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Engineered Nanomaterials for Immunomodulation: A Review

Ragini Singh, Mamta Kumawat, Himanshu Gogoi, Harishkumar Madhyastha, Eric Lichtfouse, Hemant Kumar Daima

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host immune system to persuade an immune response, which can be either immunoinflammatory or immunosuppressive.^{20,25,26} The nanomaterials can mediate subtle or robust changes within the immune system, like affecting immune cascade pathways, modulating gene regulations, altering cellular mobility, and even regulating cellular and physiological changes.^{27–29} In this context, potassium chloride nanoparticles have been reported to induce immunogenic cell death in cancer immunotherapy via altering the osmotic pressure and thus inducing hypotonic conditions.⁵ Therefore, monitoring the immunomodulatory behavior of nanomaterials is extremely important for their safety assessment and biomedical implementations. While major research related to nanomaterials has focused on deliverables, the underlying mechanism of nanomaterial evoked immune response is yet to be deciphered in detail.

The immunoinflammatory properties of different types of nanomaterials have been extensively utilized in pharmaceutical applications like vaccine delivery and antitumoral therapeutics.^{30–32} The nanomaterials-based vaccines or drug delivery have been highly successful as the most recent FDA approved therapeutic to deliver cytarabine and daunorubicin to treat acute myeloid leukemia (VYXEOS), hafnium oxide nanoparticles to treat locally advanced squamous carcinoma in the cell (NBTXR3/Hensify), and to deliver Spike-mRNA in Covid vaccines.^{33–40} Apart from the applications, over 20 nanomaterial-based formulations are currently prescribed to treat various cancers, fungal infections, kidney diseases, and even imaging purposes.^{41–48}

Nevertheless, nanomaterial-mediated immunostimulatory effects sometimes act as a double-edged sword, and they have been associated with diverse side-effects like hypersensitivity, inflammation, toxicity, inhibition of phagocytic ability of antigen presenting cells (APCs), and anaphylaxis.²⁸ Further, recent human and animal studies have demonstrated biological dispersal of nanomaterials in liver, heart, spleen, kidney, and brain upon oral and inhalation exposure.⁴⁹ Moreover, during metabolism, nanomaterials have been observed to congregate on the liver and inhaled nanomaterials in the lungs. Considering the estimated half-life of nanoparticles to be 700 days, they can result in a consistent threat to the tissues and organs.⁵⁰ Contemporary studies related to nanomaterial noxiousness have identified their diverse properties (i.e., particle size, surface charge, and crystallinity) in correlation with their cellular toxicity.^{51–56} The toxicity also tends to induce structure damage to mitochondrial, depolarization of mitochondrial membrane, deoxyribonucleic acid (DNA) damage, lactate dehydrogenase (LDH) overproduction, electron transport chain impairment, alteration in gene responses involved in apoptosis, and cellular ion dysregulation.^{57–62}

Remarkably, suppression of the immune system is desirable in numerous medical applications like (i) autoinflammation or autoimmunity, when the immune system reacts to self-antigens, (ii) organ or tissue transplant to avoid graft rejection, (iii) post pathogen infection to dampen the inflammatory response, and (iv) reduction of the inflammatory response in lieu of exposure to environmental and dietary irritants. Nanomaterial-mediated immune suppression can be categorized as either “direct immune suppression” or ‘indirect immune suppression’. In the context of indirect immune suppression, nanomaterial-mediated delivery of immunosuppressive drugs like cyclosporine, tacrolimus, and sirolimus

are under evaluation.^{63–68} Reformulation of these drugs with nanotechnology platforms has alleviated the toxic side-effects, inferior bioavailability, and poor water solubility. Most of the studies related to immune suppression have relied on the delivery of immune-suppressive drugs using nanoparticle-based delivery vehicles, while direct immune suppression has been assessed for engineered physicochemical properties of nanomaterials to directly interact with the immune system. The engineered properties of nanomaterials can induce anti-inflammatory and immune-suppressive responses in complement to immunosuppressive drugs.

Herein, metal nanoparticles like gold, metal oxide nanoparticles like iron and cerium, and carbon-based nanomaterials like carbon nanotubes (CNTs) and fullerenes have demonstrated the potential to mount an anti-inflammatory response by the induction of immune-suppressive cytokines, transforming growth factor- β , sequestering reactive oxygen species (ROS), generation of regulatory T cells, reduction of T helper type 1 (Th1) response, and reduction of T helper type 2 (Th2) allergic response against ovalbumin sensitization.^{69–71} However, the same nanoparticle preparations have also been reported to induce a pro-inflammatory response.^{72–76} Therefore, further analyses pertaining to surface characteristics, route of exposure, and experimental model need to be optimized to reach a conclusive opinion. Nevertheless, fundamental studies about nanoparticle-mediated immune-stimulatory properties have contributed to understanding and development of this important area of medicine.^{77–79}

Realizing the importance of nanomaterial-mediated immune responses and their potential role in medicine, in this review, existing up-to-date knowledge of nanoparticle-mediated immunomodulation has been provided. Herein, in-depth discussion about the essential surface and physicochemical properties of nanomaterials, which are important to exhibit a controlled immune response, has been discussed. Moreover, attempts are made to explore the signaling pathways and to interpret the mechanism of action shown by the engineered nanoparticles. Later, the focus is on the existing setbacks associated with nanotechnology-mediated immunostimulant and immunosuppression performances. Finally, perspectives for better understanding of nanoengineering toward immunomodulation and development of target-oriented nanomaterials are suggested with experimental model analysis and potential application in nanomedicine.

2. THE IMMUNE SYSTEM AND NANOMATERIALS

The immune system is categorized as innate or adaptive because of the mechanism of action. The innate system has been considered a nonspecific immune response, and it destroys foreign elements upon interaction with them. The innate immune system contains neutrophils, mast cells, macrophages, and dendritic cells, and it reacts primarily by engulfing foreign particles and cytokines release. The adaptive immune system responds by specialized B cells or T cells. In the innate immune system, phagocytic cells serve as APCs and supply specific antigens to B and T cells for their degradation and removal.⁷⁹ Presently, various nanoparticle-based formulations exert significant impact on the immune system by explicitly interacting with immune cells and molecules. In immunized mice, nanomaterials exposure induces a high serum level of antigen-specific Immunoglobulin G (IgG) and is known to involve the complement system and toll-like receptors, or both.^{80,81}

Even though reports show that nanoparticles may cause inflammation, this is not necessarily an indicator of toxicity. In several ways, the nanoparticles can intermingle with the immune system and may elicit inflammation due to the involvement of macrophages, neutrophils, and other effector cells. Nevertheless, it is crucial to differentiate chronic and acute inflammation to analyze their severe effect over human health.⁸² An early and short-term response of the body to adverse stimuli is known as acute inflammation, whereas in chronic inflammation, the body transmits inflammatory cells even in the absence of an outside danger. The chronic inflammation may last for several months or years. Studies have revealed that nanoparticles can also induce inflammasome activation in macrophages, which is a multiprotein complex and serves as an innate immune system-mediated inflammatory response.⁸³ In addition, a few caspases like caspase-1, -4, -5, and -12 in humans and caspase-1, -11, and -12 in mice activate the inflammatory responses in combination to inflammasomes. Thus, studies regarding activation of “noncanonical” inflammasomes are expected to open new avenues to explain the inflammatory effect of nanomaterials. Besides, nanomaterials exposure can also upregulate the production of inflammatory cytokines via dendritic cells. Negatively charged polyethylene glycol-coated gold nanoparticles are reported to enhance production of TNF- α in human blood monocyte-derived dendritic cells, whereas positively charged poly(vinyl alcohol)-coated gold nanoparticles induce production of IL-1 β in the presence of lipopolysaccharide.⁸⁴ However, attention has been limited regarding the inflammatory effect of such nanoparticles due to the presence of lipopolysaccharide, which is ubiquitously present as a contaminant. Various reports suggest that extreme and frequent exposure of nanomaterials can alter the gut microbiota, which, in turn, has potential to modulate the inflammatory activity and epithelium integrity of the intestine. Nanoparticle exposure reduces the short chain fatty acid (SCFA)-producing bacteria, which play an essential role in regulation of gut immunity and thus disturbing the immune homeostasis to stimulate inflammation.⁸⁵ Nanomaterials such as silver nanoparticles, graphene oxide, and CNTs have been reported to disrupt the gut microbiota, and they can increase the level of inflammatory cytokines IL-1 β , IL-6, and TNF- α and upsurge intestinal permeability.^{86,87} Likewise, adsorption of different biomolecules on nanoparticles may affect the plasma protein folding, and it can be recognized by immune cells to induce significant inflammatory reaction.⁸²

On the contrary, due to the important role of macrophages in several pathogenic processes, different nanomaterials have been investigated for their interaction with macrophages. Nanomaterials decorated with ligands such as peptides or monoclonal antibodies can specifically bind to the receptors, which are overexpressed at the macrophage surface. Nanomaterials exposure to macrophages can cause monocyte mobilization, polarization modulation, bone marrow activation, and microvascular permeability enhancement. In the treatment of inflammatory diseases, nanomaterials can efficiently target various inflammatory monocyte production stages. In this context, nanomaterials loaded with corticosteroids and CCR2 siRNA have revealed bone marrow activity modulation under an inflammatory response. The nanomaterials interaction reduces monocyte accumulation at inflammation sites and suppresses occurrence of myocardial infarction, atherosclerosis, and pancreatic islet transplantation in diabetes.^{7,88} Chronic inflammation induces mobilization of macrophages via differ-

ent chemokines like CCL2 and CCL7 and their accumulation at the site of inflammation.^{89,90} Consequently, nanomaterials can directly affect the mobilization and localization of macrophages and thus serve as anti-inflammatory agents. Recently, zinc oxide nanoparticles have been shown to induce metabolic reconfiguration which in turn stimulates the macrophage polarization of THP-1 cells toward classical activation.⁹¹

Taking all of this into consideration, the active participation and accumulation of neutrophils in acute inflammation has been investigated postinteraction with nanoparticles. In the recent past, a range of nanomaterial formulations are reported to efficiently inhibit the migration and proliferation as well as depletion of inflammation-related neutrophils.⁹² For example, pH-responsive doxorubicin conjugated albumin nanoparticles have been shown to target and deplete the activated neutrophils. Further, it has been indicated that nanomaterials internalized in neutrophils were cleaved in the acidic environment to release doxorubicin, which induces apoptosis in neutrophils. This can be efficiently used in acute inflammation. Nanoparticles with neutrophil membrane coatings acquire some characteristics that are similar to those of normal neutrophils. They could target inflamed cells, evade immune surveillance, and combat pathogenic molecules. For the management of inflammatory diseases, neutrophil imitating nanoparticles have consequently been considered as an essential therapeutic approach.⁹³

In the context of above, polymeric nanomaterials coated with a neutrophil membrane are developed for treatment of rheumatoid arthritis as displayed in Figure 1.⁶ In a collagen-induced arthritis mouse model and a human transgenic mouse

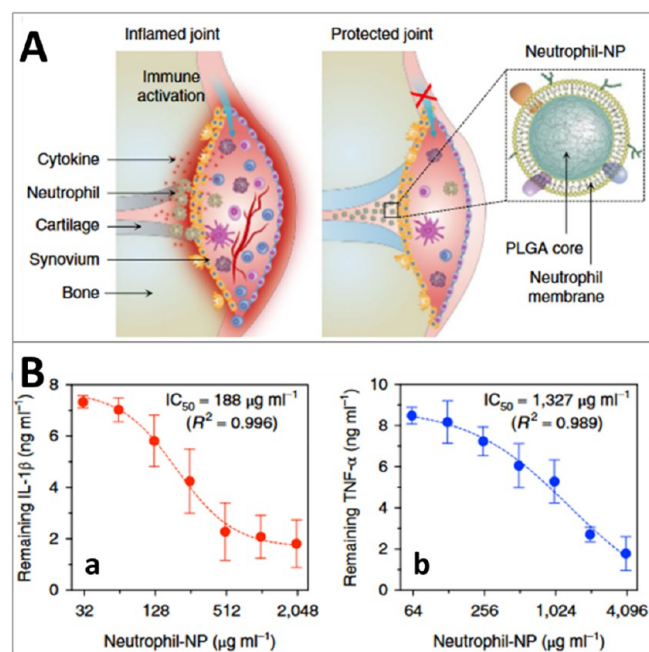


Figure 1. (A) Neutrophil-nanoparticles are intended to reduce joint degeneration and synovial inflammation in inflammatory arthritis. Natural human neutrophil membranes are used to encase polymeric cores to create neutrophil-nanoparticles, mimicking source cells to bind immunoregulatory molecules without amplifying immune cascades that enhance disease. (B) Binding capacity of human neutrophil-nanoparticles with (a) IL-1 β and (b) TNF- α . Adapted with permission from ref 6. Copyright 2018, Nature.

