan et al., 2009). This study indicated through in vitro mechanistic tests that the suppression of COX-1 (see Alexander et al., 2013c for nomenclature) and COX-2 (Chauhan et al., 2009) was responsible for the observed anti-inflammatory effect of amine- and aminoethylethanolamine-terminated PAMAM dendrimers. According to Boridy et al. (2012), a different study showed that hydroxyl-terminated G4 PAMAM dendrimers inhibited the production of LPS-triggered IL-6 by interfering with the LPS signaling pathway and p38 phosphorylation in N9 microglia cells.

Antioxidants

Certain nanoparticles have inherent antioxidant qualities, even if the toxicity of particular nanomaterials is linked to their capacity to cause oxidative stress and the production of free radicals (Nel et al., 2006). For instance, cerium oxide nanoparticles have "reactive sites" that quench free radicals because of their capacity to transition between a 3+ and 4+ oxidative state. Cerium oxide nanoparticles have the potential to decrease levels of inducible NOS (iNOS) at the mRNA and protein levels, in addition to directly quenching radicals (Hirst et al., 2009). In macrophages treated with gold nanoparticles, a decrease in NO and iNOS mRNA induced by LPS was also noted (Ma et al., 2010). Additional mechanistic research demonstrated that gold nanoparticles can disrupt the NF-κB and STAT1 signaling pathways during that preparatory phase Putting gold nanoparticles on macrophages reduced p-Akt levels and IκB-α degradation in response to LPS stimulation (Ma et al., 2010). In vitro, oxidative stress-induced cell death can be successfully prevented and levels of reactive oxygen species can be significantly lowered by certain fullerene derivatives (Chen et al., 2004). Furthermore, a few of these fullerene derivatives have demonstrated efficacy in vivo by reducing oxidative stress in rats caused by ischaemia-reperfusion (Chen et al., 2004). The primary issue restricting the use of fullerenes as antioxidants is their toxicity at high concentrations and their dose-dependence in terms of their oxidation protecting activity.

Anti-cytokine manifestation

Numerous instances of gold colloids' anti-cytokine properties have been reported. In THP-1 cells, in particular, citrate stabilized gold nanoparticles inhibited the growth of pro-inflammatory responses triggered by IL-1β (Sumbayev et al., 2012). The selectivity of this action is interesting: only an IL-1β-induced response was suppressed by gold nanoparticles, not responses elicited by TLR7/8 ligand R848 or stem cell factor. According to Sumbayev et al. (2012), the anti-inflammatory characteristics of gold nanoparticles were depending on their size, with smaller particles exhibiting more efficacy than bigger ones. Citrate stabilized gold nanoparticles have been shown in another recent work to reduce TNF-α induction caused by CpG-oligodeoxynucleotides (ODNs; Tsai et al., 2012). Ligands to other TLRs (lipoteichoic acid to TLR4, Poly I:C to TLR3, imiquimod to TLR7, and LPS to TLR4)TLR2) were also examined in this investigation; yet, Tsai et al. (2012) found that persistent suppression of TNF secretion was only shown in response to the TLR9 ligand CpG ODN. It's interesting to note that gold nanoparticles only suppressed imiquimod-induced TNF-α at one concentration (1 μg·mL−1), not at 10 μg·mL−1. According to Tsai et al. (2012), the reduction of TNF-α production in this instance was based on particle size, with smaller particles having a greater potency than bigger ones, which is in line with the IL-1 research previously described. Proteins are known to bind easily to colloidal gold. This characteristic has been exploited extensively for many years in immunoelectron microscopy, where antibodies labeled with gold nanoparticles are employed to identify cellular antigens (Baschong and Wrigley, 1990). It makes intuitive sense that the binding of gold nanoparticles could be the mechanism of cytokine inhibition to the cytokine, its receptor, or any other component essential to the signal transduction process that results in the production of cytokine proteins. It was proposed by Ivanov et al. (2007) that gold nanoparticles obstruct TLR9 trafficking and

gather in lysosomes where they attach to the high-mobility group box-1 protein, which is necessary for TLR9 activity. The variation in particle number and surface area is most likely the cause of the size-dependence that has been observed. There are more smaller-sized particles than larger-sized particles at equivalent gold concentrations. As such, smaller nanoparticles have a larger overall surface area. The specificity and concentration-dependence of the observed inhibition are more difficult to explain. Additionally, one must exercise caution when interpreting studies of cytokine inhibition because nanoparticles present may tamper with Elisa and other immunoassays used for cytokine detection in supernatants used for cytokine analysis, producing inaccurate results (Dobrovolskaia et al., 2008; Kroll et al., 2012; Guadagnini et al., 2013).

