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Review

Nanoparticle impact on innate immune cell pattern-recognition receptors and inflammasomes activation

Ana Luísa Silva[a,1], Carina Peres[a,b,1], João Conniot[a,1], Ana I. Matos[a], Liane Moura[a], Bárbara Carreira[a], Vanessa Sainz[a], Anna Scomparin[c], Ronit Satchi-Fainaro[c,d], Véronique Préat[b], Helena F. Florindo[a,*]

[a] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal
[b] Université Catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, 1200 Brussels, Belgium
[c] Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel and dSagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[d] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Nanotechnology-based strategies can dramatically impact the treatment, prevention and diagnosis of a wide range of diseases. Despite the unprecedented success achieved with the use of nanomaterials to address unmet biomedical needs and their particular suitability for the effective application of a personalized medicine, the clinical translation of those nanoparticulate systems has still been impaired by the limited understanding on their interaction with complex biological systems. As a result, unexpected effects due to unpredicted interactions at biomaterial and biological interfaces have been underlying the biosafety concerns raised by the use of nanomaterials.

This review explores the current knowledge on how nanoparticle (NP) physicochemical and surface properties determine their interactions with innate immune cells, with particular attention on the activation of pattern-recognition receptors and inflammasome. A critical perspective will additionally address the impact of biological systems on the effect of NP on immune cell activity at the molecular level. We will discuss how the understanding of the NP-innate immune cell interactions can significantly add into the clinical translation by guiding the design of nanomedicines with particular effect on targeted cells, thus improving their clinical efficacy while minimizing undesired but predictable toxicological effects.

1. Introduction

Nanotechnology is an emerging field that has been revolutionizing modern medicine for almost three decades, with the first nanoparticle (NP)-based therapy consisting of a PEGylated liposomal formulation of doxorubicin, Doxil®, being approved by the FDA in 1995 for the treatment of Kaposi's sarcoma [1]. Since then, a variety of NP have been approved for application in diagnostics and therapeutics, as contrasting agents or drug delivery systems [2]. A multiplicity of nanocarriers in the size range of 1–1000 nm has been reported for the delivery of a wide range of drugs, genes, or other biomolecules, such as polymeric particles, inorganic nanobeads, liposomes, *virus-like* particles (VLP) and virosomes, immune stimulatory complexes (ISCOM), emulsions, polyplexes, quantum dots (QD) and carbon nanotubes (CNT) [3]. Particulate systems have many desirable features for drug delivery, enhancing the delivery of hydrophobic drugs, nucleic acids, or proteins, increasing their circulation times and bioavailability, reducing degradation and clearance by the kidneys, and improving therapeutic efficacy [4,5]. Moreover, NP allow the concomitant delivery of multiple components in a sustained manner at the target site, enhancing therapeutic synergistic effects. NP delivery systems have been extensively used in cancer therapy, as they are passively targeted to tumors through the enhanced permeability and retention (EPR) effect, which results in the accumulation of nanomaterials at the tumor site due to abnormal pathophysiologic characteristics of tumor blood vessels and a deficient lymphatic drainage system, making them ideal for the delivery of chemotherapeutic agents, while decreasing their systemic toxicity [6]. NP-based formulations have also many desirable features for immunomodulation, as NP have the inherent ability to passively target antigen presenting cells (APC) by mimicking the size and shape of an

* Corresponding author.
E-mail addresses: veronique.preat@uclouvain.be (V. Préat), hflorindo@ff.ul.pt (H.F. Florindo).
[1] Equally contributors.

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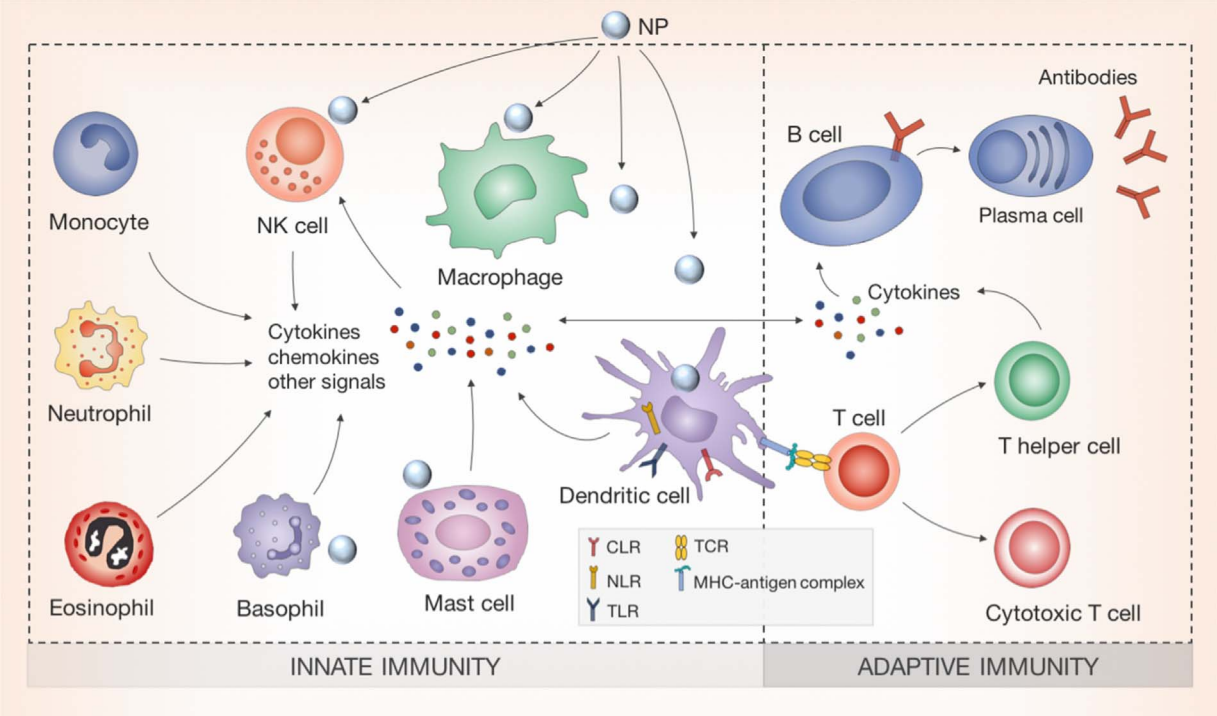

Fig. 1. Interaction of nanoparticles (NP) with cells of the innate immune system and subsequent impact on adaptive immunity. The dendritic cells (DC) are central elements that upon activation of pattern-recognition receptors (PRR; C-type lectin receptors (CLR), leucine-rich repeat-containing receptors (NLR), toll-like receptors (TLR)) will secrete cytokines that activate natural killer (NK) cells and also modulate T cell differentiation. The recognition of antigen-Major Histocompatibility Complex (MHC) by T Cell Receptor (TCR) will also impact on T cells expansion.

invading pathogen, increasing antigen uptake, processing and cross-presentation [7]. NP can be engineered to either inhibit or enhance immune responses, being ideal vehicles for vaccine delivery, cancer immunotherapy or allergy treatment [8].

The design of particulate systems must be guided by their final application, either for imaging, drug delivery or vaccination purposes.

On one hand, for drug delivery purposes, the exposure to nanomaterials and their interaction with the immune system may lead to undesired responses, due to non-specific recognition and uptake of NP by phagocytes [4,9]. Upon administration, NP will interact with a variety of biomolecules, including proteins, sugars and lipids that are present in blood, lymph or interstitial fluid, which coat NP surfaces, forming the so-called "protein corona" [10]. The "protein corona" consists of a variety of proteins including signaling and transport proteins, apolipoproteins, coagulation factors, adhesion mediators, or complement components, which can opsonize NP, giving it a distinctive "biological identity" [11,12]. Unintended recognition of NP as foreign material may lead to opsonization and phagocytosis by the mononuclear phagocyte system (MPS), which consists of blood monocytes, dendritic cells (DC), splenic and liver-resident macrophages, that are responsible for *in vivo* uptake and clearing of foreign materials from circulation [13]. Therefore, it will affect NP clearance mechanisms through the kidneys and liver, significantly limiting the half-life, as well as NP bioavailability [4,10,14]. As a consequence, NP therapeutic efficacy at target sites will be impaired due to the lower dose of the drugs being delivered, and toxicological events may arise from the induction of host inflammatory and immunology biological responses [2,9]. For instance, adsorbed proteins can modulate the activation of complement cascades, cause thrombosis or anaphylaxis, and lead to delayed or chronic toxicity, or affect the innate or adaptive immune responses leading to immunostimulation or immunosuppression [10,15]. Examples of well-known chronic inflammatory diseases caused by environmental exposure to particles are mesothelioma, pneumoconiosis and silicosis [4]. Long-term exposure to silica particles within the MPS and reticulo endothelial system (RES) has shown to induce long-term inflammatory responses and fibrotic-like lesions in the lung, liver and spleen *via* recruitment and infiltration of macrophages [16,17].

Conversely, in vaccine development strategies, these processes may be beneficial, as these particulate delivery systems can mimic the size and shape of an invading pathogen [18,19]. NP can be specifically designed to be recognized and promote the sustained delivery of antigens to APC, as well as to further modulate intracellular signaling pathways towards the stimulation of long-lasting specific immune responses and consequently increase overall vaccine efficacy [20].

Understanding how NP interact with the biological environment and how their physicochemical characteristics influence phagocytic recognition and uptake, clearance, cellular processing and toxicological effects would allow the rational design of safer and more effective nanoparticulate delivery systems. These nanomaterials would then specifically target or avoid the host innate immune system, thus improving drug delivery and efficacy, while reducing inflammatory side effects, and consequently predicting possible risks that would heavily impair their successful clinical translation. This manuscript reviews the major findings on nanomaterial properties that have a major impact on their interaction with distinct components of the innate immune system, discussing the approaches currently explored to modulate that interaction towards effective biomedical applications and minimal adversarial toxicological effects.

2. Innate immune system

The immune system is a network of specialized bone marrow-derived cells that work together to protect the body from infection. Thus, the immune system must be able to determine what belongs to the body, often called "self", from foreign invaders, *i.e.* "non-self" [21]. Aside from infection, tissue damage can also lead to the release of danger signals, enabling the immune system to be activated against "self" that can cause damage to the body, leading to non-physiological

cell death, a model proposed by Polly Matzinger [22].