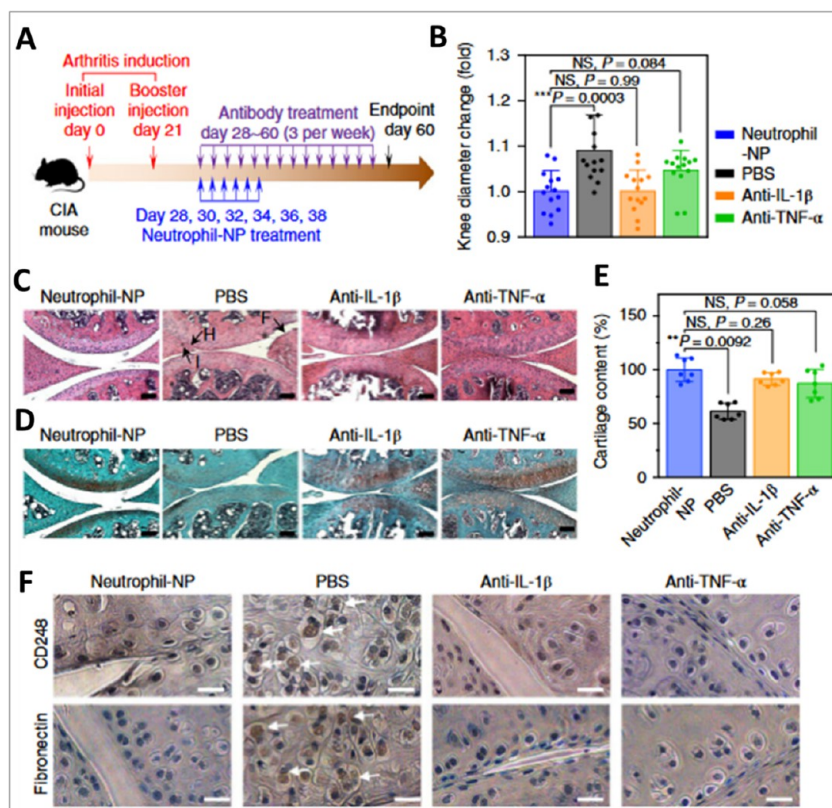


Figure 2. (A) The treatment strategy was studied using a collagen-induced arthritis (CIA) mouse model. (B) Change in hind knee diameter from day 0 to day 60 following the CIA introduction. (C, D) Knee section of neutrophil-nanoparticles, phosphate buffer saline (PBS), anti-IL-1 β antibody, or anti-TNF- α antibody-treated mice stained with hematoxylin, eosin, and safranin-O. (E) Using safranin-O-stained sections of mice from distinct treatment groups; the cartilage content was measured. (F) Pictorial representation depicting immunohistochemical staining on sections of a mouse knee treated with different groups for CD248 and fibronectin. Scale bars: 10 μ m. Adapted with permission from ref 6. Copyright 2018, Nature.

model, the advanced nanomaterials could efficiently suppress synovial inflammation, neutralize pro-inflammatory cytokines, and target deeply in the cartilage matrix to offer chondroprotection for joint damage. The neutrophil-nanoparticles were expected to resemble the source cells by showing neutrophil plasma membranes on their surface, thereby binding with immunoregulatory substances that otherwise target endogenous neutrophils (Figure 1A). The potential of human neutrophil-nanoparticle binding capacity to IL-1 and TNF is examined, which plays a key role in the onset and progression of rheumatoid arthritis. The Hill equation was used to calculate the neutrophil-nanoparticles half-maximum inhibitory concentration (IC₅₀), which was found to be 188 and 1327 g mL⁻¹ for IL-1 and TNF, respectively, based on the measured binding kinetic profiles as shown in Figure 1B.

Additionally, employing a collagen-induced arthritis mouse model, neutrophil-nanoparticle's ability to prevent joint damage was investigated. When arthritis was induced in collagen-induced arthritis mice, the knee joints where mouse neutrophil-nanoparticles were introduced began to expand slightly, as shown in Figure 2A. As in controls, mice received injections of phosphate buffer saline (PBS), anti-IL-1 β , or anti-TNF- α . The transverse knee diameter of mice given neutrophil-nanoparticles injections at the study's end point was akin to that of animals given anti-IL-1 β or anti-TNF- α treatment, but much lower than the phosphate buffer saline group, indicating a decrease in cellular influx and edema formation as displayed in Figure 2B. The mice's knee joints

were also divided into sections for histological examination. The neutrophil-nanoparticles group's hematoxylin and eosin (H&E)-stained sections revealed chondrocyte's uniform distribution without any clear signs of degradation in the articular cartilage. In contrast, the control group had a significant neutrophil infiltration in the synovium and joints, and chondrocytes were largely absent. Anticytokine-treated groups displayed reduced neutrophil infiltration but mild chondrocyte hypertrophy and depletion as represented in Figure 2C. Sections stained with safranin-O revealed that the cartilage of the neutrophil-nanoparticles group had more sulfated glycosaminoglycans (sGAGs) than that of the control group, but similarly to that of the anticytokine groups (Figure 2D and E).

Besides, the fibroblast-like synoviocyte phenotype in the synovial inflammatory lining was investigated. Herein, specifically stained fibroblast-like synoviocytes for CD248 and fibronectin expression are used, since these molecules have been shown to upregulate IL-1 β and TNF- α . The aggressive phenotype that enters the extracellular matrix to provoke joint destruction in rheumatoid arthritis is indicated by an elevated expression of these markers. As witnessed in Figure 2F, the neutrophil-nanoparticles group had poor CD248 staining and few positively stained cells in the synovium, but the control group's sections had a significant number of CD248-positive cells. Control group joints, neutrophil nanoparticles, and anticytokine groups' synovium did not contain any fibronectin-positive cells.

Table 1. Different Types of Nanomaterials and Response Shown by the Immune System after Interaction with Nanomaterials

Nanomaterials	Immune response	ref
Titanium dioxide nanoparticles	Monocyte activation, inflammation, histamine release, apoptosis and necrosis induction in macrophages, ROS production.	101
Zinc oxide nanoparticles	Induces inflammation and stimulate apoptosis via ROS production.	102
Cerium oxide nanoparticles	Anti-inflammatory effect, reduce ROS production, inhibit release of pro-inflammatory cytokines in murine macrophages, activates APCs for production of IL-10 to induce T-cell proliferation with Th2 dominance.	2
Iron oxide nanoparticles	Stimulate release of transforming growth factor- α , immunoglobulin E (IgE), cytokines IL-2, -12, -4, and -5, and pro-inflammatory cytokines, induction of T regulatory cell expansion, depletion of autoreactive B cells, inhibiting CD4 ⁺ T cells.	98, 103–105
Silicon dioxide (silica) nanoparticles	Macrophage polarization modulation, no inflammatory cytokines production in RAW 264.7.	106
Gold nanoparticles	Anti-inflammatory effects induce apoptosis, oxidative stress, liver inflammation, and release of IL-1 α , -1, -2, -4, -6, -8, and -10. Accumulate in macrophage and Kupffer cells, modulation of macrophage polarization, and depletion of autoreactive T cells.	99, 107–109
Silver nanoparticles	Induces immunotoxicity, ROS production and inflammation.	110
Carbon nanotubes	Induces immunosuppression by releasing prostaglandins, IL-10, CCL11, IL-6, interferon (IFN), IL-13 and transforming growth factor- β , intravenous injection of multiwalled carbon nanotubes (MWCNTs) induces Th2 mediated immune response, increases the quantity of CD4 ⁺ and CD8 ⁺ T lymphocytes in mouse spleens.	111
Graphene	Induces Th2-facilitated immune response and release of IL-5, IL-13, and IL-33.	112
Quantum dots	Induces ROS generation and causes immunosuppression via reducing TNF- α , Kc/CXCL-1, and IL-8.	113
Lipid-based nanomaterials	Inflammatory effect, stimulation of immune response by IFN - α , T lymphocyte cytotoxicity, modulation of monocyte recruitment.	79, 114
Liposomes	Monocyte production inhibition, egression in bone marrow, macrophage depletion.	7, 115
PLGA nanoparticles	Reduces IL-1 β and TNF- α level, neutralization of endotoxins, proinflammatory cytokines, and pathogenic cytokines.	6, 116, 117

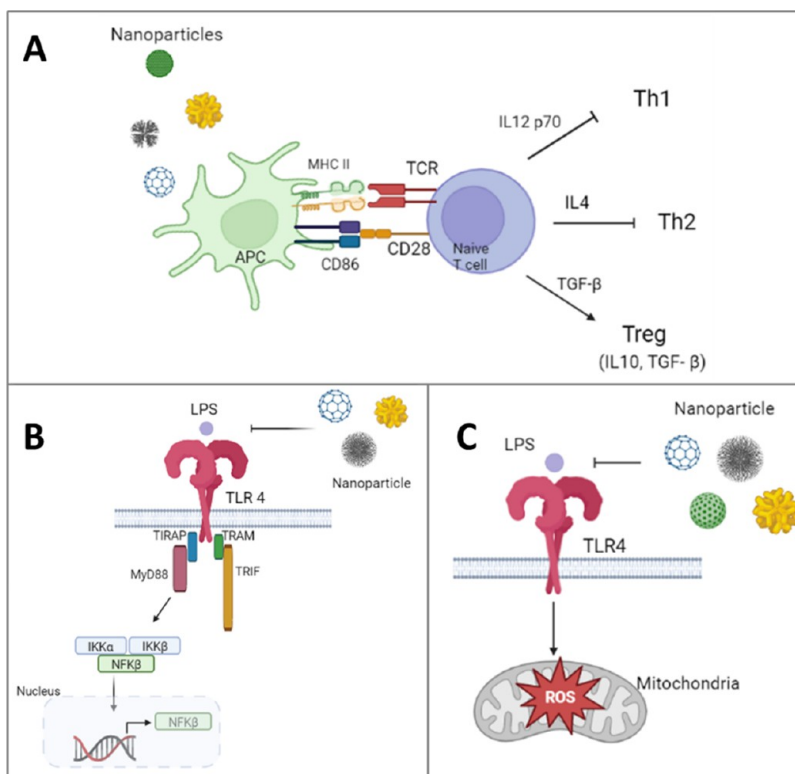


Figure 3. (A) Illustration of mechanism of action for induction of the immune-suppressive environment. Gold nanoparticles, C₆₀ fullerenes, dendrimers, and PLGA nanoparticles suppress production of IL-4 and IL-12p70 cytokines limiting Th2 and Th1 CD4⁺ T cell proliferation and induces IL-10 and transforming growth factor- β (TGF- β) producing regulatory T cell. (B, C) Possible mechanism of action of suppression of the inflammatory response. C₆₀ fullerene, gold nanoparticles, and dendrimers inhibit lipopolysaccharide (LPS) mediated nuclear factor kappa (NF- κ B) transcription, pro-inflammatory cytokines, and mitochondrial ROS production by obstructing toll-like receptor-4 pathway.

In recent times, the emphasis is on coronavirus-induced neutrophil-related inflammation and pro-inflammatory cytokine release.^{94,95} It has been confirmed that exogenously administered DNase-1-conjugated polydopamine-poly(ethylene glycol) nanoparticles efficiently suppress the cytokine elevation and neutrophil activity.⁹⁶ Treatment with

nanoformulations indicates a significant reduction in inflammatory cytokine level and neutrophil cell count, which in turn enhances the survival rate. Further, nanomaterials interact with lymphocytes to modulate immune response during inflammatory diseases treatment. It has been proven that the development of poly(lactide-co-glycolide) nanomaterials con-