Suppression of immunity mediated by cells

Delay-type hypersensitivity (DTH) is a type IV (cell-mediated) hypersensitivity reaction that is brought on by Th1 and Th17 cells. According to Kobayashi et al. (2001), Th1 lymphocyte cytokines, specifically IFN-γ, play a major role in the development of the DTH. It has been demonstrated that various nanoparticle kinds diminish DTH via various ways. As an illustration, in the mouse model of DTH, a colloidal suspension of crystalline fullerene C60 and IONPs (Resovist®) both decreased footpad swelling brought on by methyl BSA and OVA, respectively (Yamashita et al., 2009; Shen et al., 2012). In the latter instance, a drop in IFN-γ and an increase in IL-4 production were noted in splenocytes treated with these nanoparticles, leading to the suggestion that the IONPs reduced DTH by changing the cytokine balance from Th1 to Th2 (Shen and others, 2012). Unlike Resovist, fullerene did not alter IFN-γ secretion but instead reduced IL-4 and increased TNF-α production. Moreover, fullerene inhibited the synthesis of IL-6 and IL-17, two pro-inflammatory cytokines (Yamashita et al., 2009). According to Yamashita et al. (2009), these findings imply that the immunosuppression linked to the colloidal solution of crystalline C60 is caused by an increase in T-reg cell count and an inhibition of Th17 cells. Nevertheless, in both the fullerene and iron oxide examples, the precise mechanism or mechanisms are unknown and obviously need more research.

Disruption of the typical immune response to antigens

Inadvertent immunosuppression may make a host less resistant to cancer and infections. One hour before Balb/c mice were challenged with the model antigen (OVA), a single intraperitoneal (i.p.) dose of iron oxide nanoparticles (Resovist) attenuated creation of antibodies unique to OVA. Moreover, splenocytes extracted from these animals exhibited a marked reduction in IFN-γ and IL-4 production (Shen et al., 2011). When exposed to the sheep red blood cell challenge, inhaling multi-walled carbon nanotubes (MWCNT) inhibited the generation of antibodies and the proliferation of T lymphocytes (Mitchell et al., 2009). It was hypothesised that the observed immunosuppressive effect was not due to a direct interaction between the carbon nanotubes and spleen cells because inhaled MWCNT do not penetrate the systemic circulation. Mitchell et al. showed via their series of tests that alveolar macrophages produced TGF-β in response to inhaled MWCNT. TGF-β produced IL-10 in the spleen and activated the COX pathway when it diffused systemically, which suppressed the formation of antibodies (Michell and others, 2009). Certain nanoparticles may have an impact on DC's ability to deliver antigens. It was shown that poly(vinylalcohol)-coated super-paramagnetic iron oxide nanoparticles (PVA-SPIONs) disrupted antigen processing rather than preventing monocyte-derived dendritic cells (MDDC) from absorbing antigen. This was achieved by using various fluorescent dyes conjugated to OVA. Furthermore, according to Blank et al. (2011), PVA-SPION boosted the production of the anti-inflammatory cytokine IL-10 in response to LPS and dramatically reduced the proliferation of T-cells stimulated by the autologous MDDC. It also decreased the production of pro-inflammatory cytokines (IL-1β, IL-5, IL-6, IL-12p70, IFN-γ, and TNF-α). Because they are more likely to internalize nanoparticles, phagocytic cells are more vulnerable to nanoparticle toxicity. For instance, in vitro, quantum dots aggregated in J774A.1 macrophages but not in Hepa-1 hepatocytes at non-cytotoxic concentrations. Such a buildup decreased the usefulness of J774A.1 via interfering with the regular operation of the cytoskeleton (Qu et al., 2012).