Immune responses are mediated by leukocytes and lymphocytes, which are formed in the bone marrow and migrate to peripheral tissues to detect, isolate and eliminate potentially harmful pathogens or malignant cells [23]. The immune system can be divided into an innate and an adaptive branch, which mainly differ in response time and the level of specificity (Fig. 1). The myeloid progenitor is the precursor of the granulocytes, macrophages, DC, and mast cells, whereas the lymphoid progenitor originates the lymphocytes. The two major types of lymphocytes belong to the adaptive immunity and are constituted by B and T cells. A third lineage of lymphoid cells, called natural killer (NK) cells, circulate in the blood as large lymphocytes that lack antigen specific receptors and are part of the innate immune system against intracellular pathogens, being able to kill tumor or virus-infected cells [23].

Communication between those immune cells upon encountering a pathogen is mediated by the release of signaling molecules, in particular cytokines and chemokines, which play important roles in immunity by interacting with specific receptors [21,24]. Cytokines are a diverse group of proteins that have the ability to recruit and activate other cells, induce differentiation and enhance cytotoxic activity [21,25]. Chemokines typically function as chemotactic factors, helping to guide other immune cells to the site of infection or tissue damage [26,27].

The innate immune system is activated almost immediately after the detection of danger signals, such as an invading pathogen, and involves the migration of phagocytic cells to the site of infection, forming the first line of defense [28]. Innate immune cells are characterized by their lack of antigen-specificity and immunological memory. Instead, innate immune cells recognize self from non-self through genetically conserved molecular patterns that are frequently present in pathogens, but not in host cells [23,29]. Charles Janeway [30] named such molecules as pathogen-associated molecular patterns (PAMP), which are recognized by a limited number of germline-encoded pattern-recognition receptors (PRR) present on the surface of innate immune cells (Fig. 1). Key players in the first line of response include macrophages, neutrophils and soluble bactericidal proteins, such as complement and lysozyme [21].

Failure of the innate immune system to eliminate an invading pathogen leads to the activation of the adaptive immune system. The adaptive immunity is antigen-specific and retains memory of a previous infection, improving upon each encounter with a specific pathogen [21]. This feature supports the concept of vaccination. The adaptive immune response is mediated primarily by T and B lymphocytes, which display specific receptors that can be tailored to recognize an extensive range of molecules, called antigens. B cells can differentiate into plasma cells that secrete antibodies when become activated, and T cells can further differentiate into cytotoxic T cells, which are able to destroy virus-infected or malignant cells, and helper T cells that mediate the activation of other immune cells. However, adaptive immune responses may take 3–7 days upon first exposure to a new pathogen, as they depend on the generation of a diversity of antigen receptors on T and B lymphocytes, as well as on the specific clonal proliferation of antigen-specific B and T effector cells [31]. The adaptive immune system can form immunological memory resulting in a rapid specific response upon reinfection with the same pathogen. Induction of adaptive immunity depends on direct instruction by the innate immune system for when to respond, how to respond and for how long [21,31].

2.1. Pattern recognition receptors

Inflammatory response is a protection mechanism of the body against harmful stimuli induced by microbial infection or tissue injury [32,33]. Responding to this attack, the innate immune system constitutes the primary line of defense by recognizing invading pathogens and triggering nonspecific pro-inflammatory and antimicrobial responses mediated by innate immune cells, such as granulocytes (neutrophils, basophils, eosinophils, mast cells), phagocytic macrophages,

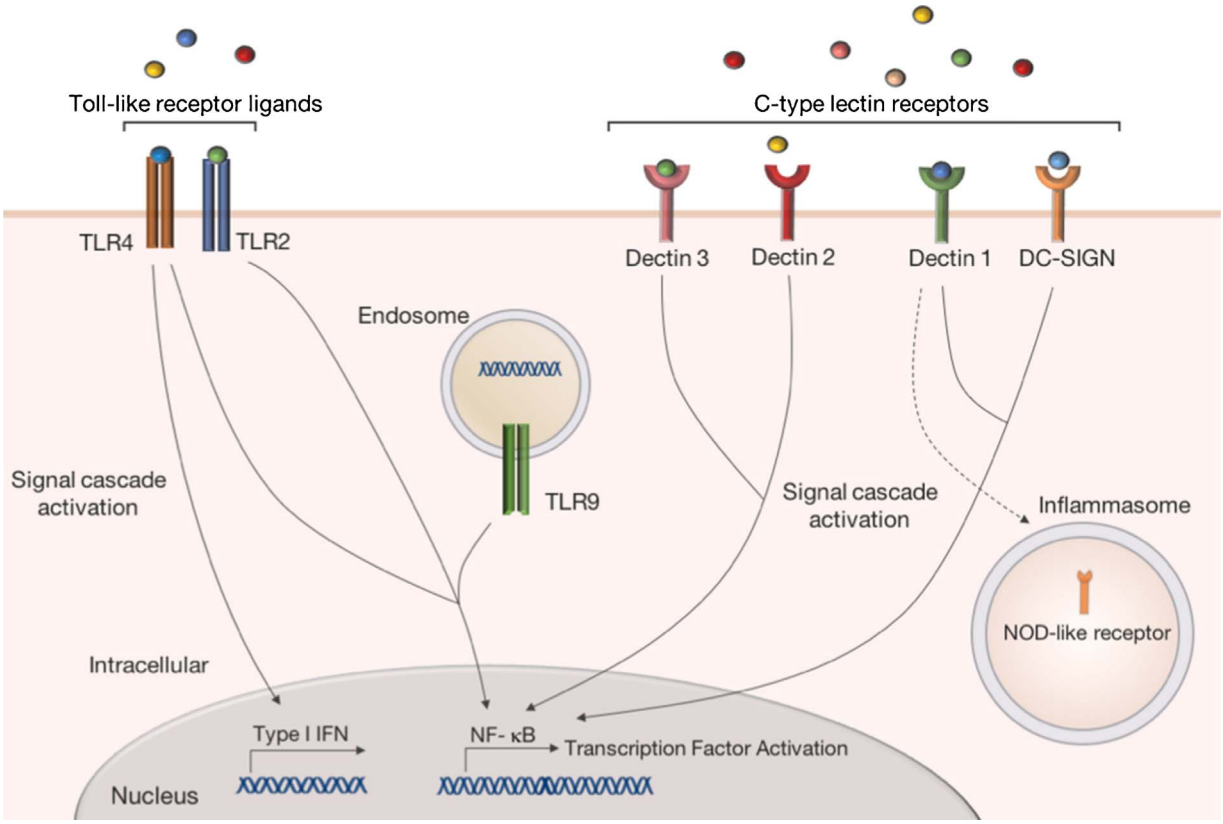

Fig. 2. Principal Pattern recognition receptors (PRR) and signal cascade activation in antigen-presenting cells involved in the innate immune response.

antigen-presenting dendritic cells (DC), and cytotoxic NK cells [33].

The beginning, promotion and concretization of the innate immune response against foreign signals of microbial pathogens depend on the recognition of PAMP through a broad spectrum of intracellular or cell surface receptors, known as PRR [34]. Upon PAMP recognition by PRR, several intracellular signal transduction pathways are triggered to notify the host about the unknown pathogens and promote antimicrobial responses through the transcription of genes encoding a wide range of proinflammatory molecules, including cytokines, chemokines, type I interferons (IFN), antimicrobial proteins, cell adhesion molecules and immune receptors that recruit additional components of the immune system [32,34].

The repertoire of PAMP is extensive, such as lipids, lipoproteins, proteins, carbohydrates and nucleic acids, and similarly the classes of PRR are very diverse, including transmembrane proteins such as the mannose receptor, scavenger receptors, toll-like receptors (TLR) and C-type lectin receptors (CLR), as well cytoplasmic proteins such as nucleotide-binding oligomerization domain (NOD) and leucine-rich repeat-containing receptors (NLR), retinoic acid-inducible gene (RIG)-I-like receptors (RLR) and AIM2 (absent in melanoma 2)-like receptors (Fig. 2) [34]. Due to the existence of multiple receptors per each class, a single phagocyte may express as much as 50 distinct PRR at any given time [21].

Accordingly, the knowledge developed around the recognition of pathogen was further inspired by TLR identification in 1997 [35]. In mammals, the TLR family is the most studied and best characterized PRR class for sensing distinct PAMP derived from invading pathogens, such as viruses, bacteria, fungi and protozoa, and to promote downstream signaling pathways that trigger inflammatory responses [32]. TLR are composed by integral glycoproteins that are constituted by an extracellular ligand-binding domain holding leucine-rich repeat (LRR) motifs followed by a cytoplasmic Toll/interleukin (IL)-1 receptor homology (TIR) domain [36]. Ten different TLR were identified in humans and twelve in mice. Mammalian TLR can be classified into several groups according to the category of recognizing PAMP, type of interaction with PAMP (direct interaction or *via* intermediate PAMP-binding molecule) and TLR cellular distribution. Regarding PAMP category, lipids are detected by TLR1, 2, 4 and 6, whereas TLR3, 7–9 recognize nucleic acids [7].

According to subcellular localization, TLR can also be divided into two subfamilies. The primary subfamily includes TLR1, 2, 4–6 and also TLR10 in humans and TLR11 in mice that appear on plasma membrane at the cell surface and mainly recognize unique bacterial products. In contrast, nucleic acid-sensing TLR, which comprises TLR3, 7–9, are essentially localized in the endolysosome intracellular compartment after being recruited from the endoplasmic reticulum (ER) following stimulation by viral and bacterial nucleic acids [37] (Table 1). TLR are mainly expressed by APC, including DC, macrophages, and B lymphocytes, but also by adaptive immune cells, such as T cells, αbT cells, regulatory T (Treg) cells, γdT cells, and NKT cells [38].

Although less explored, RLR are a family of genomic RNA sensors localized in the cytoplasm and composed by a C-terminal regulatory domain and RNA helicases, including RIG-I, MDA5 (melanoma differentiation-associated gene 5), and LGP2 (laboratory of genetics and physiology 2), which contain two N-terminal caspase recruitment domains (CARD) and a central DExD/H box RNA helicase domain with ATPase activity essential for RNA-activated signaling [39] (Table 1). RLR are expressed at low levels in a variety of cell types, including myeloid cells, epithelial cells, cells of the central nervous system, and plasmacytoid DC. However, their expression is further increased by IFN exposure and virus contact. In addition, RLR and TLR cooperate synergistically in immune signaling during virus recognition. While RLR signaling and IFN production are initially promoted within infected cells to initiate a RLR-dependent innate immunity against virus

Table 1
Human pattern-recognition receptors (PRR) and their natural and synthetic ligands [46].