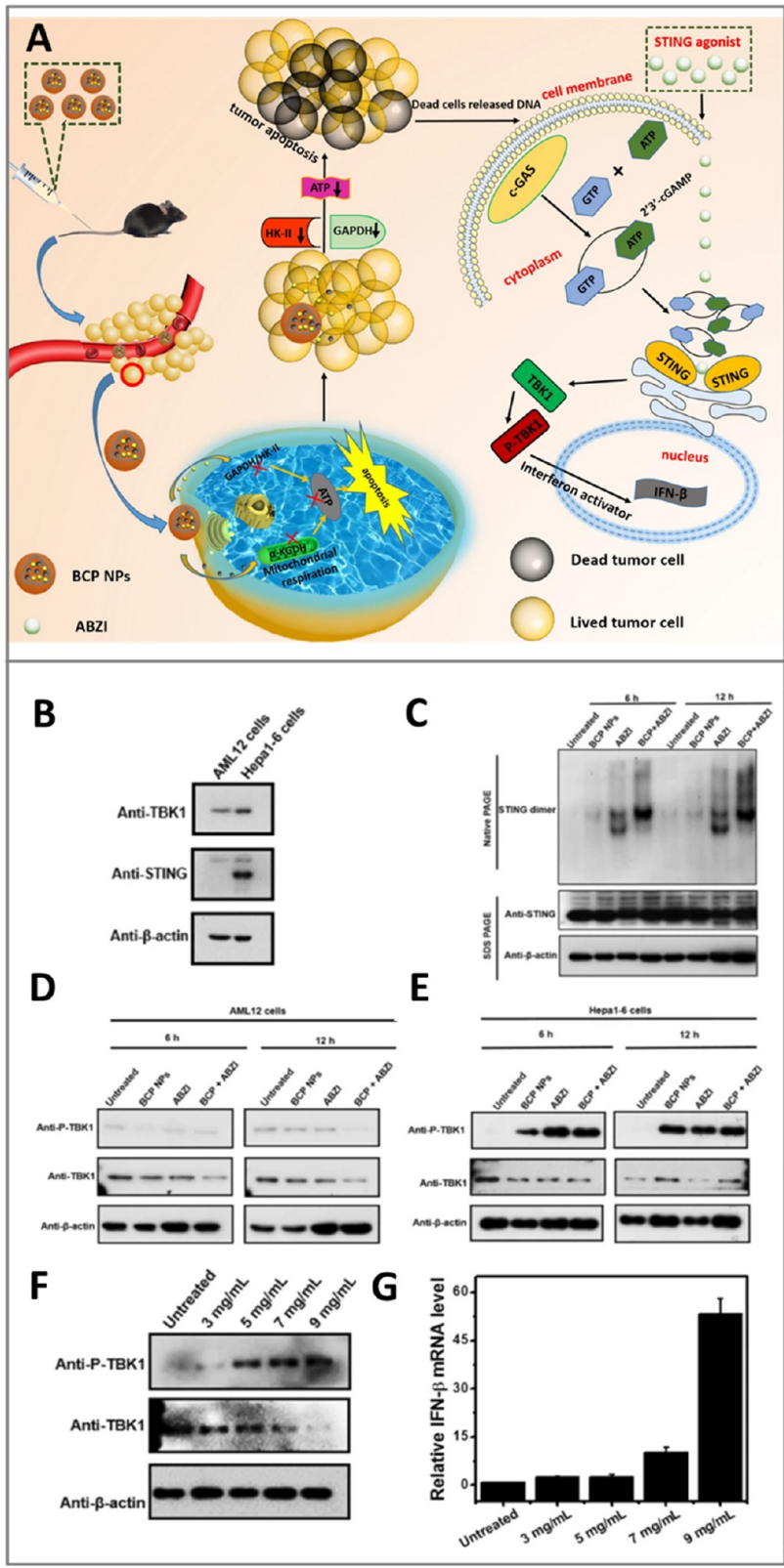


Figure 4. (A) Schematic showing the antitumor activity of CPI-613 and 3-bromopyruvate (3-BPA) conjugated BCP nanoparticles. (B) Western blotting of TBK1 and STING in AML12 and Hepa1-6 cells. (C) STING dimerization effects in Hepa1-6 cells treated with BCP nanoparticles, amide benzimidazole (ABZI), and BCP nanoparticles + amide benzimidazole. (D) Effects of BCP nanoparticles, amide benzimidazole, and BCP nanoparticles + amide benzimidazole-treated Hepa1-6 cells-activated TBK1 in AML12 cells' phosphorylation. (E) Hepa1-6 cells and (F) Hepa1-6 cells treated with BCP nanoparticles triggered the phosphorylation of TBK1. (G) Hepa1-6 cells incubated with BCP nanoparticles show the relative production of IFN- β . Adapted with permission from ref 133. Copyright Creative Commons Attribution 4.0 International License.

tain encapsulated antigen [PLG(Ag)] for treatment of Th2-mediated allergic airway inflammation. A specific nanoformulation can significantly suppress the ovalbumin-induced response and inflammation both prophylactically and therapeutically.⁹⁷ Additionally, iron oxide nanoparticles can suppress the lung inflammation induced by ovalbumin, and they can lower the production of IL-5 and IL-13, thus slowing the differentiation and expansion of CD4⁺ T cells.⁹⁸

Depletion of T lymphocytes is another important way by which nanomaterials exert anti-inflammatory effects. In one of the studies, methotrexate drug conjugated gold nanoparticles exhibited a superior anti-inflammatory effect in comparison to methotrexate alone by significantly reducing the gamma delta ($\gamma\delta$) T cells, CD4⁺ T cells, and neutrophils.⁹⁹ Further, it is explained that nanoformulations can significantly reduce the proliferation and keratinocyte differentiation. The engineered nanomaterials act on the immune cells directly by blocking the proliferation of T cells, apoptosis promotion, and diminishing Th1 and T helper type 17 (Th17) cytokine production. Other than this, autoreactive B cells are known to secrete autoantibodies, and they are also involved in various inflammatory diseases.¹⁰⁰ Thus, the current nanomaterial strategy majorly focuses on the depletion of autoreactive B cells to manage inflammatory conditions. Table 1 and Figure 3 show the responses of the immune system to different nanomaterials.

Beyond the cellular components, several other molecules such as cytokines (IL-1, -6, and TNF- α) and enzymes (proteases and lipases) are also responsible for inflammatory conditions. Nanomaterials can affect these inflammation-related molecules either by modulating their production through altering source cells or by direct contact like neutralizing effect, absorption, energy, etc. The neutralization of endotoxins and proinflammatory cytokines in a sepsis model has been achieved by macrophage membrane-coated nanomaterials.¹¹⁶ Various investigations have revealed the development of melanin-based nanomaterials to scavenge reactive oxygen and nitrogen species and inhibit the production of proinflammatory cytokines like IL-1 β , and thus display an anti-inflammatory effect.^{118,119}

On the divergent side, a few reports have suggested that exposure of nanomaterials shows no significant effect on intestinal immunity due to their rapid excretion. It has been reported that mice fed zinc oxide (ZnO) nanoparticles (1600 mg/kg chow) for 270 days straight had no detectable particle dispersion in the gastrointestinal tract. Therefore, it has been recommended that there is not a generic influence on biodistribution and accumulation; rather, it should be unique to each nanomaterial.¹²⁰

3. NANOMATERIALS-MEDIATED ANTI-INFLAMMATORY RESPONSE AND IMMUNE SUPPRESSION

Immunosuppression can be defined as effective reduction of the immune system in response to either drug or other materials, which influences the onset and enhances disorders like cancer and autoimmune diseases. Herein, the innate immunity encompasses macrophage and neutrophil activation to secrete cytokines, thus leading to production of local inflammation. This kind of inflammation is typically followed by the adaptive immune response, which stimulates antigen specific T and B cells.¹²¹

In this context, various types of nanomaterials with engineered physicochemical assets have the potential to

modulate the immunological response. Upon interaction with biological fluids, proteins, and biomolecules, nanoparticles tend to form surface protein corona, which alters physicochemical assets of nanomaterials.¹²² Further, the engineered properties like shape, size, surface charge, surface roughness, and surface chemistry of nanomaterials also have significant effects on the immunological responses. Regardless of the core material, the smaller the particle size is, the greater is the material's capacity to penetrate biological barriers and provoke an inflammatory reaction.^{123,124} The engineered nanomaterials are reported to carry and locally deliver immunosuppressive agents. In addition to the above beneficial effects, the interaction between nanomaterials and the immune system can be adverse in nature if the nanomaterials are not designed with desired properties. For example, *in vitro* experiments have revealed that nanomaterials can trigger the production of ROS in lung epithelial cells and macrophages leading to possible lung injury. Thus, the properties of nanomaterials need to be viewed very carefully before proposing, and the properties must be tailored for the end applications.^{125,126}

Immunosuppression or immunosuppressive agents can be beneficial when they promote the inhibition of inflammatory or autoimmune conditions.¹²⁶ Inflammation is the defense mechanism originating from infectious or physical agents, ROS, and metabolic stress. However, in certain conditions, the inflammatory processes become detrimental and lead to the progression of many prevalent conditions ranging from cardiovascular, rheumatoid arthritis, osteoarthritis, sepsis to genetic diseases.^{127–130} Motivated from the above beliefs, various nanomaterials have been specifically engineered to regulate the pro- and anti-inflammatory responses *via* preferentially targeting the tissue from the administration site. It can be achieved due to the modulation of nanomaterials to pass through the metabolic barriers without affecting the healthy cells and tissues.^{131,132}

Recently, 3-bromopyruvate (3-BPA) and CPI-613 conjunctively combined BCP nanoparticles are revealed to act as immune activators for effective immunotherapy-based tumor suppression as shown in Figure 4A.¹³³ The BCP nanoparticles activate the stimulator of interferon genes (STING) signal pathway and antitumor innate immunity in Hepa1–6 cells. First, Hepa1–6 cells had a significant levels of STING expression, while normal hepatocyte AML12 cells had little to no STING (Figure 4B). Following BCP nanoparticles treatment, the STING agonist amide benzimidazole (ABZI) was chosen as the positive control to identify STING dimerization in Hepa1–6 cells. The outcomes demonstrated that STING dramatically dimerized after being exposed to BCP nanoparticles for either 6 or 12 h (Figure 4C). The finding suggested that BCP nanoparticles could function as agonists to activate STING. According to previous reports, the cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase (cGAS) enzyme will first activate cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) before activating STING and producing type-I interferon and proinflammatory cytokines. Here, it has been assumed that the BCP treatment of Hepa1–6 cells may cause some cells to die, and the released DNA triggers the STING of neighboring cells. After BCP nanoparticles treatment, it has been shown that TBK1 was phosphorylated in both AML12 cells and Hepa1–6 cells. The findings demonstrated that Hepa1–6 cells significantly phosphorylated TBK1, but not AML12 cells (Figure 4D and F). Additionally, the Hepa1–6