Negative consequences

Myelosuppression

In myelosuppression, the bone marrow's activity is reduced, resulting in a decrease in the amount of platelets, lymphocytes, and erythrocytes in the blood. A reduction in the bone marrow's fine activity can result in potentially fatal diseases like cancer, thrombocytopenia, anemia, and lowered resistance to infections. Bone marrow cells may be harmful to certain types of nanoparticles. For instance, antimony oxide (Sb2O3) and cobalt nanoparticles have been shown to be harmful to hematopoietic progenitors (Bregoli et al., 2009). In primary cultures of human hematopoietic progenitor cells, only two of the seven tested nanoparticles (Fe2O3, Fe3O4, Sb2O3, Au, TiO2, Co, and Ag)—Co and Sb2O3 at concentrations of 100 and 25 ppm—suppressed the formation of colonies from both erythroid and granulocytic-monocytic precursors (Bregoli et al., 2009) Another frequent dose-limiting effect of cytotoxic cancer medications is myelosuppression. The primary goal of employing nanoparticles to deliver cytotoxic medications is to reduce the toxicity of the latter by dose reduction, delayed release, and specific targeting. Not every nanoparticle, though, is able to accomplish this. A drug's toxicity may be increased if a nanoparticle carrier is toxic to bone marrow. Cobalt and antimony nanoparticles in the aforementioned scenario would not be appropriate for the delivery of cancer drugs (Bregoli et al., 2009). It's also important to remember that, while nanoparticles by themselves might not injure bone marrow cells, their altered biodistribution may intensify the myelosuppressive effects of the medications they transport. Doxorubicin conjugated to polyisobutyl, for instance compared to the free drug, (PIBCA) and polyisohexylcyanoacrylate (PIHCA) nanoparticles exhibited a much higher myelosuppressive effect (Gibaud et al., 1994). Furthermore, the myelosuppression's intensity varied depending on the carrier and was higher in PIHCA nanoparticles than PIBCA ones. This regrettable outcome resulted from conjugated doxorubicin building up and being retained in the spleen and bone marrow as a result of increased phagocytic cell absorption of the particles. It is well acknowledged that passivation of nanoparticle surfaces using hydrophilic polymers, like PEG, is a dependable technique to make nanoparticles more "stealthy," which reduces accumulation in mononuclear phagocytic cells. It makes intuitive sense to design nanoparticles to prevent myelosuppression by avoiding greater phagocytic absorption, which causes an increase in myelosuppression of cytotoxic medicines.

Injurious effects on immunological cells

Various kinds of main Different immune cells may respond differently to the same type of nanoparticle. For instance, ZnO nanoparticles, which are frequently found in sunscreens and cosmetics, are hazardous to monocytes but have no effect on lymphocyte viability (Hanley et al., 2009). When exposed to the same amount of nanoparticles, NK cells exhibit greater sensitivity to ZnO than T and B lymphocytes, but lower sensitivity than monocytes (Hanley et al., 2009). Another study (Andersson-Willman et al., 2012) showed that ZnO nanoparticles were highly cytotoxic to MDDC at concentrations that led to modest toxicity in human peripheral blood mononuclear cells (PBMC), which largely supported these findings. Since the viability of different cell types in PBMC was not assessed in this investigation, it is difficult to determine whether the toxicity seen in bulk PBMC resulted from the impacts of nanoparticles on monocytes only, or if lymphocytes were also impacted? (Andersson-Willman et al., 2012). According to Kao et al. (2012), the mechanism of toxicity was ascribed to the dissolution of ZnO nanoparticles, which raised the concentration of Zn ions inside the cells and consequently caused mitochondrial malfunction, which in turn prompted apoptosis. TiO2, a different metal oxide nanoparticle, was shown to significantly depress the immune system in vivo but not to be lethal in vitro (Moon et al., 2011; Andersson-Willman et al., 2012). The systemic delivery of TiO2 nanoparticles was linked to increased vulnerability to a melanoma challenge and suppressed T-cells, B-cells, macrophages, and NK cells (Moon et al., 2011; Andersson-Willman et al., 2012).

Conclusion and recommendations for the future

Studies reveal that nanoparticles have the ability to either trigger or repress the immune responses. Their surface chemistry and physicochemical characteristics plays a major role in determining how well they interact with the immune system. By purposefully altering the physicochemical characteristics of nanoparticles and utilizing them as carriers for immunosuppressive and anti-inflammatory drugs, engineered nanomaterials can have

immunosuppressive and anti-inflammatory effects. On the other hand, systematic structure–activity relationship (SAR) investigations are required to improve this field of nano immunology. Future research should concentrate on understanding the processes underlying nanoparticle-mediated immunosuppression as well as identifying critical components (viz dosage, mode of administration, physicochemical qualities, and composition) that initiate immunomodulatory effects, in addition to SAR investigations. It is crucial to comprehend why the identical nanoparticle acts as an immunostimulant in one model and as an immunosuppressive one in another. This will assist scientists working on drug delivery formulation selecting the right nanoparticle carriers. And will undoubtedly progress the quickly expanding subject of nano immunotoxicology.

Conflict of interest

The authors declare that they do not have conflicting interest.

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