PRR	Location	PAMP Recognized	Pathogens	Synthetic Agonists	Immune Response
TLR					
TLR 1 & 2	Cell membrane	Triacylated lipoproteins	Bacteria	Pam3Cys	Induce production of inflammatory cytokines
TLR 2 & 6	Cell membrane	Diacylated lipoproteins	Mycoplasma	Pam2Cys	Induce production of inflammatory cytokines
		LTA	Gram-positive bactéria	MALP-2	
TLR 3	Endosome	dsRNA	Viruses	Poly(I:C)	Synthesis of type 1 interferons
				Poly(A:U)	
TLR 4	Cell membrane	LPS	Gram-negative bacteria	MPLA	Synthesis of type 1 interferons
		Heat shock proteins	Host	LPS analogs	
		Envelope proteins	Viruses		
TLR 5	Cell membrane	Flagellin	Bacteria	–	Induces production of TNF- α
TLR 7 & 8	Endosome	ssRNA	Viruses	Resiquimod (R848)	Anti-viral response
				Imiquimod (R837)	
				Gardiquimod	
				Loxoribine (Guanosineanalogs)	
TLR 9	Endosome	CpG DNA motifs	Bacteria	CpG ODN	Dependent on type of CpG:
		DNA	Viruses		Type A/D induces IFN− α
		Malaria hemozoin	Protozoa		Type B/K induces IL-12 and TNF- α production
TLR 10	Cell membrane	Profillin-like proteins	Unknown	Unknown	Unknown
RLR					
RIG-I	Cytosol	Short dsRNA	Viruses	5′ppp-dsRNA, Short Poly(I:C)	Synthesis of type 1 interferons
MDA5	Cytosol	Long dsRNA	Viruses	Long Poly(I:C)	
LGP2	Cytosol	RNA	Viruses	–	Signaling modulator of RIG-I and MDA5
NLR					
NOD1	Cytosol	DAP	Gram-negative bacteria	DAP analogs	Induce production of inflammatory cytokines
NOD2 & NLRP3	Cytosol	MDP	Gram-positive/negative bacteria	MDP analogs	Inflammasome activity (caspase-1, IL-1β, IL-18)
		MDP, DNA, RNA, ATP	Bacteria, viruses, host		

CpG ODN: Cytosine-guanine rich oligonucleotide; LPS: Lipopolysaccharide; LTA: Lipoteichoic acid; MALP-2: Macrophage-activating lipoprotein-2; MPLA: Monophosphoryl lipid A; Pam2Cys: Dipalmitoyl-S-glyceryl cysteine; Pam3Cys: Tripalmitoyl-S-glyceryl cysteine; poly(I:C): Polyribo(inosinic-cytidylic) acid; TLR: Toll-like receptor; ss/dsRNA: Single/Double stranded RNA; RIG-I/RLR: retinoic acid-inducible gene (RIG)-I-like receptors (RLR); MDA5: Melanoma differentiation-associated gene 5; LGP2: Laboratory of genetics and physiology 2; NOD/NLR: Nucleotide-binding oligomerization domain (NOD) and leucine-rich repeat-containing receptors (NLR); DAP: Diaminopimelic acid; MDP: Muramyl dipeptide; ATP: Adenosine triphosphate; IL: Interleukin.

infection, TLR appear as a secondary tool mediated by previous IFN production to trigger cell mediated immune responses [40].

Considering the wide family of innate immune receptors, NLR appear as cytosolic pathogen sensors of bacterial peptidoglycan components and are essentially composed by a C-terminal domain rich in leucine repeats and involved in ligand detection and autoregulation, an N-terminal CARD or pyrin domain (PYD) that mediates signaling initiation by protein–protein interactions, and a central NOD that induces oligomerization and transcriptional activation of proinflammatory mediators [41]. NOD1 and NOD2 are both the best explored members of NLR family being able to recognize diaminopimelic acid produced by gram-negative bacteria and muramyl dipeptide evidenced by both gram-positive and −negative bacteria. Also as RLR, NLR act synergistically with TLR to upregulate proinflammatory cytokine production and to prime immune responses against the pathogen [42]. Moreover, other NLR proteins are still involved on the modulation of cell death after the detection of PAMP but also danger-associated molecular patterns (DAMP) derived from endogenous and environmental non-infectious stimuli [43]. To regulate the activation of caspase-1 and consequently the maturation and secretion of proinflammatory mediators (including IL-1β and IL-18) against infection and injury, a multiproteic and signaling complex termed the inflammasome and composed by the adaptor ASC (apoptosis-associated speck-like protein containing a CARD), procaspase-1, and an NLR family member was identified by Martinon et al. [44]. As such, some NLR family members presenting inflammasome activity, such as IL-1β-converting enzyme protease-activating factor (IPAF) and PYD-containing NLR (NLRP), such as NLRP1, NLRP3 and NLRP6, were identified and their dysregulation was also associated with several non-microbial disorders, including arthritis, obesity, diabetes, neurodegenerative disorders, atherosclerosis and dermatitis [43]. More recently, inflammasome composition was proposed to be more complex, since the cytosolic DNA sensor AIM-2 was suggested to be associated with ASC and promote the formation of a caspase-1-activating inflammasome and maturation of proinflammatory IL-1β cytokine [45].

PRR stimulate two types of innate immune responses, namely the inflammatory responses and the phagocytosis by neutrophils and macrophages, which can occur promptly after recognition [29]. Alternatively, it also includes soluble pattern recognition molecules present in the blood that belong to the complement system and are able to opsonize foreign materials, thus leading to phagocytosis or direct killing of the intruder through the disruption of the plasma membrane [21].

2.2. Major cellular players within innate immune system

The innate immune system is constituted by leukocytes that include mast cells, neutrophils, eosinophils, basophils, macrophages, DC, and NK cells (Fig. 1). Neutrophils, eosinophils, and basophils are collectively known as granulocytes due to the presence of granules in their cytoplasm, or as polymorphonuclear cells due to their distinctive shaped nuclei [23]. These cells circulate in the blood and are produced in increased numbers during immune responses, when they are recruited as effector cells to sites of infection or inflammation.

Phagocytic cells constitute the major subset of the innate immune system and include macrophages, neutrophils, and DC. They are essential for fighting infections and are distributed throughout the body continuously scavenging for the presence of invading threats, being able to engulf pathogens or particles. Phagocytic cells use a combination of degradative enzymes, antimicrobial peptides, and reactive oxygen species (ROS) inside their lysosomal compartments to digest and kill the invader [23].

Monocytes are the largest type of leukocytes that circulate in the blood and can differentiate into macrophages and DC upon migration into the tissues [47,48]. These cells perform three main functions in the immune system, namely phagocytosis, antigen presentation, and cytokine production.

The primary function of macrophages is to clear tissues from pathogens, having extraordinary phagocytosis ability. They are distributed widely in the body tissues as resident macrophages, such as alveolar macrophages, splenic macrophages and liver-resident macrophages, commonly called Kupffer cells (KC) [49]. These phagocytic cells are able to move across the walls of capillary vessels by amoeboid movement and to enter the areas between cells in pursuit of invading pathogens through continuous phagocytosis [21]. Phagocytic macrophages conduct the innate immune response when encountering a pathogen *via* recognition of common constituents by PRR. Macrophages express a number of surface receptors, such as Fc-γ receptor, complement and scavenger receptors to allow recognition of foreign material [49].

Upon activation, macrophages become extremely effective at taking up and killing any pathogens they may encounter. Their killing capacity is caused by the release of strong oxidizing agents, including hydrogen peroxide, free oxygen radicals and hypochlorite, generated by lysosomal nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and other enzymes, in a process known as the “respiratory burst” [23]. Activated macrophages also secrete cytokines and chemokines, such as IL-1, IL-6, and tumor necrosis factor α (TNF-α), increasing vascular permeability and attracting other immune cells from the bloodstream to sites of infection, such as neutrophils and monocytes [21,23].

The release of cytokines, chemokines and growth factors by activated macrophages triggers the process known as inflammation. Inflammation may also be elicited by the activation of the complement, which is initiated rapidly in response to many types of infections [49]. Complement proteins opsonize microbial surfaces with fragments that are recognized and bound by phagocytic receptors on macrophages and neutrophils, activating a cascade of proteolytic reactions and inducing an inflammatory response [23,29]. Complement factors can also activate local mast cells to recruit neutrophils, eosinophils and basophils to the site of infection, by increasing the permeability of local blood vessels through the release of histamine and heparin, causing the characteristic signs of inflammation [21,23].

Neutrophils are the most abundant cellular components of the innate immune response, normally representing 50% to 60% of the total circulating leukocytes. Neutrophil granules contain a variety of cytotoxic molecules that kill or inhibit growth of pathogens. Under normal circumstances, neutrophils do not have access to tissues due to their potentially destructive behavior [21]. However, during the acute phase of inflammation, neutrophils are usually the first responders that migrate toward the site of infection, in a process called chemotaxis [50]. Like macrophages, they have surface receptors for common bacterial constituents and complement, and upon entry into an infected tissue, activated neutrophils attack and engulf the invading microorganisms. Yet, unlike macrophages, neutrophils are short-lived cells, dying soon after performing phagocytosis [23].

NK cells are innate immune lymphocytes capable of killing target cells and producing immunoregulatory cytokines, thus providing a first line of defense against a variety of infections [51]. NK cells are able to detect abnormal patterns of protein expression in host cells, which may indicate the presence of a virus or malignant transformation [21]. Thus, NK cells play a central role in tumor elimination [52]. They are able to detect and kill cells “missing self”, lacking normal expression of major histocompatibility complex (MHC) molecules, which are usually expressed in practically all nucleated cells. NK can also identify and destroy cells expressing “altered self”, thus recognizing the expression of molecules that are not normally expressed in healthy cells, but rather appear in response to viral infection or DNA damage [21]. NK cells can kill target cells by two major pathways: the death receptor pathway or the granule-dependent pathway, both leading to apoptosis [21]. Activation of NK cells also leads to the production of immunoregulatory cytokines, particularly IFN-γ, which enhance the innate immune response and mediate the subsequent adaptive immune response [51].

IFN-γ production enhances the microbicidal activity of macrophages, as well as the production of cytokines, such as IL − 12, but also enhance the antigen presentation function on DC, contributing to the activation and definition of adaptive immune responses [21]. Recently, new studies have suggested that NK cells may be involved on both innate and adaptive immunity, such as immunological memory [51].