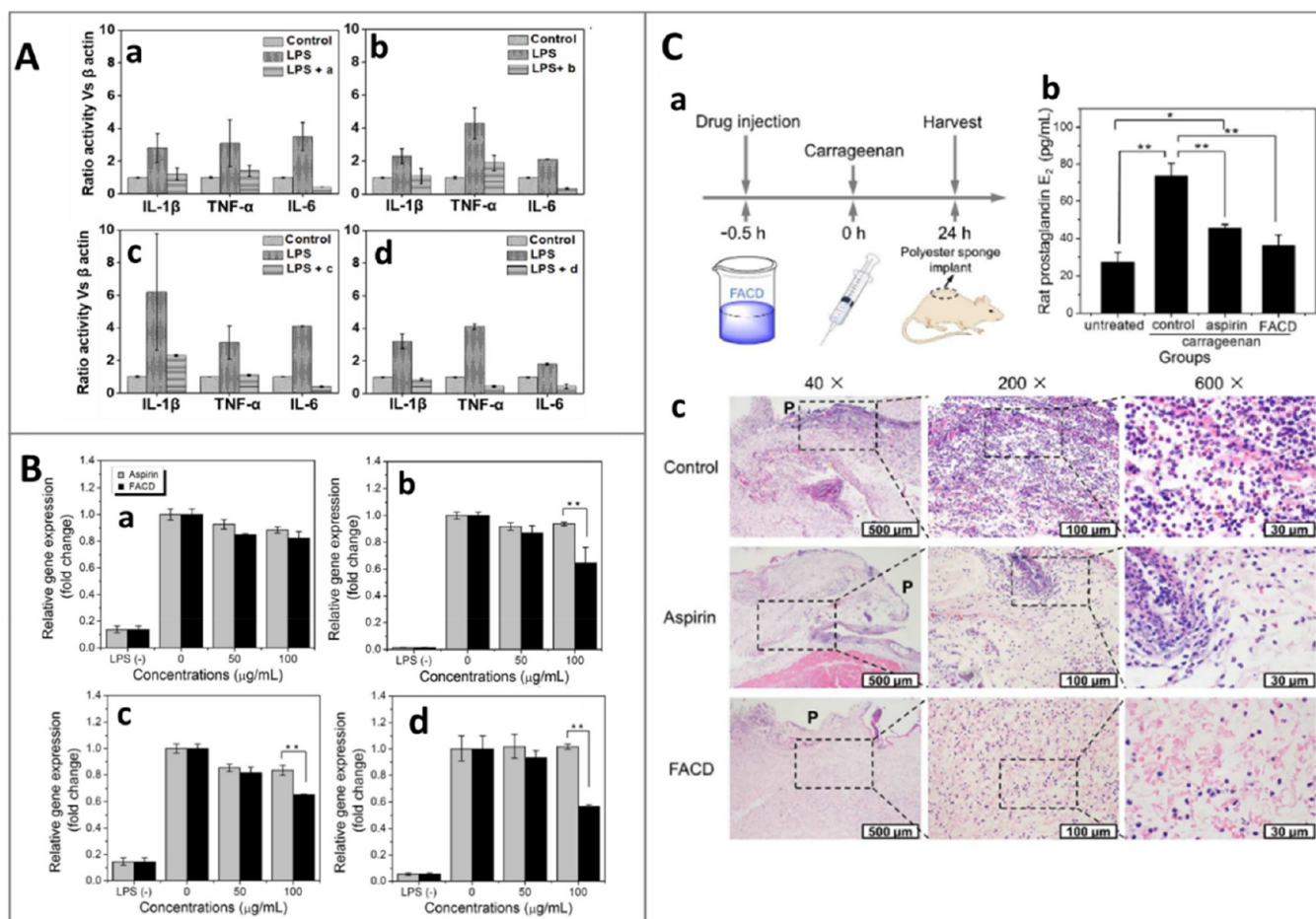


Figure 5. (A) Mouse macrophages showing pro-inflammatory expression due to treatment of (a) Ser-Ag, (b) Ser-Ag^{INH}, (c) Ser-Ag^{Strep}, and (d) Ser-Ag^{PMA} nanozymes. Adapted with permission from ref 148. Copyright 2022, Elsevier. (B) Real-time PCR showing anti-inflammatory activity of aspirin and FACD, *in vitro*. (a) Experiment evaluating the expression levels of TNF- α after a 24 h treatment with either aspirin or FACD. (b) Expression levels of IL-1 β after a 24 h treatment with either aspirin or FACD. (c) Assessment of the expression levels of TNF- α after a 48 h treatment with either aspirin or FACD. (d) Evaluation of the expression levels of IL-1 β after a 48 h treatment with either aspirin or FACD. *: $P < 0.05$, **: $P < 0.01$. (C) Aspirin and FACD anti-inflammatory effect, *in vivo*. (a) Displays a scheme outlining the drug administration and the evaluation of the anti-inflammatory effects. (b) shows the levels of PGE₂ in rats after treatment with either PBS, aspirin, or FACD for 5 h. (c). Histological evaluation of aspirin or FACD (each at 25 mg/kg, intraperitoneally) administered and carrageenan-induced anti-inflammatory, with the control group receiving at the same volume of sterile PBS at 5 h. P: polyester sponge implant interface. *: $P < 0.05$, **: $P < 0.01$. Adapted with permission from ref 151. Copyright 2016, American Chemical Society. Here, Ser-Ag nanozymes are serine amino acid-synthesized silver nanoparticles which show enzyme-like action. The Ser-Ag nanozymes are modified with isoniazid, streptomycin, and phosphomolybdic acid to generate Ser-Ag^{INH}, Ser-Ag^{Strep}, and Ser-Ag^{PMA}, respectively. FACD is a fluorescent aspirin-based carbon dot.

cells treated with BCP nanoparticles generated higher interferons (Figure 4G).

Encapsulation of conventional drugs into liposomes for inflammatory diseases treatment, enhanced efficacy, and localization has been shown in comparison to conventional approaches.^{134,135} Toita et al. successfully demonstrated the synergistic anti-inflammatory effect of liposome conjugated IL-10. Nanoformulation exhibited improved anti-inflammatory effect and better macrophage targeting compared to liposomes alone. Cells of the innate and adaptive immune system produce IL-10 which is employed in macrophage directed therapeutics for inflammation and related diseases.¹³⁶ In another study, glucocorticoids-entrapped liposomes are demonstrated for targeted delivery at inflammatory sites to improve the therapeutic ratio.¹³⁷ Herein, glucocorticoids act as an anti-inflammatory agent. Authors have utilized the zebrafish model and two nanoformulations, i.e., polyethylene glycol-coated and novel AmbiMACs, to confirm the biodistribution and anti-

inflammatory effect of liposomes. The outcome of the research showed that the polyethylene glycol-coated liposome has high circulation time, whereas the liposome specifically targets the macrophages. Both nanoformulations accumulate at targeted inflammatory sites, and drug encapsulation enhances anti-inflammatory effects with reduced toxic effect. However, encapsulation of the drug reduces the tissue regeneration inhibitory effect and hinders the glucocorticoid-responsive gene expression.

Dendrimers are another class of branched and multivalent nanoparticles that show an anti-inflammatory effect. Phosphorus dendrimers, i.e., polyanionic phosphorus dendrimers consisting of 12 aza-bisphosphonic groups at their surface, exhibit an anti-inflammatory response to isolated monocyte/dendritic cells and experimental arthritis model.¹³⁸ Other phosphorus dendrimers coated with trimannopyranosides reduce the accumulation of neutrophil in lungs of mice bearing acute lung inflammation.¹³⁹ It has been demonstrated

that two different phosphorus dendrimers display anti-inflammatory activity both *in vivo* and *in vitro*.¹⁴⁰ G3bis and G4bis phosphorus dendrimers occur in human inflammatory cells, effective in monocyte differentiated M0 macrophages polarized to an M1 state by lipopolysaccharide stimulation. They also inhibited the lipopolysaccharide-induced NF- κ B activation with a decrease in nitric oxide production and CD86 and nitric oxide synthase expression. Thus, it can be suggested that anti-inflammatory activity of G3bis and G4bis phosphorus dendrimers also has effects on human macrophages. Results displayed reduced proinflammatory cytokine secretion by tissue macrophages in a mice model suffering from subchronic inflammation. Further, it is shown that the anti-inflammatory properties of polyamidoamine (PAMAM) dendrimers depend on the core and surface functionalization of dendrimers. Besides, the dendrimers are reported to inhibit cyclooxygenase-1 and cyclooxygenase-2.¹⁴¹

Likewise, gold nanoparticles-treated macrophages express reduction in nitric oxide synthases mRNA and nitric oxide levels triggered by lipopolysaccharide, wherein the gold nanoparticles can interfere with the nuclear factor kappa B (NF- κ B) and STAT1 signaling pathways.¹⁴² The gold nanoparticles exhibited their anti-inflammatory property *via* NF- κ B pathways and other inflammatory mediators including cyclooxygenase-2, nitric oxide synthases, and pro-inflammatory cytokines production. NF- κ B regulates different genes, which are involved in inflammatory responses. It is concluded that it is a novel approach toward the treatment of arthritis using gold nanoparticles.¹⁴³ In a similar direction, Kumawat et al. has shown the surface modification of gold nanoparticles using antibiotic, amino acid, and antioxidant molecules, wherein the engineered gold nanoparticles cotreated with lipopolysaccharide displayed reduced activity of pro-inflammatory genes including TNF- α , IL-6, and IL-1 β .¹⁴⁴

Further, gold nanoparticles tend to deposit on a variety of metal oxides including iron oxide, cobalt (II, III) oxide, and nickel oxide. The gold/metal oxides have attracted much attention because of their high catalytic performance.¹⁴⁵ Different studies, for instance, revealed gold/cerium oxide nanoparticles' antioxidant activity against Hep38 and HeLa cells in a model of cellular oxidative stress. There are reports indicating higher antioxidant activity compared to glutathione, the main cytosolic antioxidant compound.¹⁴⁶ In another study, it is presented that gold/metal oxides apart from having antioxidant activity have anti-inflammatory effects for medical utilization. A study on murine macrophages showed that the anti-inflammatory effect depends upon the metal oxides nature with particle internalization.¹⁰⁸

Apart from gold, silver nanoparticles also encourage anti-inflammatory mechanisms by inducing the NF- κ B response in both inflammatory and anti-inflammatory effects.¹⁴⁷ Recently, silver nanoparticles cotreated with lipopolysaccharide have been shown to downregulate the expression of IL-6, TNF- α , and IL- β cytokines (Figure 5A).¹⁴⁸ It has also been well reported that silver nanoparticles can regulate the expression of pro-inflammatory genes including cyclooxygenase-2 by reducing the expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF1 α).¹⁴⁹

Likewise, carbon nanomaterials possess an anti-inflammatory nature due to their capabilities of reducing the pro-inflammatory cytokines production. C₆₀ fullerenes have been reported to suppress mast cell-driven inflammatory response by inhibiting the cellular ROS. Fullerene derivatives can also

inhibit IL-33-induced IL-6 mRNA expression, which contributes to chronic autoimmune disease pathogenesis. Graphene oxide inhibits the release of pro-inflammatory cytokines like IL-1 β and IL-6 expression in murine-immortalized bone marrow-derived macrophages.¹⁵⁰ In one of the studies, fluorescent aspirin-based carbon dots (FACD) have been synthesized to show the anti-inflammatory effect both *in vitro* and *in vivo*.¹⁵¹ Results presented that the same amount, especially (100 μ g/mL) of fluorescent aspirin-based carbon dots, had higher effects than pristine aspirin (Figure 5B). Further, after 24 h of lipopolysaccharide exposure, both aspirin and fluorescent aspirin-carbon dots can inhibit the expression of TNF- α and IL-1 β (Figure 5B(a and b)). Whereas Figure 5B(c and d) shows that after 48 h of post lipopolysaccharide treatment, aspirin inhibited TNF- α expression with no effect on expression of IL-1 β , while fluorescent aspirin-based carbon dots displayed the inhibitory effect on both TNF- α and IL-1 β expression. Further, the *in vivo* effect of fluorescent aspirin-based carbon dots by inducing inflammation in mice *via* implanting a polyester sponge with 1% carrageenan (inflammation inducer) soaked subcutaneously for 30 min after fluorescent aspirin-based carbon dots administration was studied (Figure 5C(a)). Figure 5C(b) clearly displays that carrageenan exposure increased expression of prostaglandin E₂ in serum, which can be significantly decreased by aspirin and fluorescent aspirin-based carbon dots treatment. Further, hematoxylin and eosin staining shown in Figure 5C(c) discloses that control groups treated with carrageenan exhibit clear inflammatory cell layers, with various neutrophils infiltration under the epidermis. However, fluorescent aspirin-based carbon dots-treated rats show much smaller inflammatory cell layers with only scattered neutrophils infiltration beside the epidermis. All of these data clearly suggest that fluorescent aspirin-based carbon dots possess effective anti-inflammatory function *in vivo*.

From the above discussion, it can be concluded that synthesized nanomaterials find utility in biology and medicine due to their anti-inflammatory properties. In this direction, Johnson et al. proposed a study by selecting surfactin-loaded k-carrageenan oligosaccharides-linked cellulose nanofibers (CO-CNF) against periodontitis. Three different surfactin-loaded nanoparticles have been developed by increasing the concentration of surfactin. Surfactin is a biosurfactant exhibiting anti-inflammatory, antibacterial, antiviral, anticancer, antifungal, and thrombolytic activities.¹⁵² Thus, the properties of surfactin can be used against periodontitis, a disease depicted by alveolar bone loss and gingival inflammation, which is associated with a high level of pro-inflammatory cytokines.¹⁵³ The study was performed by three different concentrations of surfactin, wherein 200SNPs (200 mg surfactin-loaded CO-CNF nanoparticles) reduced the bacterial viability by inducing the oxidative stress in periodontal pathogens *Fusobacterium nucleatum* and *Pseudomonas aeruginosa*. Additionally, 200SNPs can also reduce the ROS and cytokine production under inflammatory conditions which is useful in the treatment of periodontitis.¹⁵⁴

Similarly, chitosan-alginate nanoparticles, because of the antimicrobial and anti-inflammatory activity, find suitable applications in targeted therapy for cutaneous bacterium, *Propionibacterium acnes*. The chitosan-alginate nanoparticles disrupted the bacterial cell wall by inflammatory cytokine IL-12 production in human monocytes and IL-6 in human keratinocytes. The chitosan-alginate nanoparticles also reduce

the risk of resistant species.¹⁵⁵ The engineered polymeric nanoparticles of chitosan display antimicrobial activity and anti-inflammatory activity, which is prepared using chitosan nanoparticles and antimicrobial peptide. They show fast mortality and have the ability to bind to lipopolysaccharides and downregulate NF- κ B and mitogen-activated signaling pathways of protein kinase.¹⁵⁶

Additionally, nanomaterial platforms functionalized with targeting ligands can serve as powerful tools for the management of inflammatory disease, and several other biological applications are indicated in Table 2. The functionalization of nanomaterials with the specific molecule helps in the enhanced activity of nanomaterials including delivery to the targeted site, lower doses of required antibiotic, control toxicity, and better penetration; for example, RBC membrane-coated nanomaterials show extended blood circulation and have improved cancer targeting activity.^{157–159} The nanocarrier functionalization helps in the improvement of target specific immune cell receptors, improvement of adjuvant, and antigen delivery toward the discriminatory immune response.