2.3. Innate immune system activates adaptive immunity

Although involved in the early pathogen recognition, the innate immune response makes a crucial contribution to the activation, type, and duration of the adaptive immunity [31]. Inflammation increases transport between the infection site and lymph nodes, while complement activation induces phagocytes that can activate lymphocytes. Several studies have demonstrated an evident bridge between innate and adaptive immunity provided not only by the direct interaction of TLR on B and T cells with their ligands, but essentially by indirect TLR-mediated DC maturation [53]. DC are scattered throughout the body at peripheral tissues, such as the skin and mucosal surfaces, functioning as the sentinels of the immune system [54,55]. These APC are crucial for both innate and adaptive immunity. Upon pathogen recognition through their PRR and internalization at peripheral tissues, immature DC became mature and migrate to regional lymph nodes to present antigenic peptides in the context of MHC class molecules to naïve T or memory T cells, and initiating adaptive immunity [23,56]. These cells do not identify and respond directly to native antigens like B cells do, but can rather recognize processed antigen presented by MHC complexes through their T-cell receptors (TCR). DC express both MHC class I and class II molecules, being able to stimulate antigen-specific $CD4^+$ and $CD8^+$ T cells, which respectively differentiate into $CD4^+$T helper (Th) cells and cytotoxic T lymphocytes (CTL) [7,55,57]. CTL are able to eliminate virus-infected or tumor cells, while Th cells promote B cell activation, macrophage function and maturation of other T cells. In this complex process, the DC-mediated polarization of different Th subsets, including Th1, Th2 or Th17, after stimulation of naïve CD4+ T lymphocytes is mediated by several events, as TLR-induced cytokines. While IFN-ɣ-producing Th1 cells central for protection against intracellular viral and bacterial infections are stimulated by IL-12, Th2 responses crucial against extracellular protozoa and allergens are mostly dependent on IL-4 [58,59]. On the other hand, Th17 responses involved in protection against certain bacterial infections and autoimmunity seems to be largely dependent of IL-23, IL-1β, TGF-β and IL-6 [59].

Intracellular antigens, such as proteins produced by viruses, or tumor cells are presented by MHC class I molecules to $CD8^+$ T cells. On the contrary, extracellular pathogens are presented to $CD4^+$ T cells by MHC class II-antigen complexes. However, DC also have the ability to process exogenous antigens and present them *via* the MHC class I pathway, leading to the activation of antigen-specific $CD8^+$ T cells, a phenomenon that is called cross-presentation. It is this ability that allows them to cross-present tumor antigens and generate tumor-specific CTL responses [60].

3. Nanoparticle properties with major impact on innate immune system

In order to reach target cells, NP delivery systems must be stable in the blood and be able to cross biological barriers. Subsequently, NP can be transported *via* the cell membrane through the endocytic pathways, including phagocytosis, macropinocytosis, clathrin-mediated endocytosis and caveolae-mediated endocytosis [3,61]. Non-phagocytic cells mainly transport NP *via* clathrin, caveolae-mediated endocytosis or macropinocytosis, while “professional phagocytes”, such as monocytes, macrophages, or neutrophils are capable of phagocytosis, enabling the uptake of larger particles [61,62].

Receptor-mediated endocytosis occurs when the particle binds to a specific cell surface receptor and is selectively internalized. Thus, proteins or other targeting moieties present at NP surfaces may trigger those cell surface receptors and activate NP uptake. In addition, NP may also enter cells by passive penetration of the cell membrane, especially for cells lacking endocytosis machinery [11]. Still, regardless of the internalization mechanism, the endocytosed material is usually sorted at the early endosome and directed to distinct endocytic pathways, which will determine its intracellular localization, bioavailability and consequent biological effect [61,62].

NP behavior when administered *in vivo*, including their recognition and interaction with cell surfaces and endocytic pathways are modulated by several factors, such as route of administration and NP physicochemical properties including size, shape, surface charge, surface area-to-volume ratio and surface chemistry/bioactivity [63,64]. These dictate NP clearance, biodistribution and overall balance between tolerance and nano-mediated toxicity. In addition, cell-specific parameters such as cell type, cell cycle phase or nature of endocytic machinery also have a major impact on NP-cell interaction [1,4].

NP can be synthesized to be recognized or avoided by the innate immune system depending on their final goal. Understanding these factors is, therefore, important for designing and engineering NP that will preferentially interact with target cells, thus minimizing non-specific biodistribution and consequent side effects [11]. NP physicochemical properties with major impact on the interaction with immune system are the primary focus of the following sections and are summarized on Table 2.

3.1. Size, size distribution and nanoparticle aggregation

Particle size is one of the most critical factors influencing NP interactions with living cells, NP biodistribution and circulation time, as well as NP capture by cells from the MPS. The size of NP strongly affects their uptake efficiency and kinetics, internalization pathway, intracellular localization, cytotoxicity and ensuing immune responses [11].

Smaller particles are usually considered more effective drug carriers, as lower dimensions potentiate their delivery across biological barriers to target tissues. NP for drug delivery may range from less than 10 nm to around 500 nm [65,66]. Nanocarriers of 10–200 nm can accumulate at tumor sites through the EPR effect, while larger (> 200 nm) and smaller (5–10 nm) particles are eliminated by the MPS and *via* renal clearance, respectively [67]. Thus, NP of 100–200 nm are preferred for targeted drug delivery [68].

NP diameter also affects the endocytic pathways involved in particle internalization, such as phagocytosis, macropinocytosis, clathrin, or caveolae- mediated endocytosis [68]. NP in the range of 20–200 nm are usually taken up *via* clathrin or caveolae-mediated endocytosis, whereas larger particles (> 500 nm) are mainly taken up *via* phagocytosis or macropinocytosis [68,69].

However, smaller NP seem to increase cellular toxicity compared to larger NP, as their higher surface area potentiates the interaction with biomolecules present in the environment, triggering adverse reactions [11]. Oxidative stress caused by NP is one of the outcomes of inflammation. Differences in internalization mechanisms due to distinct NP sizes have been shown to affect the production of ROS and enhance the expression of pro-inflammatory cytokines [4,49].

Size-dependent cellular uptake has been observed in different cell lines for diverse types of NP, including gold [70,71], iron oxide [72], silica [73,74], polystyrene NP [75,76], QD [77], liposomes [78] and polymeric NP [79,80].

Silica-titania hollow NP (HNP) with uniform diameters of 25, 50, 75, 100, and 125 nm revealed the size-dependent viability, ROS, and apoptosis/necrosis of HNP-treated macrophages, with 50-nm HNP demonstrating the highest toxic effector macrophages measured by the production of IL-1, IL-6 and TNF-α [74]. Iron oxide NP of 35 ± 14 nm induced higher levels of inflammation and immunodepression than

Table 2
Summary of nanoparticle (NP) properties with major impact on their interaction with different branches of innate immunity.

Properties/features	Major Impact on NP-cell Interactions and Biological Effect
Size	• Modulates the capture by mononuclear phagocytic system (MPS) cells, subsequent biodistribution and circulation time. • NP renal clearance occurs mostly in the size range of 5–10 nm. • Delivery across biological barriers is more effective with 10 nm to 500 nm NP, but it depends on type and composition of NP. • Larger particles (500–2000 nm) are preferentially captured by macrophages, while dendritic cells (DC) mainly internalize NP in the size range of 20–200 nm. • NP < 50 nm efficiently drain to the lymph nodes following subcutaneous administration; NP of 500–2000 nm are mainly transported by skin phagocytic cells. • 20–200 nm NP are internalized by *via* clathrin or caveolar-mediated endocytosis, while NP > 500 nm are captured *via* phagocytosis or macropinocytosis. • Higher inflammatory and toxicological effects, including the secretion of reactive oxygen species (ROS) and pro-inflammatory cytokines, as well as the induction of immunodepression, is verified for smaller NP due to an increased interaction with environmental biomolecules. But, NP composition and structure also play a significant role.
Hydrophobicity	• Hydrophobic materials or presence of hydrophobic ligands at NP surface act as danger signals, triggering inflammation and innate immunity. • Hydrophobic surfaces promote opsonisation and, consequently, enhance the uptake by phagocytic cells and subsequent clearance from blood circulation.
Surface Charge	• PEGylation neutralizes NP charge, increases hydrophilicity, thus preventing recognition by the reticuloendothelial system (RES). • Cationic NP are recognized at higher extent than negatively surface charged carriers, of similar sizes. • Surface charged NP have lower circulation times compared to neutral NP. • Chitosan is used to confer positive charge to NP surface, but also presents immunostimulatory properties by activating NLRP3 inflammasome.
Surface Chemistry/Bioactivity	• NP surface functionalization with targeting moieties triggers receptors at the surface of immune cells and activates NP uptake. Mannose, anti-CD205 or anti-CD40 are examples of ligands used to increase recognition and capture by DC. • Coating NP surface with red blood cell membranes avoids immune recognition, and consequently increases circulation time.
Surface Area-to-Volume	• Higher surface area leads to increased charged density, leading to more biologically reactive surfaces and prone to opsonisation.
Impurities, Contamination and Endotoxin levels	• Sub-products from NP synthesis or by endotoxin contamination decrease mitochondrial membrane potential and increase intracellular ROS; • During NP synthesis, it is crucial to detect lipopolysaccharide (LPS) contamination by surfactants or bacterial fragments, even upon material sterilization. This will avoid NP toxicity and uncontrolled innate immune system activation.

147 ± 48 nm [81]. Monodisperse polypyrrole (PPy) NP with five different diameters (20, 40, 60, 80, and 100 nm) were prepared in order to evaluate their cytotoxicity and cellular uptake in lung fibroblasts and macrophages, with 60 nm PPy NP triggering the highest adverse effects on both cell lines [82]. In these studies, mid-sized NP (40–60 nm) showed the highest effects on macrophages, whereas gold and silver NP have shown the highest toxicities for smaller (< 10 nm) NP.

Exposure to 5 nm silver NP induced higher expression of IL-8, as well as stress genes against ROS, than 100 nm NP [83]. Park et al.[84] compared 4 nm, 20 nm and 70 nm silver NP, observing size-dependent inflammatory and toxicological effects, with 4 nm NP inducing the highest levels of cytotoxicity, ROS production and IL-8 secretion. Pan et al.[85] observed that small gold NP (1–2 nm) were highly toxic and caused rapid cell death in comparison to 15 nm NP.