The engineered cell membrane-coated nanomaterials can efficiently be utilized in targeting and treating localized lung inflammation *via* systemic administration.¹⁶⁰ In this context, Park et al. proposed the targeted delivery of dexamethasone (DEX) to inflamed lungs using nanoparticles covered with a genetically engineered cell membrane.¹⁶⁰ In the inflamed endothelial cell, the expression of pro-inflammatory cytokines of specific surface markers including VCAM-1 or ICAM-1 has been upregulated. The anti-inflammatory drug dexamethasone loaded into poly(lactic-co-glycolic acid) caused an increased level of pro-inflammatory cytokine IL-6 and TNF. The study concludes the significant therapeutic efficacy *in vivo* with the targeting specificities.^{160–163} Pro-inflammatory cytokines showed increased expression in the presence of nanoparticles containing hydrocarbon groups-dominated surface chemistry adding to the formation of protein corona, whereas amine-rich coatings led to increased expression of anti-inflammatory markers.¹⁶⁴ In another study, budesonide-based site-specific delivery to inflamed tissue by a mannosylated nanostructured lipid carrier (MN-NLCs) system was proposed, to avoid drug elimination.¹⁶⁵ Thus, a stronger interaction with targeted tissues is necessary to achieve the full potential of the antibiotic and enhancement of therapeutic outcomes.¹⁶⁶

The mechanism of nanomaterial-mediated cytotoxicity has been well documented and related to diverse physiological changes like membrane damage and cytoskeleton modification. Molecular pathways of cytotoxicity include mitochondria damage, disturbance of lysosome functioning, oxidative damage of DNA, over-expression of pro-inflammatory cytokines, etc.^{167,168} However, mechanistic studies pertaining to the molecular mechanism of nanomaterial-induced immunosuppression are still in a nascent stage. Nanoparticle-mediated immunosuppression can be due to a direct interaction of the nanomaterial with the immune system or used to deliver immunosuppressive drugs. For example, studies have demonstrated poly(lactic-co-glycolic acid), chitosan, polylactic acid nanomaterials, and dendrosomes to effectively suppress type-I and type-II allergies and treat animal models of autoimmune uveoretinitis with betamethasone-loaded polylactic acid.^{169,170} They have also been used to deliver poorly bioavailable immunosuppressive drugs like cyclosporine and tacrolimus *via* polymeric nanoparticles, liposomes, and lipid

Table 2. Different Types of Nanomaterials, Their Surface Modification to Impart Functional Properties, Mechanism, and Applications in Biology and Immunology

Nanomaterials	Molecules for surface modification	Action mechanism	Applications	ref
Gold nanocages	Poly(<i>N</i> -isopropylacrylamide) (pNIPAAm)	Conformation changes in response to temperature variations	Controlled release of anticancer drug in near-infrared region	174
Gold nanoparticles	Snake venom protein toxin NN-32 with PEG ligand	Preventing nonspecific binding of peptides and enzymes	Increase cytotoxicity and apoptosis against human breast cancer cell lines	175
Superparamagnetic iron oxide nanoparticles	Dendritic guanidine	Enhances cellular transportation	Magnetic resonance imaging	176
Silver nanoparticles	Titanium substrate	Fabrication of antibacterial biocomposites	Antimicrobial and biomedical applications	177
Gold nanoparticles	N-Heterocyclic (NHC) carbene	Selective and active catalytic reduction of CO ₂ to CO in water	Catalytic applications	178
Multivalent gold and silver nanomaterials	Herceptin antibody	Targeting particles for imaging and photothermal therapy	Possesses six-fold higher affinity for cancer cell imaging in comparison to noncancer cells	179
Gold nanoparticles	Polyoxometalates and lysine	Polyoxometalates and lysine provide functional surfaces and selectively direct nanoparticles to bacterial and mammalian cells	Potent antimicrobial and cytotoxic materials against A549 human lung carcinoma cells	180
Mesoporous silica nanoparticles	Gold particles	Biocompatible capping agent and add weight to each individual mesoporous silica nanoparticles to increase the density	DNA and drugs delivery into cells and tissues	181
Polymeric nanomaterials	1,25-Dihydroxyvitamin D3 (aVD ₃)	Anti-inflammatory and immunomodulatory effects due to dendritic cells modulation	Induce antigen-specific immune tolerance, important in the treatment of autoimmune diseases	182

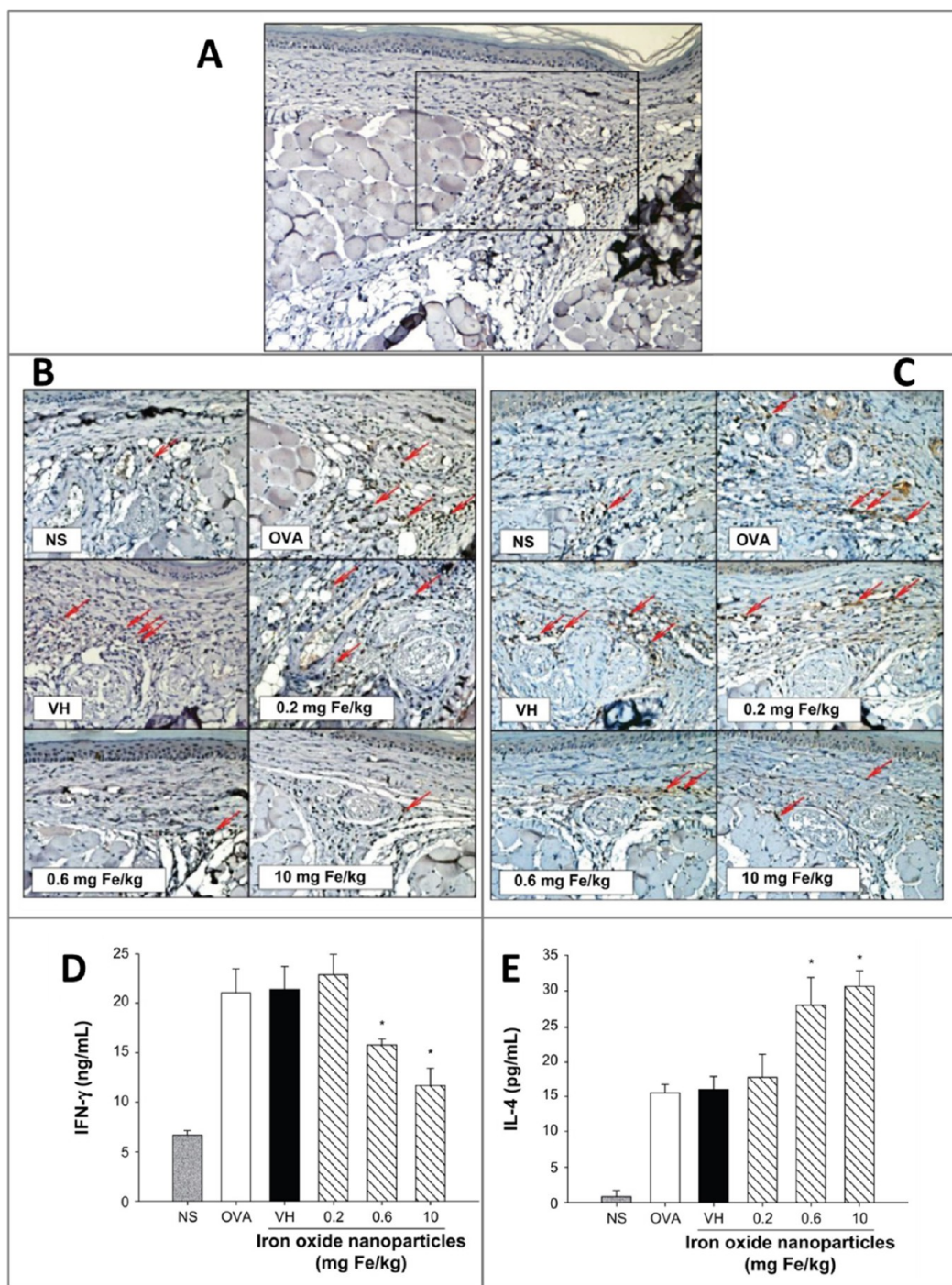


Figure 6. Interferon- γ and TNF- α inhibition by iron oxide nanoparticles treatment. (A) Representative light micrographs showing footpad sections that were IFN- γ -stained. The original magnification was $\times 200$. The box in the image highlights subcutaneous regions where IFN- γ signals were observed in the ovalbumin-sensitized group that did not receive treatment. (B, C) Characteristic light micrographs of footpad sections were IFN- γ and TNF- α -stained, respectively. The original magnification was $\times 400$, and the arrows in the images indicate positive cells. (D, E) Iron oxide nanoparticles have a differential effect on splenocyte for antigen-specific IFN- γ and IL-4 production. Splenocytes isolated from each test group of mice were cultivated in ovalbumin ($50 \mu\text{g}/\text{mL}$) for 72 h, and collected supernatants were measured (D) IFN- γ and (E) IL-4 by enzyme-linked immunosorbent assay. Adapted with permission from ref 70. Copyright Creative Commons Attribution, NonCommercial (unported, v3.0) License.

nanomaterials.^{63,65,171–173} The next section highlights the

mechanism of nanomaterial-mediated direct immunosuppres-

sion and probable suppression cascades.

4. ACTION MECHANISM OF IMMUNOSUPPRESSIVE NANOMATERIALS

Cytokines like transforming growth factor- β (TGF- β) and IL-10 and immune cells like T regulatory cells and myeloid-derived suppressor cells contribute toward suppressing the immune system. Initial reports of nanoparticle-mediated

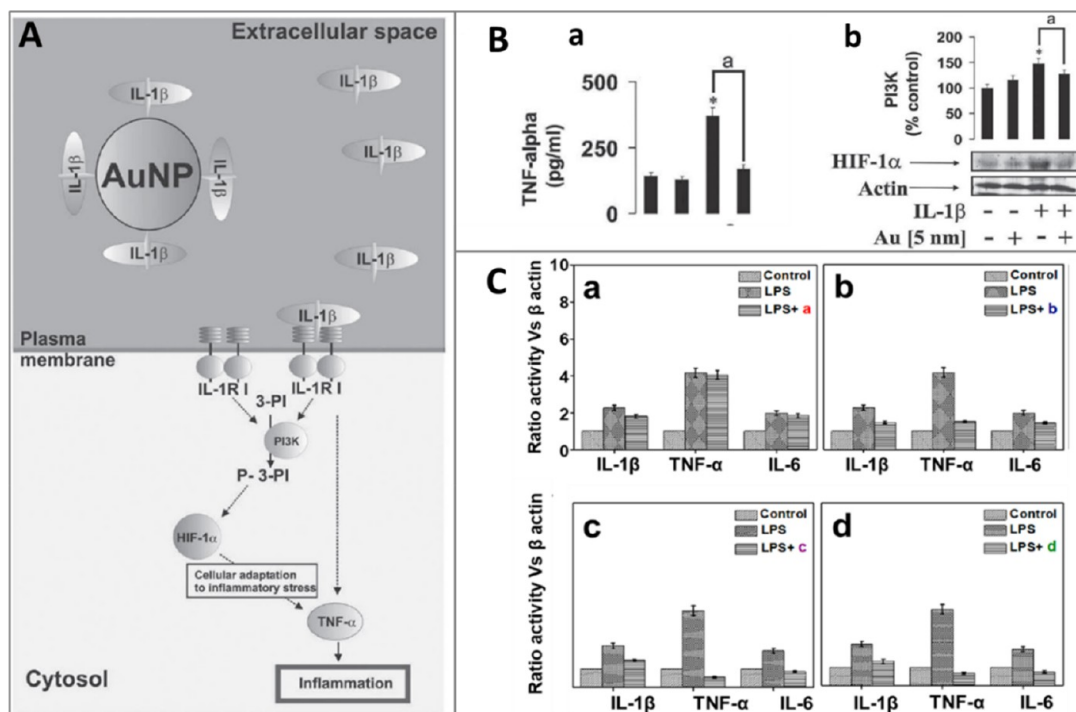


Figure 7. *In vivo* response of gold nanoparticles (AuNPs) downregulating the IL-1 β -induced responses. (A) Mechanisms of gold nanoparticles' down-regulation of IL-1 β cellular responses. (B) IL-1 β (2500 ng/kg) injected C57/BL6 mice. Gold nanoparticles (100 nmol Au/kg) were simultaneous injected into some of the animals. Adapted with permission from ref 192. Copyright 2012, John Wiley and Sons. (C) The Western blot assay was used to assess the protein expression of inflammatory cytokines in RAW 264.7 macrophages. The nanoparticles tested were Cur-Au, Cur-Au^{INH}, Cur-Au^{Tyr}, and Cur-Au^{Qrc}, represented by a, b, c, and d, respectively. Adapted with permission from ref 144. Copyright 2022, American Chemical Society. Here, Cur-Au nanoparticles are curcumin-reduced gold nanoparticles, which are further surface modified with isoniazid, tyrosine, and quercetin to generate Cur-Au^{INH}, Cur-Au^{Tyr}, and Cur-Au^{Qrc} nanoparticles, respectively.