The increased cellular toxicity of smaller NP compared to larger NP may be related to increased specific surface area and increased charged density, making their surfaces more reactive and prone to opsonization.

Regarding the development of vaccine delivery systems, the interaction of NP with phagocytic cells of the innate immune system is highly desired. In fact, the efficient internalization of NP by APC, especially DC and eventually macrophages, is crucial to achieve effective antigen presentation and to elicit an immune response against entrapped antigens. However, while macrophages mostly capture larger particles of 500–2000 nm, compared to bacteria, DC internalize smaller particles of 20–100 nm, like viruses [86]. Various studies have shown a strong correlation between particle size and the mechanism of antigen uptake, processing and presentation by APC [68,87,88]. NP smaller than 50 nm efficiently drain to the lymph nodes after subcutaneous administration, where they can interact with immune cells [89,90]. In contrast, larger particles (500–2000 nm) depended on their cellular transport by skin DC [66]. However, there is conflicting evidence about the most effective particle sizes for vaccine delivery, and processing of particulate antigens [68,87]. It has been reported that NP in the range of 20–200 nm are efficiently taken up by DC and facilitate the induction of cellular immune responses, whereas particles of 0.5–5 μm mainly generate humoral responses [68,69,87]. NP made from single-stranded RNA (ssRNA) mixed with protamine induced production of IFN-α, whereas microparticles (MP) mainly induced the production of TNF-α, with size appearing to trigger antivirus (IFN-α) or anti-bacterial/anti-fungal (TNF-α) immune responses [91]. Joshi et al. prepared 17 μm, 7 μm, 1 μm, and 300 nm PLGA particles loaded with a model antigen ovalbumin (OVA) and CpG oligodeoxynucleotides (CpG ODN), showing size dependent internalization and activation of DC, with smaller particles displaying highest particle uptake and upregulation of MHC class I and CD86 expression on DC [87]. Limited uptake has been observed of particles larger than 10 μm leading to defective immune activation [87,92].

3.2. Nanoparticle surface composition, coating and charge

NP can be composed by a variety of materials, including biodegradable polymers and biomolecules, as well as inorganic compounds such as gold, silver, carbon, iron, and silica [63]. In fact, different compositions and surface coatings can influence the interaction of immune cells with NP. The surface electrostatic charges of the NP and their hydrophobicity are crucial parameters that influence the uptake by APC, as reviewed [93]. Hydrophobicity of the materials used to engineer NP is usually considered to be DAMP. When these materials entirely hydrophobic or mainly composed by hydrophobic surfaces are exposed to an aqueous environment, their hydrophobic portions prefer to depart from water molecules by aggregating unsymmetrically with each other. Therefore, these hydrophobic exogenous ligands mimicking

a danger signal act as an immunostimulatory alarm, being easily detected by specific surface receptors that trigger inflammation and generate an innate immune response [94]. NP surface hydrophobicity increases opsonization by serum proteins and, as a result, higher uptake by APC and further clearance from circulation [95]. If the aim is to design NP to avoid the recognition by the immune system, coating the NP surface with polyethylene glycol (PEG) in order to neutralize the charge and increase the hydrophilicity of the nanosystem is one of the most used strategies [96,97]. Thus, PEGylation is a way to camouflage NP from the RES. According to Sheng et al. the PLA-hemoglobin NP uptake by macrophages was avoided with PEG coating. Therefore, NP circulation time was prolonged and their clearance was reduced compared to non-PEGylated PLA-hemoglobin NP [98]. However, some studies show that the immune system can produce anti-PEG IgM antibodies after repeated PEGylated liposome administrations leading to the clearance of subsequent doses [99,100]. This issue needs to be better explored due to the lack of studies that investigated the specificity and related pharmacokinetic of these antibodies [101]. The coating of NP surface with natural cell membranes, namely red blood cells, is another approach to overcome the immune recognition and avoid an unexpectedly immune response. According to Chambers et al. attaching red blood cells to polymeric NP increased their circulation time without the need for changing surface functional groups [102]. In fact, red blood cells have surface proteins that avoid their uptake and effect on the complement system. For example, the CD47 surface marker downregulates the activity of phagocytic cells due to the interaction with signal regulatory protein alpha (SIRP-α) [103]. However, if the main goal is to improve the immune targeting of APC, functionalization of NP surface with polysaccharides moieties, such as chitosan [104,105] or mannose [106,107], or addition of antibodies specific to DC receptors, such as anti-DEC205 or anti-CD40 [108,109] are strategies that have been adopted. Cationic NP are taken up more efficiently by these phagocytic cells than anionic and neutral ones with the same size due to the interaction with the negatively charged cell membrane [93]. In addition, charged NP have lower circulation times compared to neutral ones [110,111]. Regarding chitosan, this polymer has the ability to strongly activate NLRP3 inflammasome in macrophages by stimulating the release of the inflammasome-associated cytokine IL-1β, and has been largely applied for the coating of metallic NP [112]. Metallic NP by themselves have the ability to modulate the expression of TLR that influence the production of cytokines. Cui et al. showed that TiO_2 NP increased the levels of TLR2 and TLR4 and Lucarelli et al. demonstrated a higher expression of TLR3 and TLR7 after the use of ZrO_2 NP [113]. Metallic NP, such as silver and silica ones, also induced inflammasome formation and further caspase initiation [114,115]. Regarding CNT, these structures have the ability to activate the complement system [116]. According to Salvador-Morales et al. high amounts of fibrinogen and apolipoproteins (AI, AIV and CIII) bound to CNT [116]. In addition, cationic lipids, such as RPR206252, can also be used for the development of cationic nanocarriers and to stimulate inflammatory responses dependent on both TLR2 and NLRP3 inflammasome pathways through the production of TNF-α, IL-1β, IL-6 and IFN-γ [117].

3.3. Nanoparticle surface area and reactivity

Nanomaterials exhibit superior bioactivity due to the exponential increase of surface area with decreasing diameters [74]. As particle size decreases, the surface area increases and a greater proportion of molecules are found at the surface, which may render them more biologically reactive. Large surface area of NP increases adsorption of proteins which can affect their interaction with macrophages ad other immune cells. It has been suggested that NP composed of low-toxicity material, such as polystyrene, have pro-inflammatory activity due to their large surface area [118]. Brown et al. observed a significantly greater neutrophil influx into the rat lung after administration of 64 nm polystyrene NP compared with 202 and 535 nm particles, with inflammation levels being directly proportional to surface area [118]. A study using polystyrene particles (PSP), carbon black (CB), and diesel exhaust particles (DEP), showed that at a given mass dose, the small particles (0.0588 and 0.202 μm PSP, CB, and DEP) increased the allergen-specific IgE serum levels in proportion to surface area. It also increased the expression of surface markers (CD19, MHC class II, CD86, and CD23) and the *ex vivo* production of IL-4 and IL-10, in contrast to the largest particles did not [119]. The surface areas of 15, 51 and 95 nm CB NP were correlated with oxidative stress, DNA damage and pulmonary cell infiltration in rats [120]. Silicon dioxide (SiO_2)NP of 10 or 100 nm triggered size dependent cytokine inflammatory response and oxidative stress *in vitro*, with smaller NP showing more cytotoxicity due to significantly higher surface area interaction with the cells [121]. Equivalent toxicity levels were found when similar surface areas were used by increasing 100 nm NP concentration 10-fold. Titanium dioxide (TiO_2) and crystalline SiO_2 NP, led to an upregulation of MHC-II, CD80, and CD86 on DC, and activated the inflammasome and enhanced production of ROS, which for TiO2 NP was dependent on surface area [122]. Porosity also appears to affect inflammatory activation, as porous silica NP were reported to increase ROS generation and adversely affect ATP and TNF-α content in macrophages [4,123]. However, other study comparing porous and non-porous silica NP showed a drastic increase in MAPK, TNF-alpha, IL-1β and NF − κ B production when macrophages were subjected to non-porous silica NP rather than porous silica NP [124].

3.4. Crystallinity

Inhalation of SiO2, also known as crystalline silica, induces inflammation in the alveolar space, and prolonged exposure can lead to the development of silicosis, an irreversible fibrotic pulmonary disease [125]. The mechanisms by which crystalline silica and other crystals activate immune cells are still not well understood [125]. However, studies have shown that silica and aluminium salt crystals activate inflammasomes by triggering the cytoplasmic receptor NALP3 upon phagocytosis of crystals [125]. The NALP3 inflammasome recognizes crystalline material as a 'danger' signal [125]. NLRP3 activation has been proposed to be dependent on several mechanisms, such as ATP-induced efflux of potassium ions *via* P2 × 7 ion channels and pannexin-1, ROS induction, and lysosomal destabilization and rupture after phagocytosis of crystals leading to the release of lysosomal proteins that activate the NLRP3 inflammasome [126]. Crystalline silica NP are known to initiate both necrotic and apoptotic cell death mechanisms, a result of mitochondrial and lysosomal damage [4]. Crystalline silica (SiO_2) was shown to activate NLRP3 inflammasomes in human lung epithelial cells BEAS-2B and primary human bronchial epithelial cells, prolonging the inflammatory signal and affecting fibroblast proliferation [127]. Sun et al.[128] found a correlation between the shape and crystallinity of AlO(OH) NP and their ability to activate DC *in vitro* and induce production of IgG and IgE against OVA *in vivo*. Gout-associated uric acid crystals activate the NALP3 inflammasome, resulting in the production of active IL-1β and IL-18 [129]. TiO_2 NP may cause different adverse health effects depending on the crystal structure, with the anatase phase of nanocrystalline TiO_2 appearing to be more toxic than the rutile phase, probably due to a high photocatalytic activity of anatase resulting in generation of ROS [130].

3.5. Impurities, contamination and endotoxin levels

Biological effects of nanomaterials can also be altered by impurities, generated as by-products in NP synthesis or by endotoxin contamination [131]. Dose- and time-dependent increase of intracellular ROS and a decrease of the mitochondrial membrane potential with commercial CNT were observed after particle administration due to metal contaminants, whereas incubation with purified CNT had no effect [132].

Vallihov et al. highlighted the importance of high purity in the production of gold NP when assessing biological activity, showing that the presence of lipopolysaccharide (LPS) contamination on conventionally formulated NP had a maturating effect on the DC, whereas low-LPS formulations had practically no effect on phenotypic maturation or cytokine production of DC [133]. In order to correctly evaluate the capacity of NP to trigger inflammation, there is a strong need to evaluate possible contamination by surfactants or bacterial fragments present in the formulation, even in sterilized material [9,134]. In particular, LPS is a common contaminant of biomaterials, which is a potent activator of inflammation [134]. Cytokine storms may be driven by endotoxin contamination of NP formulations and are also a major concern in NP toxicity and uncontrolled activation of the innate immune system by the biomaterials [135]. Studies have shown that the presence of bacterial endotoxins in chitosan derivatives can result in false-positive results in the evaluation of their *in vitro* performance [136]. Thus, it is of utmost importance the use of endotoxin-free NP in the experimental procedures *in vitro* and *in vivo* [134].

4. Role of biological external factors on the interaction of nanoparticle with innate immune cells

When NP are in contact with biological environment, such as human plasma, they selectively adsorb biomolecules at the interfacial region, forming the so-called biomolecular corona or protein corona [91,137]. To predict the NP behavior in such biological environments, it is crucial to understand this corona formation process to improve drug delivery and also avoid unexpected nano-mediated toxic events.

The protein corona is a highly dynamic process and its composition changes over time. In the first phase, there is a rapid adsorption of proteins onto the NP surface. At a second phase, there is a constant association and dissociation of proteins, until the composition of protein corona reaches an equilibrium state of constant composition [138,139]. Human serum albumin (HSA), fibrinogen and immunoglobulin (IgG) are the most common proteins found in the hard protein corona, binding firmly to the surface of the NP with distinctive stability [140]. However, the protein corona can change when NP move from one biological compartment to another, such as passing through the cellular membrane to an intra-cellular location [138]. In addition, these protein interactions with NP surfaces can disrupt the native conformation of these proteins, which can compromise their function [139].

The resulting structure of the protein corona may as well induce changes in the nature of the extracellular matrix. This matrix is consistently interacting with cell surface receptors, growth factors and cytokines, leading to different signaling cascades that are related to cell behavior. Therefore, a single change in the extracellular matrix nature may significantly modify cell behavior, supporting the need for better understanding of this dynamic interaction between NP and biomolecular species [141,142].

Thus, to acquire a deeper knowledge on the impact of nanomaterial in biological systems, we need to take into account the role of NP physicochemical properties on the protein corona composition [143,144]. In fact, the protein adsorption onto NP surface is deeply influenced by NP size [143], configuration [145], solubility, surface charge and functionalization [74], as well as by NP sedimentation, especially in *in vitro* systems [140,144–146]. Other factors, such as temperature, pH, and presence of certain functional groups, may also lead to different protein corona composition [137].

NP size is a crucial factor in determining the affinity and the type of proteins adsorbed onto NP surface [143]. It has been demonstrated that NP with similar surface charge, but with distinct sizes, adsorb proteins at different levels of affinity [147]. Moreover, NP size is determinant for NP curvature, which deeply influences the composition and conformation of the protein corona. NP highly curved showed a protein corona with composition different from the one obtained for the bulk material, which was characterized by lower inter-particle interactions [148].

NP shape also plays an important role on protein adsorption on the NP surface, and therefore may influence the general biological response to NP. Studies have showed that protein adsorption is more pronounced in spherical NP than in rod- or tube-shaped NP [147,149]. Therefore, those spherical-shaped NP had a stronger interaction with cells than the rod-shaped NP [147,150,151].

NP functionalization with various chemical groups or polymers was explored to prevent and control protein adsorption to NP used as drug delivery vehicles or targeted therapeutic systems. For instance, PEG is commonly used for NP functionalization to prevent NP recognition by the RES by reducing protein binding, thus increasing the half-life of those NP [152]. Therefore, PEG is known for reducing immunogenicity and for conferring stealth characteristic to NP. It is believed that PEG also reduce complement activation responses [153].

The NP surface charge is another NP characteristic that affects protein corona composition, as well as the overall biological effect. Charged surfaces (negative or positive) induce protein disruption, whereas NP with neutral surface charge allow the preservation of protein structure [143,148]. An increase in NP superficial charge density leads to an improved adsorption of plasma proteins. For instance, positively charged NP were rapidly recognized by serum opsonins, leading to their prompt elimination by the RES [154,155].

Another important parameter that also affects the protein corona composition is the solubility of NP, which is deeply related to their superficial charge. Hydrophilic NP present a lower plasma protein interaction than the one observed for hydrophobic NP with similar protein affinity [137,156].

That being said, unless NP are specifically designed to avoid the interaction with serum proteins, upon contact with biological fluids, NP will be rapidly covered by biological molecules, forming a surface corona, that may lead to a behavior *in vivo* different from the one initially predicted and intended to fulfill a particular biological application [140,157].

Although the NP physicochemical properties influence the composition of protein corona, this bio-corona also alters the size, aggregation state, and interfacial properties of NP, leading to a new biological identity [10,158]. The complex properties of the protein corona will control the nature of NP interactions with cells and tissues, determining their internalization pathway, and the consequent balance between NP biocompatibility and NP-related bio-adverse effects. Consequently, it has a fundamental role on the application of these NP to personalized medicine, as it can lead to a marked variability in the responseto therapy while inducing unexpected nanotoxicological effects [157,159,160].

As we well know, the immune system is more concerned with entities that can induce damage than with those that are foreign. In this way, cells of the immune system recognize alarm signals triggered by PAMP and DAMP associated to the recognition of pathogens or tissue damages. In the same way, engineered NP coated with a complex protein corona acted as danger signals, as nanomaterial associated molecular patterns (NAMP) [91,161]. These patterns were recognized by PRR including the TLR, key elements of the innate immunity. The activation of those PRR triggered the inflammation process and alerted the adaptive immune system. Additionally, it was shown that NP presenting hydrophobic surfaces displayed by protein corona, were recognized as danger signals by the immune system [91]. In fact, unmodified NP surface are stealth or at least less recognized by the immune cells, than those covered with a protein corona, which more rapidly triggered an immune response [137,161].

The protein corona activates different components of the immune system, like Type 1T helper (Th1) lymphocytes, B lymphocytes and Type 1macrophages (M1). After this, molecules such as immunoglobulin, cytokines and chemokines will be secreted, producing an acute inflammatory reaction with no neoplastic events. If, by the

other hand, the protein corona triggered the activation of Treg cells, Type 2T helper (Th2) or Type2 macrophages (M2), the secreted molecules will initiate a chronic inflammatory reaction with a possible protumorigenic action [162].

In this manner, the knowledge of protein folding, affinities and stoichiometric of association or dissociation from NP is crucial to fully understand the nature of the immunological responses induced by NP [156]. For example, in cases where the protein corona does not completely cover the NP surface, binding only at discreet sites, NP-related toxicity events may emerge [163].

Engineered NP have the capacity to activate innate immune cell responses *via* inflammasomes in macrophages, triggering the release of IL-1β and neutrophil infiltration. In addition, differences upon protein orientation and folding can lead to distinct receptor activation and thus different cytokines released patterns [164]. Variations in protein adsorption are deeply correlated with differences in the mechanism and efficiency of NP internalization by macrophage cells [158]. So, these changes in protein conformation may affect the functionality of such protein, resulting in undesirable immune responses [137]. In fact, proteins adsorbed onto NP surface may suffer conformational changes that can result on the exposure of new epitopes. These epitopes can be accessible as antigens by APC to initiate the adaptive immune system. For example, in a study using poly(acrylic acid)-conjugated gold NP, Deng et al. showed that these negatively charged NP bound to fibrinogen and induced its folding. This conformational change activated the receptor macrophage-1 antigen (Mac-1) on THP-1 cells triggering the release of cytokines *via* the NF-κB pathway [164].

Knowing that the composition of the protein corona plays an important role on the interaction between NP and the innate immune system, different scientific groups have been using dynamic light scattering (DLS) and nanoliquid chromatography tandem mass spectrometry for characterizing the protein corona of lipid and silica NP. The data show that the main proteins that are adsorbed onto NP surface are immunoglobulins, complement factors and coagulation proteins. These biomolecules have specific receptors that can bind to immune cells, triggering their activation. However, when proteins like albumin or apolipoproteins are present on the protein corona, the NP internalization is inhibited [156,165].

Additional studies defining the protein corona composition, have evidenced enhanced levels of the protein factors B and C3on the surface of NP grafted with glycopolymer chains, which are responsible for the complement activity [166]. The adsorption of a protein corona initially triggers the complement activation *via* classical pathway, when the complement protein C1q binds to sufficient number of ImmunoglobulinC(IgC) molecules adsorb on the NP surface. These C1q-IgC interaction requires the presence of a minimal number of IgC molecules to further activate the complement system [167]. These IgC fragments are present in all protein corona regardless the physicochemical properties of NP, but C1q was not found on NP smaller than 50 nm [143]. Although the innate immune system plays a crucial role on protecting a biological system from NP, excessive complement activation can cause severe clinical adverse reactions in susceptible individuals [91,168].

From a different point of view, if controlled, the presence of proteins at the surface of nanomaterials may constitute important tools to take advantage of host immune system in disease control. These danger signals can therefore also have a therapeutic positive effect, acting as vaccine adjuvants, enhancing the immunogenicity of co-administered antigen. As an example, Pluronic-stabilized polypropylene sulfide (PPS) NP conjugated with antigen OVA, generated humoral and cellular immunities. The complement system was activated, generating a “danger signal” that triggered the activation of DC, resulting in a positive vaccination reaction [169].

All these findings provide crucial knowledge for improving the design of controlled surface engineered NP immunologically safer for future nanomedicine application, by controlling the protein corona composition [162].