immunosuppression was detected in carbon nanoparticles such as CNTs and fullerenes. It has been proved that C57BL/6 mice intranasally exposed to CNTs suppressed systemic T cell activation in a direct cyclooxygenase- and cyclooxygenase2-dependent manner. Cyclooxygenase2 has been implicated in activating pSTAT3 which can be an underlying mechanism of regulatory T cell production and trafficking and the generation of an immunosuppressive setting. CNTs-mediated immunosuppression could be reversed with the aid of cyclooxygenase2 inhibitor "ibuprofen" or in the case of cyclooxygenase2 knockout mice. This mechanism of immunosuppression involved TGF- β and IL-10 leading to prostaglandin release following phagocytosis of CNTs by alveolar macrophages, leading to T cell dysfunction and immune suppression. The immune suppressive property of fullerene C₆₀ has been established in a delayed type of hypersensitivity model induced by methyl bovine serum albumin. Nano C₆₀ treatment significantly alleviated pro-inflammatory cytokines IL-6 and IL-17 and enhanced regulatory T cell population within splenocytes indicating the suppression of pathogenic Th17 phenotype and induction of T regulatory cells, which contribute toward controlling a pathogenic environment.¹⁸³ Mast cell and peripheral blood basophil activation by IgE and Fc ϵ R1 interaction is a primary mediator of systemic anaphylaxis or antigen driven type-I hypersensitivity. C₆₀ fullerene exposure to skin, lung mast cells, and basophils inhibited antigen-sensitized IgE production. Mechanistic studies also revealed the C₆₀-mediated inhibition of ROS production in the mast cells and basophil. A direct contribution of Syk, a tyrosine kinase in its role in Fc ϵ R1

signaling cascade and hypersensitivity, is previously known.¹⁸⁴ Proteomics data revealed that initial fullerene treatment inhibited tyrosine kinase Syk more than 50-fold on antigen stimulation, thereby contributing to immunosuppression.¹⁸⁵

ROS production can lead to DNA and protein damage, even altering the phospholipid bilayer membrane, compromising cellular activity and repair mechanisms. Quenching of ROS is desirable to limit inflammation and decrease damage. Metal oxide nanoparticles have also been explored as potential immunosuppressants and as ROS quenchers. Cerium oxide nanoparticles exhibit different oxidation states for cerium of +3 and +4, which has been attributed as a crucial factor to reduce ROS and nitric oxide levels in lipopolysaccharide-treated macrophages. Furthermore, cerium oxide nanoparticles could also upregulate superoxide dismutase-2 and inhibit inducible nitric oxide at both mRNA and protein levels as well.^{186,187} However, the antioxidant property of cerium oxide nanoparticles also depends on their size and oxidation state. Cerium in +3 oxidation states and smaller-sized (~3 nm) cerium oxide nanoparticles were able to suppress ROS production in fibroblast cells as compared to 8 nm particles.¹⁸⁸

Furthermore, iron oxide nanoparticles have been observed to suppress the humoral response of a T cell-dependent antigen, i.e., ovalbumin. Iron oxide nanoparticles can block T helper cell activation and thereby limit production of cytokines like IFN- γ , IL-6, and TNF- α , which are mainly involved in inflammation. In a supporting report, iron oxide nanoparticles suppressed ovalbumin-induced delayed type hypersensitivity in a mouse footpad by suppressing Th1 cytokines like IFN- γ and TNF- α .⁷⁰ Immunohistochemical staining showed that iron

oxide nanoparticle therapy significantly reduced the signals of IFN- α , IL-6, and TNF- α , which were frequently found to be perivascular in the dermis layer. Additionally, mice exposed to 0.6 and 10 mg iron/kg of iron oxide nanoparticles had considerably less CD3⁺ and F4/80⁺ cells than the vehicle-treated control group (Figure 6A–C). Results displayed that 50 g/mL of ovalbumin treatment can restimulate the splenocytes from nonsensitized and ovalbumin-sensitized mice in culture for 72 h to promote the generation of antigen-specific cytokines to study the iron oxide nanoparticles effect on the functioning of T cells in delayed-type hypersensitivity (DTH) reactions. Effective induction of antigen-specific T cell reactivity can be seen in Figure 6D and E, showing ovalbumin-sensitized groups possess significant induction of IFN- α and IL-4 by ovalbumin stimulation compared to nonsensitized groups. Iron oxide nanoparticles suppress IFN- α production, which is consistent with decreased footpad edema (Figure 6D). On the other hand, as shown in Figure 6E, its exposure also increases the production of IL-4.

Mechanistically, using a primary murine microglial cell model stimulated with lipopolysaccharide, it has been proven that iron oxide nanoparticles accumulate in lysosome of microglia enhancing lysosomal permeability and decreasing the activity of cathepsin B, which is a secretory enzyme responsible for the activation of IL-1 β converting (ICE) protease that converts immature pro IL-1 β to active IL-1 β and stimulate the inflammatory cascade.¹⁸⁹ Iron oxide nanoparticles thereby inhibit IL-1 β and negate pro-inflammatory cytokine release. A corollary article demonstrated the inhibition of lipopolysaccharide and tetanus toxoid pro-inflammatory cytokines IL-6, IL-1 β , TNF- α , IL-12p70, and IFN- γ secretion as well as CD4 T cell activation by human monocyte-derived dendritic cells with PVA-coated iron oxide particles.¹⁹⁰

Gold nanoparticles have been proven to be an excellent inclusion in the arsenal to combat inflammatory responses like rheumatoid arthritis, inflammatory bowel disease, and bacterial infection.¹⁹¹ An initial *in vitro* mechanistic study revealed that gold nanoparticles inhibit lipopolysaccharide-induced nitric oxide production and nitric oxide synthase expression in lipopolysaccharide-induced RAW 264.7 macrophages. It may be attributed to the inhibition of Akt-NF- κ B pathway and hence secretion of pro-inflammatory cytokines like TNF- α , and IL-6. Furthermore, phosphorylation of STAT1 was also inhibited via downregulation of type-I interferons expression.¹⁴² In yet another corollary report, it is demonstrated that IL-1 β regulates inflammatory signaling (phosphoinositide 3-kinases, hypoxia-inducible factor-1 α , TNF- α) inhibition by citrate-stabilized gold nanoparticles both *in vitro* and *in vivo* (Figure 7). Smaller gold nanoparticles are more effective in downregulating pro-inflammatory cytokine expression.¹⁹²

Figure 7A displays the mechanism underlying regulatory effects of gold nanoparticles over IL-1 β -induced inflammatory response *in vivo*. Further, the result has been validated by treating 4 week old male mice with IL-1 β , gold nanoparticles, and in combination. The Western blot image in Figure 7B shows that IL-1 β treatment induces inflammatory response in mice by increasing phosphoinositide 3-kinases activity and hypoxia-inducible factor-1 α accumulation in a cellular fraction as well as enhanced TNF- α concentration in blood. Whereas treatment of both IL-1 β and gold nanoparticles leads to reduction in all three inflammatory markers in comparison to the IL-1 β -treated positive control. Macrophages cotreated with gold nanoparticles and lipopolysaccharide have also been

shown to reduce the activity of pro-inflammatory genes and protein (IL-1 β , TNF- α , and IL-6) to normal levels as presented in Figure 7C.¹⁴⁴ Additionally, it has been correlated that the anti-inflammatory property of gold nanoparticles inhibits CpG oligodeoxynucleotides (CpG-ODN)-mediated toll-like receptor-9 signaling and henceforth c-Jun N-terminal kinase (JNK) and the NF- κ B inflammatory pathway in RAW 264.7 murine macrophages. Gold nanoparticles could efficiently bind to high mobility box-1 (HMGB-1) protein and inhibit toll-like receptor-9 translocation to the phagosome in response to CpG-ODN.

Furthermore, smaller-sized gold nanoparticles can accumulate in lysosomes, and they are more potent in enhancing cathepsin-K, cathepsin-L, cathepsin-S, and cathepsin-B expression and blocking toll-like receptor-9 translocation. Other metal oxide nanoparticles, like titanium oxide nanoparticles < 100 nm, have been demonstrated to be immunomodulatory and decrease lipopolysaccharide-stimulated T lymphocyte proliferation in splenocytes, but the exact route of action has not been studied in detail.¹⁹³

Apart from metal- and metal oxide-derived nanoparticles, polymer nanomaterials and macromolecules have also been explored as immunosuppressants. The polymer nanomaterials have been explored for their potential to deliver immunosuppressive drugs, and to some extent, direct immune suppression has also been addressed. Initial instances of polystyrene nanoparticles < 50 nm alleviated lung inflammation, epithelial mucus production, and serum IgE and Th2 response against allergen ovalbumin exposure and depicted inhibition of lung dendritic cell expansion leading to generation of tolerogenic microenvironment against allergen challenge.¹⁹⁴ Getts et al. demonstrated decoration of polystyrene nanoparticles with encephalitogenic antigen to prevent the onset and that it modifies the disease progression in a mouse model of multiple sclerosis by inducing T cell tolerance and generation of regulatory T cells of experimental autoimmune encephalomyelitis (EAE).¹⁹⁵

However, surface decoration of polystyrene nanoparticles can act as a double-edged sword and may result in an inflammatory response. Sulfonate- and phosphonate-functionalized polystyrene nanoparticles are reported to significantly enhance CD4⁺ T cell proliferation and a pronounced shift to Th1 phenotype with IFN- γ production.¹⁹⁶ The polymer macromolecule “dendrimer” has been described to exhibit tremendous anti-inflammatory potential. Initial reports of dendrimers possessing hydroxy terminal polyamidoamine inhibit endotoxin-mediated inflammation in microglia. The dendrimers efficiently suppress lipopolysaccharide-mediated MAPK phosphorylation and inhibit secretion of pro-inflammatory mediators like nitric oxide, IL-6, etc.¹⁹⁷ Moreover, dendrimers with highly branched chains have allowed for multivalent interactions with multiple cellular and molecular targets in autoimmune diseases such as rheumatoid arthritis. An azabisphosphonate (ABP)-capped dendrimer has been synthesized, which selectively targets human monocytes and directs them toward an anti-inflammatory phenotype and inhibits IL-2-dependent proliferation of CD4⁺ T lymphocytes. In mouse models relevant to human rheumatoid arthritis, IL-1 α ^{-/-} and K/BxN serum transfer model, ABP-dendrimer suppressed serum IL-1 β , TNF- α , IL-6, and IL-17, while increasing the IL-10 level which demonstrated a skewing of inflammatory response toward an anti-inflammatory phenotype. Mechanistically, the azabisphosphonate-dendrimer in-

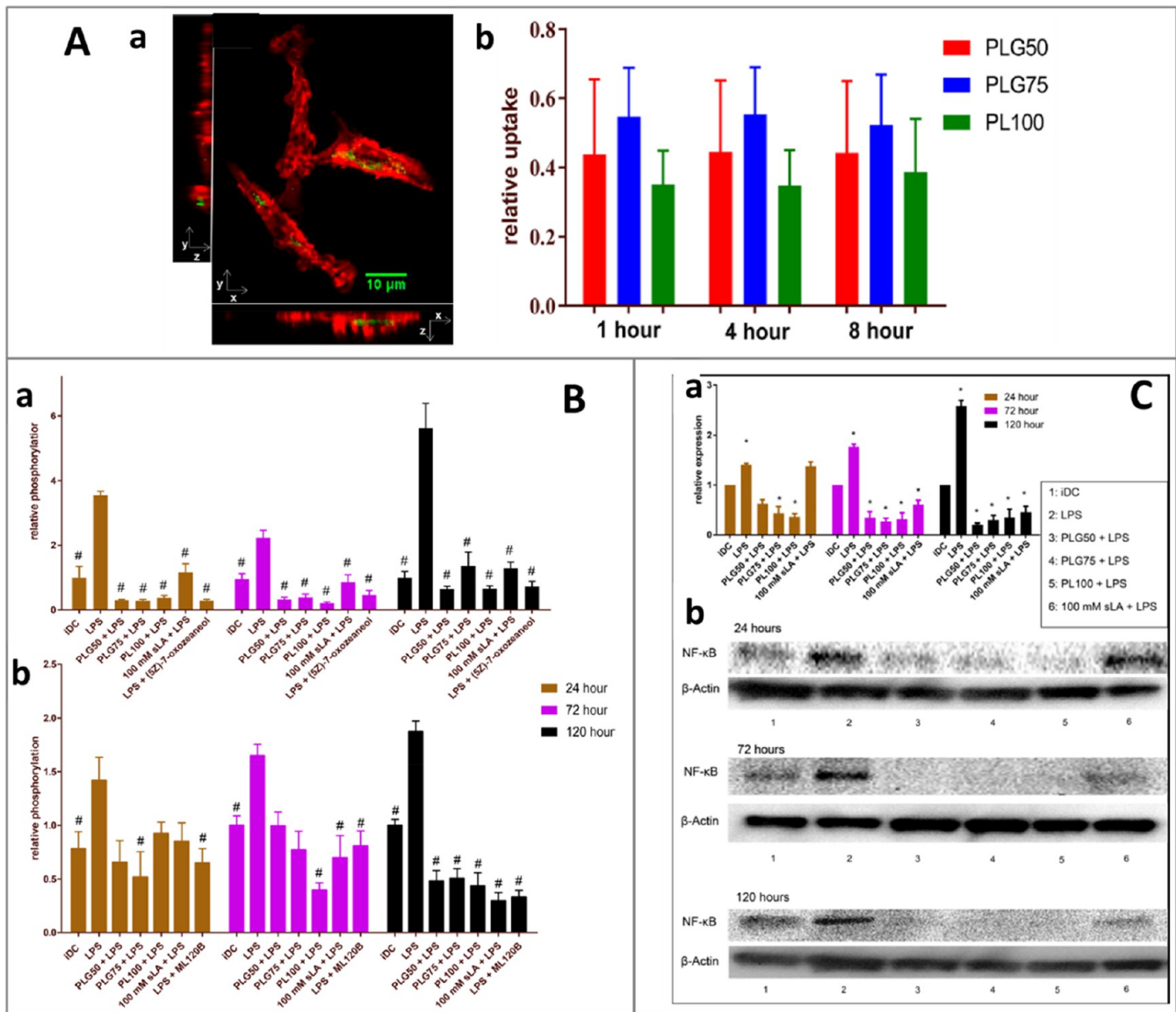


Figure 8. (A) (a) Confocal microscopy showing particles internalization by dendritic cells and (b) time dependent uptake of 1 μM poly(lactic-co-glycolic acid) microparticles. (B) Poly(lactic-co-glycolic acid) microparticles coculture with dendritic cells leads to reduced phosphorylation of two key intermediates, (a) TAK1 and (b) IKKβ, in the nuclear factor kappa B (NF-κB), canonical activation pathway. (C) Coculture with poly(lactic-co-glycolic acid) microparticles drives downregulation of the inflammatory transcription factor NF-κB in lipopolysaccharide (LPS)-stimulated dendritic cells. Adapted with permission from ref 199. Copyright 2018, American Chemical Society.

hibited monocyte and bone marrow monocyte precursor differentiation into osteoclasts, which is a major component of bone erosion. Moreover, it also suppresses rheumatoid arthritis by decreasing c-FMS and RANK expression in monocytes which directs monocyte differentiation into the osteoclast.¹³⁸ Shaunak et al. have demonstrated a glucosamine 6-sulfate dendrimer inhibition of lipopolysaccharide-toll-like receptor-4-mediated production of pro-inflammatory cytokines and chemokines (MIP-1α, CXCL8, MIP-1β) from immature human dendritic cells and macrophages.¹⁹⁸

PLGA is an attractive drug delivery vehicle due to its biocompatibility. The inert potential of poly(lactic-co-glycolic acid) as an active immune suppressant has been demonstrated against lipopolysaccharide-exposed bone marrow-derived dendritic cells. Confocal fluorescent microscopy images with all planes shown in Figure 8A(a) illustrate the internalization of particles in dendritic cells. Further, flow cytometry data

indicate no significant difference in internalization of poly(lactic-co-glycolic acid)-50, poly(lactic-co-glycolic acid)-75, and poly(lactic-co-glycolic acid)-100 at different time points of phagocytosis (Figure 8A(b)). Poly(lactic-co-glycolic acid) exposure resulted in intracellular accumulation of sodium-L-lactate which inhibited phosphorylation of transforming growth factor-β-activated kinase 1 (TAK1) and inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and downregulated expression of inflammatory transcription factor NF-κB.¹⁹⁹ Figure 8B(a) displays that low molecular poly(lactic-co-glycolic acid) particles reduced the phosphorylation of TAK1 at different time points, which is comparable to well-known TAK1 inhibitor, i.e., 7-oxozeaenol. Phosphorylation of IKKβ has also been investigated in dendritic cells, following exposure with poly(lactic-co-glycolic acid) particles. Results in Figure 8B(b) show that the phosphorylation level of IKKβ seems not as stark as of TAK1, particularly at the 24 and 72 h

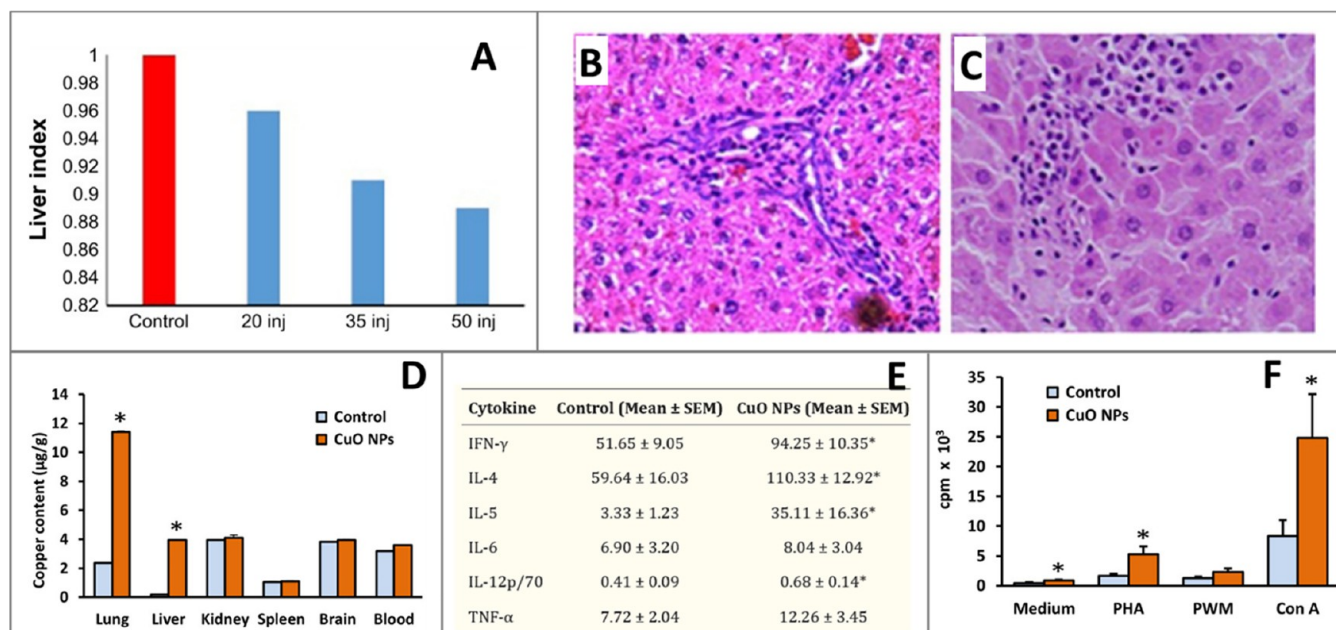


Figure 9. (A) Injection of silica (silicon dioxide) nanoparticles shows a correlation with change in the liver index. (B) Inflammatory cell aggregation in hepatic portal space indicates their infiltration. (C) Demonstration of the infiltration of inflammatory cells, primarily lymphocytes, in the hepatic strands of the lobules. Adapted with permission from ref 211. (D) The average concentration of copper present in the blood and organs of mice following a 6-week exposure to copper oxide (CuO) nanoparticles. (E) Concentrations of various cytokines in the supernatants of spleen cell cultures from mice were treated with CuO nanoparticles via inhalation for a duration of 6 weeks. (F) Spleen lymphocyte proliferative activity after 6-week inhalation of CuO nanoparticles in mice. Adapted with permission from ref 212. Copyright 2022, Creative Commons Public Domain Mark 1.0.

time points. Further, the downregulation of pro-inflammatory surface markers and the decreased production of pro-inflammatory IL-12 following ingestion of poly(lactic-co-glycolic acid) particles by dendritic cells were investigated. The outcome exposed the decrease in NF-κB expression following coculture of poly(lactic-co-glycolic acid) particles with sodium-L-lactate even with subsequent lipopolysaccharide stimulation (Figure 8C). In a pathbreaking finding, negatively charged poly(lactic-co-glycolic acid) particles reduced inflammation in mouse models imparted by sulfate-induced colitis, lethal flavivirus encephalitis, and thioglycolate-induced peritonitis and promoted tissue repair and reduced monocyte infiltration at inflammatory foci. Mechanistically, these particles were opsonized by inflammatory monocytes *via* macrophage receptors with a collagenous structure (MARCO). In contrast, positively charged and neutral particles failed to alleviate the disease burden and inflammatory responses.²⁰⁰

Even though nanomaterials possess inherent immune suppressive properties, further exploration deducing the mechanism is necessary to avoid adverse effects like myelosuppression. Moreover, a single marker like TGF-β cannot solely be used to identify immunosuppressive properties, as a combination of TGF-β along with IL-6 and IL-1 also induces an inflammatory Th17 phenotype. Nanomaterial-mediated immunosuppression should be characterized in detail with the inclusion of TGF-β and IL-10 secreting macrophages, dendritic cells, and regulatory T cells.

5. COMPLICATIONS ASSOCIATED WITH NANOMATERIALS-MEDIATED IMMUNE SUPPRESSION

As discussed in the above sections, nanomaterials can be utilized in modulation of immune responses by either

stimulation or inhibition activities due to their unique physicochemical and surface properties. The size, shape, composition, surface/volume ratio, crystal planes, stability, hydrophobicity, hydrophilicity, surface charge, surface corona, and surface functionalization of nanomaterials are the essential properties that contribute to their immune responses. However, despite the several potential advantages of employing nanomaterials in immunology, issues concerning the materials' biosafety persist to a greater extent. Like, under certain circumstances, modulating the effect of nanomaterials goes uncontrolled and leads to several adverse effects and immunotoxicity. Accounts showed that during immune stimulation, the interaction of nanomaterials with cell-surface receptors (e.g., in leukocytes) and other innate immune cells components leads to the generation of a cytokine storm, interferon response, and/or lymphocyte activation resulting in immunotoxicity.⁷⁹ Various reports have illustrated that the interaction of nanomaterials may result in immunotoxicity and produce a variety of immunological reactions that severely affect the immune system.^{21,201} Thus, critical questions need to be addressed regarding how distinct innate immune systems interact with synthetic nanomaterials, as imbalance of the immune system exerts a damaging effect on the body. Immunotoxicity causes immunosuppression or immunostimulation which may lead to tumor growth, autoimmune diseases, or vulnerability to infectious diseases. Immunosuppression may quell the normal immune response essential for maturation and proliferation of immune cells, whereas undesired immune stimulation may result in hyper-reactions called allergic reactions.²⁰²

Nanomaterials-mediated immune stimulation and immunotoxicity also depend on the activation of phagocytic cells, which leads to their engulfment. It has been reported that upon

exposure to a normal dose, nanomaterials can be engulfed into phagocytes, whereas toxic concentration induces ROS generation from phagocytic cells leading to tumorigenesis and cell death.²⁰³ In addition, the generation of ROS by activated macrophages can be interpreted as an attempt by the immune system to destroy the nanomaterial's surfaces. Increased ROS generation acts as a secondary messenger to enhance the inflammatory immune response. It also induces the production of several proinflammatory cytokines like IL-6, IL-12, and TNF- α as well as play an important role in regulation of T-lymphocytes²⁰⁴ and fibrosis.^{205,206}

The cytotoxic behavior of nanomaterials mainly depends on their several physicochemical properties including morphology, shape, size, surface chemistry, surface area, composition, and action mechanism.^{17,124,144,148,207–209} Results revealed that exposure of nanomaterials induces ROS generation in a pro-inflammatory state, which further leads to membrane, protein, and lipid damage. Immune system continuous activation causes the development of several allergic and autoimmune diseases. Reports recommend that mesoporous silica nanoparticles alter the gene expression analysis of RAW 264.7 at a nontoxic dose, whereas nonporous silica demonstrates the minimum effect to gene transcription.²¹⁰ Other studies have also showed that silica nanoparticles with a 10 nm size induce hyperplasia in liver Kupffer cells and inflammation of inflammatory cells *in vivo* as represented in Figure 9A–C.²¹¹

In addition to silica nanoparticles, continuous exposure of copper oxide nanoparticles to humans also induces an immuno-toxic response. Their toxicity in mice after 6-week continuous exposure at a concentration of 32.5 $\mu\text{g}/\text{m}^3$ has been investigated.²¹² After continuous inhalation, copper oxide nanoparticle concentration was significantly increased in mice lungs and liver (Figure 9D) and enhanced the proliferative response of T-lymphocytes. The exposure also increased the production of IL-12p70, IFN- γ Th1-cytokine, and Th2-cytokines IL-4 and IL-5, whereas TNF- α and IL-6 levels remained unchanged (Figure 9E). Phagocytic activity of granulocytes has also been suppressed, while no significant change in the phagocytosis of monocytes was observed. Comparing mice exposed to copper oxide nanoparticles to controls, the basal proliferative activity of isolated splenocytes was considerably higher in the exposed mice as shown in Figure 9F. Thus, results collectively indicate that innate immunity of mice was significantly affected by the subchronic inhalation of copper oxide nanoparticles which modulate the immune response.