5. Nanoparticle-innate immune system interplay

5.1. Pro-inflammatory effect: secretion of immunoregulatory molecules

The interaction between NP and immune cells is almost inevitable and usually triggers immune activation once NP are recognized as non-self antigens. However, these interactions with immunomodulatory potential can activate or suppress immune functions. The functionalization of NP with one or a multitude of combinatory ligands against PRR holds a great potential to improve immune system-targeting strategies for therapies against cancer and infection diseases. The targeting of intracellular and/or surface TLR with synthetic ligands is the most common approach. For instance, Kim et al. demonstrated that EG7-OVA tumor-bearing mice vaccinated with DC previously treated with antigen-loaded poly(L-lysine) (PLL)/hyaluronic acid(HA) nanocomplexes containing CpG-ODN as TLR9 ligand could induce tumor growth inhibition, as well as, a strong systemic immune memory response [170]. Ruiz-de-Angulo et al. reported the use of 40 nm lipid-coated magnetite micelles carrying OVA antigen and TLR9-agonist CpG, in addition to iron oxide-selective radiogallium for image-guided development of targeted cancer vaccines [171]. These nanosystems were able to enhance cellular and humoral immune responses against tumor challenge [171]. Hybrid polymeric NP containing quantum dots (QD) were also developed to track in real-time the synergistic effect of activator of transcription-3 (STAT3) siRNA and TLR9-ligand CpG delivered to the tumor microenvironment (TME) [172]. Doxorubicin-loaded silica NP and antigen-loaded PLGA NP carrying the TLR3 agonist polyinosinic:polycytidylic acid (poly I:C) enhanced the death of breast carcinoma cells [173] and prolonged the survival of melanoma-bearing mice [174]. Different combinations of TLR ligands in a single nanocarrier have been used to synergistically trigger Th1 immunity in vaccination. Fox et al. showed that the combination of the TLR7 ligand, imiquimod, and the TLR4 ligand, glucopyranosyl lipid adjuvant (GLA), loaded in anionic liposomal formulations synergistically triggered a Th1 biased adaptive immune response against recombinant malaria antigen by enhancing the production of IFN-ɣ [175]. Pulmonary vaccination with antigen-carrying lipid nanocapsules containing monophosphoryl lipid A (MPLA) embedded in the capsule walls and combined with soluble poly I:C (TLR4 and TLR3 agonists, respectively) was also reported by Li et al. to elicit strong effector memory-biased $CD8^+$ T cell responses in the lung mucosal surfaces [176]. Moreover, poly(anhydride) NP were also demonstrated to be active Th1-adjuvants by eliciting a CD8 T-cell response and acting as agonists of TLR2, −4, and −5 [177]. Cubillos-Ruiz et al. also showed that polyethylenimine (PEI)-based NP encapsulating siRNA were able to stimulate TLR5 and TLR7 and silence immunosuppressive molecules on tumor-infiltrating regulatory DC, triggering effective antitumor immunity [178].

Although immune suppression can act negatively against infections and cancer cells, it can also act positively in treating inflammation and autoimmunity. NP can be used to suppress the immune system through their intrinsic immunosuppressive properties. In contrast to those studies, 4 nm gold NP engulfed by macrophages inhibited TLR9 function and proinflammatory cytokine production in response to CpG ODN, contributing to the therapeutic manipulation of some diseases, such as lupus nephritis and autoimmune diseases [179]. Shaunak et al. reported that dendrimer glucosamine conjugates inhibited the synthesis of proinflammatory signals mediated by TLR4-ligand interaction in human macrophages and DC exposed to LPS bacterial endotoxin. Due to their anti-inflammatory properties, aminosaccharide dendrimer conjugates can be used to prevent systemic inflammatory response syndrome in patients after surgery, burns, and in bacterial sepsis [180].

Studies describing the activation of the important pro-inflammatory pathway NLRP3 inflammasome by distinct nanocarriers have also been reported. Sun et al. reported the design of more potent aluminum-based

vaccines by synthetizing aluminum nanorods with improved adjuvanticity able to promote the activation NLRP3 inflammasome with IL-β1 production and boost OVA-specific immune responses in mice [128]. Signaling both TLR and NLRP3 inflammasome in APC through different NP has also been reported to improve vaccine design. Antigen-loaded PLGA NP containing LPS triggered potent humoral and cellular immune responses *via* both TLR4 and inflammasome activation [181]. Moreover, cationic lipid NP presented the ability to stimulate innate immunity by activating TLR2-mediated inflammation and NLRP3 in human or mouse macrophages [182].

In contrast, silica and titanium NP have been described as harmful inducers of cytotoxicity and inflammation *in vivo* by activating caspase-1/inflammasomes proinflammatory pathway [183,184]. Therefore, the use of these NP in several care products, including food constituents, nutritional supplements and cosmetics must be carefully evaluated.

Additional concerns related to the administration of nanomedicines arise from the possible toxic effects consequence of immune hyperactivation and hypersensitivity reactions, including complement-activation related pseudo-allergy and cytokines storms. Both phenomena can be life threatening by causing the damage of local tissues and multiple organ failure [185]. Therefore, before entering in clinical trials and even receiving FDA approval, these aspects related to activation of complement system following NP must be further considered and will discussed in the next section.

5.2. Activation of complement system by nanoparticles

One of the major effector mechanisms of both innate and adaptive immunity is the complement system, acting often as the first line of defense against pathogens. Being incredibly simplistic, but at the same time, highly complicated and organized, the complement system is composed by a unique network of over thirty different plasma and membrane proteins organized into a hierarchy of proteolytic cascades that start with the identification of pathogenic surfaces, and ultimately leads to clearance of pathogens [186].

Three different pathways can initiate the complement cascade after activation. Briefly, the classical pathway is initiated by antigen–antibody interaction; the lectin pathway initiates when mannose-binding lectin (MBL) recognizes the specific spacing of mannose residues on pathogen surfaces; and the alternative pathway is activated spontaneously, after contact with a variety of surfaces, such as amine and carbohydrate structures on microorganisms [187].

Not surprisingly, NP tend to activate the complement system by the alternative pathway due to adsorption and binding of complement molecules to their surfaces [185]. The central molecule of the alternative pathway is the third complement protein (C3). Once enzymatically cleaved, C3 generates two complement fragments, known as C3a and C3b [188]. In its turn, opsonin C3b covalently binds to amine and carbohydrate groups on NP surface – opsonization, leading to the subsequent interaction with its corresponding receptors expressed by the phagocytic cells, enhancing NP clearance through receptor-mediated endocytic and phagocytic processes [188]. The complement activation "signal" can be easily amplified, leading gradually to the formation of convertases that contain an additional C3b molecule (C4b2b3b or C3bBb3b) and shift the substrate specificity from C3 to C5 molecules [188]. C5 is then cleaved into the anaphylatoxin C5a and fragment C5b. After C5b association with C6 and C7, the complex becomes inserted into cell membranes and interacts with C8, inducing the binding of several units of C9 to form a lytic pore, the terminal complement complex, also known as the membrane attack complex (MAC) [188]. In addition to the opsonization by opsonins and cell lysis by the MAC, the activation of the complement system by NP also leads recruitment and activation of immune cells, as a results of the release of anaphylotoxins, such as C3a, C4a and C5a, which are potent proinflammatory mediators [187].

NP are being increasingly implemented in drug and vaccine delivery, and as diagnostic systems, due to their promising features in protected, targeted and sustained delivery of active pharmaceutical and vaccine components, as well as contrast agents.

Systemically administered delivery systems have typically been designed to avoid complement activation in order to minimize effects, such as rapid clearance of the nanosystem and acute-type reaction, being actually a significant safety issue in nanomedicine. However, some research groups attempted to do the opposite and specifically designed a biomaterial that strongly activates complement to generate a molecular adjuvant danger signal *in situ* [169,189]. In fact, in addition to serve as a biochemical defense system, that clears pathogens non-specifically, complement can also be exploited to promote an appropriate immune response [190]. Initially, it was thought that complement was more important in B cell biology than in T cell biology since humoral responses were impaired in complement/CR-deficient models developed, while T cell responses were apparently normal [191,192]. However, the finding that priming of both CD4 and CD8T cells was reduced in C3-deficient mice suggested a more generalized role of complement mice [193]. The mechanism related to this effect is still not well characterized, but represents a crucial area of study in understanding the roles that the complement cascade may play in regulating adaptive immune responses.

Different research groups have explored the possibility of using the complement system as an alternative to the microbial-derived adjuvants, acting as a danger signal of the innate immunity, and then promoting antigen-specific immune responses [189,190,194,195].

A diverse number of polymeric NP [196,197], liposomes [198,199] and CNT [116,200] have been related to the complement cascade activation. The interaction between NP and the complement system is complex and regulated by several interfacial dynamic forces and physicochemical factors. Size, morphology, and surface characteristics (charge, repetitiveness and nature of building blocks) may affect the recognition of NP by the complement system, and consequently trigger complement activation through the three different initiation pathways, as well reviewed by Moghimi et al. [201,202]. One important property in complement activation is the hydrophobicity of the NP surface. It has been demonstrated that hydrophobic surfaces are more potent activators than hydrophilic ones, and incorporation of chemical groups such as −NH2, −OH or −COOH influences the activation of the complement [203]. Camacho et al. developed copolymer methyl vinyl ether and maleic anhydride (PVMA) NP and assessed their ability to activate complement cascade, *in vitro* [194]. It has been shown that, in addition to be recognized by TLR on DC and induce their maturation [204], hydroxylable groups presented on these poly(anhydride) NP surfaces offer a potential active surface for complement activation. Camacho and co-workers found that PVMA NP were strong activators of the complement system, contrarily to PLGA NP (used as reference), suggesting the promising use of these NP as both adjuvant and vaccine delivery system [194]. Another excellent work showing the ability of NP to activate the complement cascade, generating a danger signal *in situ* and potently activating DC was developed by Hubbel et al. [190]. After intradermal injection, ultra-small (25 nm) Pluronic-stabilized PPS NP were efficiently transported to lymph nodes, targeting resident DC. When conjugated with the model antigen OVA, NP triggered humoral and cellular immunity in mice in complement-dependent manner. According to further studies, complement activation as well as the final disposition of C3b *versus* iC3b after in situ PPS NP complement deposition were depending on surface hydroxylation, surface charge and PPS-core thiolation [205]. Ma et al. also took advantage of the efficient complement activation by NP to promote antigen-specific immune responses [189]. In this work, chitosan-based microparticles (CS-NH_2 MP) were used as a vaccine adjuvant with an active surface for complement activation due to the abundance of amino groups. Using recombinant anthrax protective antigen as a model antigen, and compared with the control amino-cross-linked MP, CS-NH_2 MP significantly increased antigen-specific IgG titers *in vivo* and enhanced the production of IL-4 and

Table 3
Example of nanosystems' effect on different components of the innate immune system.