Zinc oxide nanoparticles also proved toxic to primary and immortalized immune cells. Their intranasal exposure leads to immunotoxicity in *in vivo* mice as evidenced by splenocyte death due to Zn²⁺ release from zinc oxide nanoparticles and their internalization into immune cells. Increased intracellular ROS generation might be attributed as another factor toward zinc oxide nanoparticles-mediated toxicity effect.²¹³ Apart from humans and mice, zinc oxide nanoparticles also exhibit immuno-toxic effects in aquatic life due to their extensive use in cosmetics and other industries. Zinc oxide nanoparticles are described to induce immunotoxicity in crucian carp (*Carassius carassius*) as several inflammatory cells were filled in the liver's central vein accelerated by zinc oxide nanoparticles. Results also revealed the elevation of neutrophil extracellular traps (NETs) levels composed of myeloperoxidase, citrullinated histone 3, and neutrophil elastase.²¹⁴

Furthermore, other metal oxides like titanium dioxide nanoparticles were also proven to be toxic to humans and mice. After exposure for 9 consecutive months, titanium dioxide nanoparticles were shown to be accumulated in the thymus and led to reduction of lymphocyte subsets including CD3⁺, CD4⁺, CD8⁺ T, B cell, and natural killer (NK) cells.²¹⁵ Additionally, titanium dioxide nanoparticles enhanced expression of NF- κ B, I κ B kinase 1/2, IL-1 β , IL-4, and neutrophil gelatinase-associated lipocalin, whereas suppressed the expression of I κ B and trefoil factor 1. Thus, it can be concluded that titanium dioxide nanoparticles exert significant toxicity to T cells, lymphoid organs, and immune cell homeostasis.

Other than metal oxide nanoparticles, carbon-based nanomaterials are proven to exert immuno-toxic effects in various life forms.^{216,217} A study showed that 13 weeks of exposure of C₆₀ fullerenes to mice via nose inhalation leads to increases in rat's monocyte chemoattractant protein (MCP)-1 (rats) and mice macrophage inflammatory protein (MIP)-1 α in bronchoalveolar lavage (BAL) fluid. All C₆₀ fullerene-exposed rats indicated phenotype shifts in cells recovered from the bronchoalveolar lavage regardless of the exposure level. Other studies have also showed the immuno-toxic effect of C₆₀ fullerenes as they can provoke inflammation of monocytes-macrophage cells.²¹⁶ Fullerenes also induce an excessive expression of specific cytokines and chemokines, including IL-8 and monocyte chemoattractant protein-1.

6. FUTURE STRATEGY TO FINE-TUNE SURFACE PROPERTIES OF NANOMATERIALS TO ELICIT THE DESIRED IMMUNE RESPONSES

From the above analysis, it is apparent that nanotechnology applications in immunology depend on the appropriate fabrication of nanomaterials with molecules exhibiting natural polymer-like properties and the ability to evade the immune system. For the immunology aspects, nanomaterials should be developed in a manner that escapes from the immune system. Nonetheless, the interactions of nanomaterials with the immune system can be governed by controlling their shape, surface charge, size, steric effect, and hydrophobicity/hydrophilicity behavior. There are several ways to mitigate the immune response of nanomaterials including biocompatible materials, immuno-manipulative payload, and coating of nanomaterials with biomimetic or synthetic entities including several receptors, macromolecules, or membranes from endogenous cells or sterically inhibited polymers.²¹⁸ These modifications can produce synthetic engineered, "stealth" nanoparticles which go undetectable by most immune cells, allowing them to release their payload at targeted site. Further, surface modification of the nanomaterials using a specific ligand or polypeptide can alter their functionality from passive to active targeting. The "invisibility" of nanomaterials to the immune system can be achieved by several methods, and each of the procedures has advantages and disadvantages.

In this regard, polyethylene glycol and other hydrophilic polymers are proved to be ideal candidates as a coating over a nanoparticle's surface with water molecules, which facilitates their escape from macrophages and opsonization.^{219,220} Polyethylene glycol surface functionalization can also significantly increase the half-life of nanoparticles in bloodstream. All of these studies enable the discovery of new natural compounds mimicking molecules to escape the immune system. Nanomaterials can also be successfully used to reduce the toxicity of therapeutic vaccines. To create effective vaccines

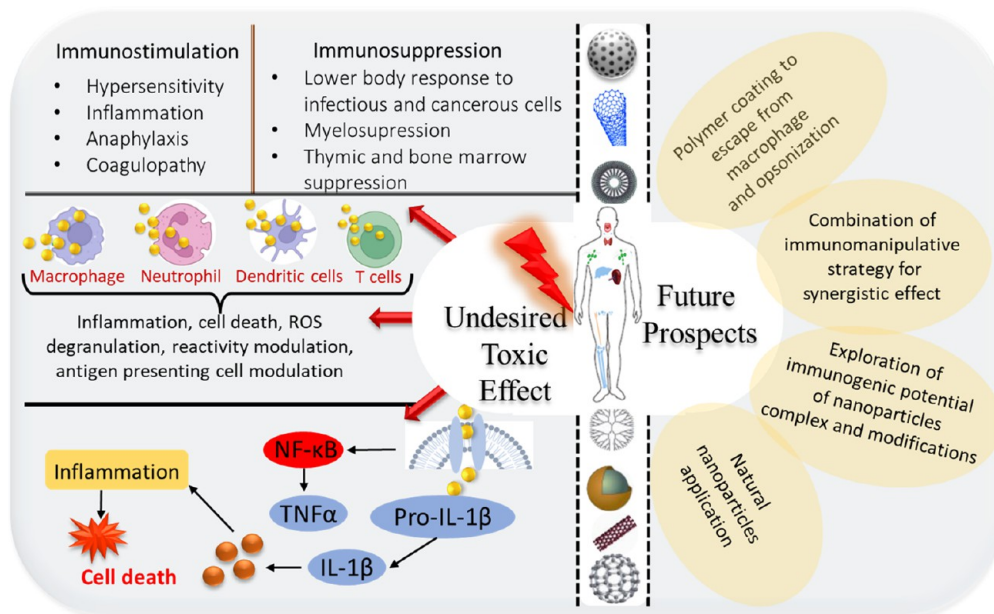


Figure 10. Schematic representation of current limitations and future aspects of employing nanomaterials in immunomodulation.

and vaccine delivery systems, medical researchers attempted to alter nanomaterials in various ways. For instance, the use of recombinant TNF- α vaccines has been prohibited due to their severe side effects. However, conjugation of the vaccine to polyethylene glycol-coated gold nanoparticles has demonstrated an enhanced maximum tolerated dose.²²⁰

In the human body, each immune cell behaves differently in response to nanomaterial exposure. For instance, zinc oxide nanoparticles induce high toxicity effect to monocytes, whereas no toxic response has been observed in the case of lymphocytes.²²¹ Although it would be impractical to detect every interaction that might take place due to the large variety of immune cell types and nanomaterials, focused research into the more promising subcategories of nanomaterials might be appropriate to expand this technology. Therefore, apart from the modifications, several research developments have been required to fulfill nanomaterials' early promise in applications for drug delivery.

Combining a few immuno-manipulative strategies together for "synergistic effect" can be evolved as a new area of development by exploring the different materials and surface modification strategy. As discussed earlier, all of the immune cells react differently in response to different analytes. To overcome this factor, several nanomaterial designs can be combined to produce an appropriate immunological response. Although several aspects have been investigated regarding the immunomodulatory effect of surface modified nanomaterials, further research is required to explore the immunogenic potential of these complexes and modifications. A lot of research is still required in this area, while the current approaches provide a very fascinating picture of theranostics for the future of science and health.

However, the ideal balance of nanostructure attributes is highly challenging due to the vast array of potential nanostructure bases, chemical changes, payload alterations, and surface modifications/coatings. Even after identification of the ideal mixture for the treatment or diagnosis of disease, the immunological repercussions must be carefully assessed. This is especially true since there is not a single "catch-all"

nanomaterial that can be applied in all circumstances. Many times, particular characteristics are necessary that significantly change toward how well the nanomaterial functions. The future of employing nanomaterials in a range of applications, including medication delivery and theranostics, is quite promising, even though there may be much investigation to be done. Consequently, nanomaterials can be engineered and utilized to trigger a variety of immunological responses, indicating their importance in the immune system or immune cells treatment. Figure 10 illustrates nanomaterial-mediated toxicity to the immune system and various future aspects.

In the discussed milieu, natural nanomaterials have also attracted much attention due to their potential in biomedical applications. Currently, cytoplasmic ribonucleoprotein is being studied as a therapeutic for delivery of drugs and antigen.²²² Additionally, other biomimetic particles are being developed for their application in the biomedical industry with exosomes (natural extracellular vesicles).²²³ Overall, the development of new, biocompatible imaging and drug delivery systems based on templates taken from viruses, pathogens, or inspired by endogenous particles, all of which employ immune recognition and/or immune evasion strategies, has been fine-tuned by evolution.

CONCLUSION

The immunomodulatory effects of nanomaterials have attracted significant attention, but the ideal balance between different characteristics of nanomaterials is challenging. Therefore, efforts are being made to tailor the physicochemical and surface properties of different nanomaterials to unitize their full biomedical capabilities. In this review, we discuss recent trends in nanoengineering, which are at the forefront for targeted immunomodulation and do not induce immunotoxicity. The signaling pathways associated with nanomaterial-based immunotherapy have also been explored. Further, recommendations are provided for regulating different immune responses toward target specific drug delivery and to reduce possible risks to human health, if any. Nevertheless, the existing approaches are not enough to realize the full potential

of nanomaterials, and future-in-depth studies are required for nanomedicine applications of immunomodulatory-nanomaterials.

AUTHOR INFORMATION

Corresponding Authors

Hemant Kumar Daima – Department of Biochemistry, School of Life Sciences, Central University of Rajasthan, Bandarsindari 305817 Ajmer, India; orcid.org/0000-0002-9109-430X; Email: hemant.daima@curaj.ac.in

Ragini Singh – Liaocheng University, Shandong 252059, China; Phone: +91 8884774863; Email: singh@luc.edu.cn

Authors

Mamta Kumawat – Department of Biotechnology, School of Sciences, JECRC University, Jaipur 303905 Rajasthan, India

Himanshu Gogoi – Translational Health Science and Technology Institute, NCR Biotech Science Cluster, Faridabad 121001, India

Harishkumar Madhyastha – Department of Cardiovascular Physiology, University of Miyazaki, Miyazaki 8891692, Japan; orcid.org/0000-0002-7143-4821

Eric Lichtfouse – State Key Laboratory of Multiphase Flow in Power Engineering, Xi'an Jiaotong University Xi'an, Shaanxi 710049, China

Complete contact information is available at: <https://pubs.acs.org/10.1021/acsabm.3c00940>

Notes

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ABBREVIATIONS

ABP = Azabisphosphonate
ABZI = Amide benzimidazole
AgNPs = Silver nanoparticles
AMPs = Antimicrobial peptide
APCs = Antigen presenting cells
AuNPs = Gold nanoparticles
BAL = Bronchoalveolar lavage
CCL = C–C motif chemokine ligand
CCR2 = C–C chemokine receptor type 2
CeO₂ = Cerium oxide
CNTs = Carbon nanotubes
CpG-ODN = CpG oligodeoxynucleotides
DEX = Dexamethasone
DNA = Deoxyribonucleic acid
DTH = Delayed-type hypersensitivity
EAE = Experimental autoimmune encephalomyelitis
FACD = Fluorescent aspirin-based carbon dots
FDA = U.S. Food and Drug Administration

Fe₂O₃ = Iron oxide
H&E = Hematoxylin and eosin
HIF1 α = Hypoxia-inducible factor
ICAM-1 = Intercellular adhesion molecule-1
IgE = Immunoglobulin E
IgG = Immunoglobulin G
IKK β = Inhibitor of nuclear factor kappa-B kinase subunit beta
IL-1 β = Interleukin-1 β
JNK = c-Jun N-terminal kinase
LDH = Lactate dehydrogenase
LPS = Lipopolysaccharide
MAPK = Mitogen-activated protein kinase
MCP-1 = Monocyte chemoattractant protein
MIP-1 α = Macrophage inflammatory protein-1 α
MN-NLCs = Mannosylated nanostructured lipid carrier system
NETs = Neutrophil extracellular traps
NF- κ B = Nuclear factor kappa B
PAMAM = Polyamidoamine
PBS = Phosphate buffer saline
PLGA = Poly(lactic-co-glycolic acid)
QDs = Quantum dots
ROS = Reactive oxygen species
SCFA = Short chain fatty acid
SiO₂ = Silicon dioxide
siRNA = Small interfering RNA
STING = Stimulator of interferon genes
TAK1 = Transforming growth factor- β -activated kinase 1
TNF- α = Tumor necrosis factor-alpha
Th = T helper
TiO₂ = Titanium dioxide
VCAM-1 = Vascular cell adhesion molecule-1
VEGF = Vascular endothelial growth factor
ZnO = Zinc oxide

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