Innate immune system component	Nanosystem	Composition & Properties	Immune response	Potential application	Ref
Dendritic cells	Polymeric NP	Mannose-functionalized poly(lactic-co-glycolic acid) (PLGA) NP, entrapping MHC class I and MHC class II melanoma antigens and Poly (I:C) and CpG ODN as adjuvants. NP presented a mean diameter ranging 140–190 nm and a surface charge close to neutrality	Mannose-coated NP were efficiently internalized by dendritic cells (DC), triggering activation and maturation. High IgG2c/IgG1 ratios and high levels of IFN-γ and IL-2 were also obtained. These NP allowed also tumor growth delay, when compared with control groups.	Cancer immunotherapy	[214]
	Polymeric NP	Polylactic acid (PLA) NP coated with HIV Gag antigens (p24)	PLA-p24 captured by myeloid derived DC (MDDC) from HIV-1 individuals induced a slight degree of MDDC maturation, cytokine and chemokine secretion and migration towards a gradient of CCL19 chemokine and highly increased HIV-specific CD8 + T cell proliferation compared with p24 alone.	HIV immunotherapy	[215]
	Lipid-based NP	Ionizable-cationic lipidYSK12-C4 containing a multifunctional envelope-type nanodevice (MEND) loaded with siRNA, presented 200 nm of mean diameter	This lipid-based NP allowed silencing of the suppressor of cytokine signaling 1 (SOCS1), inducing a drastic enhancement in cytokine production, resulting in the significant suppression of tumor growth when it was applied to DC-based therapy against a mouse lymphoma	Cancer immunotherapy	[216]
	Polymeric NP	Surface-assembled poly(I:C) onto PLGA microspheres modified by poly (ethylene glycol) (PEG)	These NP activated MoDC with respect to the expression of maturation-related surface markers, proinflammatory cytokine secretion as well as directed migration	Immunotherapy	[217]
Dendritic cells and macrophages	Polymeric NP	Lipopolysaccharides (LPS) coated PLGA entrapping ovalbumin (OVA, model antigen)	PLGA NP triggered potent humoral and cellular immune responses against OVA after efficient internalization by DC. When engulfed by macrophages, PLGA NP triggered inflammasome activation, producing the proinflammatory cytokine IL-1β.	Immunotherapy	[181]
Macrophages	Metal NP	CpG ODN (TLR9 ligand) modified gold NP (AuNP) with a short triethylene glycol (TEG) spacer in between the poly-T and the CpG sequence, presenting 15 nm	CpG conjugated AuNP significantly enhanced macrophage stimulation *in vitro* and inhibit tumor growth *in vivo* when compared to treatments with the equivalent dose of free CpG. Moreover, the anti-tumor activity of the NP treatment appeared to be mediated by the significant infiltration of macrophages and DC to the tumor site.	Cancer immunotherapy	[218]
	Metal NP	Blank AuNP with 4 nm mean diameter	AuNP were efficiently taken up by macrophages. After accumulation in lysosomes, AuNP seemed to modulate TLR9 signaling and function, inhibiting proinflammatory cytokine production by CpG ODN.	Treatment of different diseases, such as lupus nephritis and autoimmune diseases	[179]
	Liposome	Cationic lipid RPR206252 (polyamine lipids bearing C14-acyl chains)	Liposome stimulated the innate immunity by activating TLR2-mediated inflammation in human or mouse macrophages, inducing NF-κB activation, and the production of TNF-α, IL-1β, IL-6 and IFN-γ by human or mouse macrophage cell lines	Immunotherapy	[182]
Neutrophils	Metal NP	Silica (SiO_2), zirconium dioxide (ZrO_2), cobalt (Co) and titanium dioxide (TiO_2) NP	Metal NP can rapidly and differentially alter all steps involved in the degranulation process in human neutrophils, including cell surface expression of granule markers, liberation of proteins into the external milieu, and preservation of active enzymatic activity	Immunotherapy	[219,220]
	Metal NP	Silver NP (AgNP) of 20 nm mean diameter	AgNP rapidly interacted with the cell membrane, penetrated neutrophils, localized in vacuole-like structures, and were randomly distributed in the cytosol after 24 h incubation. After internalization, neutrophil cell size increased. AgNP induced apoptosis and seem to act as potent inhibitors of *de novo* protein synthesis in human neutrophils	Immunotherapy	[221]
Natural Killer cells	Magnetic NP	Iron oxide (Fe_3O_4) NP coated with silica and conjugated with Cy5.5	These magnetic NP controlled the movement of human NK cells by *in vivo* manipulation, when applying an external magnetic field, enhancing NK cell infiltration into the target site.	Alternative clinical treatment for cancer	[52]
	Dendrimer	*N*-Acetyl-D-glucosamine-coated polyamidoamine dendrimer ($GlcNAc_8$) entrapping DNP-LPS or KLH	*In vivo* administration of $GlcNAc_8$ dendrimer activated NK cells. In addition, an increase in serum levels of IgG2aspecific for both T-	Immunotherapy	[222]

(continued on next page)

Table 3 *(continued)*

Innate immune system component	Nanosystem	Composition & Properties	Immune response	Potential application	Ref
			independent (DNP-LPS) and T-dependent (KLH) antigen were observed, which seems to be modulated by NK cell stimulation.		
Natural Killer T cells	Liposome	Stearylated octaarginine-modified liposomes entrapping α-galactosylceramide (α-GC)	Liposome drastically enhanced αGC presentation on CD1d in antigen presenting cells and the expansion of NKT cells population, leading to a therapeutic effect against highly malignant B16 melanoma cells.	Cancer immunotherapy	[223]
	Polymeric NP	α-galactosylceramide analogue KRN7000 (KRN) encapsulated in PLGA-based NP (90 nm) and MP (715 nm)	Both NP and MP entrapping KRN were rapidly internalized by APC inducing a potent primary activation of iNKT cells *in vitro* and *in vivo*.	Immunotherapy	[224]
Mast cells	Metal NP	Silver NP presenting 20 nm and a negative surface charge (−40 mV)	AgNP induced the activation of signal transduction pathways that culminate in increased intracellular calcium levels and consequent degranulation of the mast cell.	–	[225]
Complement system	Polymeric NP	Blank copolymer methyl vinyl ether and maleic anhydride (PVMA) NP, with 150 nm of mean diameter and a negative surface charge (–50 mV), highly hydroxylated	PVMA NP highly activated the complement cascade and acted as agonists of various TLRs, mainly TLR2 and TLR4.	Immunotherapy	[177,194]
	Polymeric NP	Pluronic-stabilized polypropylene sulfide (PPS) NP entrapping OVA (model antigen) with 25 nm of mean diameter and a surface highly hydroxylated	Pluronic-PPS NP triggered humoral and cellular immunity in mice in complement-dependent manner, showing a very similar effect to LPS (TLR4 ligand).	Immunotherapy	[190]
	Polymeric MP	Chitosan-based MP entrapping anthrax protective antigen (model antigen) presented a mean diameter of 1 μm and a positive charge of 22 mV, with abundant amino groups	CS-NH_2 MP triggered complement activation, inducing a significant increase of antigen-specific IgG titers *in vivo* and enhanced the production of IL-4 and IFN-γ with *ex vivo* restimulation.	Immunotherapy	[189]
	Hydrogel NP	80 × 180 nm cylindrical hydrogel NP made of hydroxy-PEG with a negative surface charge (−40 mV)	NP triggered complement activation, inducing a prolonged antigen presentation to APC and eliciting a strong immune response. NP promoted the immunogenicity of OVA, showing comparable adjuvant effect to alum.	Immunotherapy	[195]

IFN-γ with *ex vivo* restimulation. More recently, DeSimone and co-workers observed that hydrogel particles made of hydroxy-PEG were also able to activate the complement system by the alternative pathway, inducing a prolonged antigen presentation to APC and eliciting a strong immune response [195]. These 80 × 180 nm cylindrical NP, fabricated *via* PRINT technology, promote the immunogenicity of a model antigen, OVA, showing comparable adjuvant effect to alum.

As referred above, for most of the systemically administered delivery systems, complement activation is highly undesirable. The predominantly observed effect of NP-mediated complement activation is the surface opsonization, labeling NP for recognition, adherence and clearance by phagocytic cells, which can influence their therapeutic effectiveness [206]. Moreover, activation of the complement system by nanomedicines can trigger degranulation of cells, such as endothelial and mast cells, and release of inflammatory cytokines, which may elicits allergic-like responses (*e.g.* complement activation related pseudo-allergy – CARPA) and even anaphylaxis [207,208]. CARPA represents a novel subcategory of acute (type I) hypersensitivity reactions (HSR), frequently associated with increase in heart rate, hypotension, flushing of the skin (erythema), and decreased cardiac output, pulmonary pressures, and blood gas levels [185,198]. CARPA is mostly mild, transient, and preventable by appropriate precautions. However, in occasional patients, it can be severe or even lethal [199].

It is well known that long-circulating nanomedicines may passively accumulate in interstitial spaces of solid tumors [6]. However, the majority of long-circulating clinically approved anti-cancer nanomedicines have shown a limited therapeutic efficacy in humans, which may be explained by the immune suppressive TME [185,209]. Once in the tumor, accumulated NP can trigger complement activation, which may further proceed through NP opsonization and the release of C5a, resulting in the recruitment of immune cells with immunosuppressive activities into the tumor site, such as Tregs, M2 (alternatively activated) macrophages and neutrophils [210].

One of the most well-known nanomedicines for cancer therapy, Doxil® – a PEGylated nanoliposomal formulation of doxorubicin, induced hypersensitivity reactions (HSR) after administration in clinical studies, caused by complement activation [211].However, other liposomal drugs (Myocet®, Abelcet®, Ambisome®, Amphotec/Amphocyl®, DaunoXome®andVisudyne®) were shown to cause HSR with symptoms corresponding to CARPA, as reviewed by [199]. In addition, some iron oxide formulations for MRI contrast have been withdrawn from the clinic also due to complement activation [212]. Moreover, complement-associated reactions were also reported in a small number of patients who received intravenous NP iron infusions for severe anemia [213].

As the complement system plays a central role in nanomaterial and nanomedicine performance, a better understanding of material properties in relation to complement activation is therefore required. To avoid complement activation in nanomedicine, an important lesson can be learned by studying the complement-escaping strategies used by bacteria. Surface camouflaging with synthetic polymers or alterations in particle geometry or both can modulate NP pharmacokinetics and delay their recognition and clearance by macrophages in contact with blood.

6. Nanoparticle as delivery systems for the modulation of innate immune system cellular components

Although the effect of size, shape, surface charge and surface modification of NP on their biocompatibility has been extensively described, the influence of their properties on the immune system is still underexplored. Regarding their physicochemical properties, NP can modulate innate and adaptive immune response, by interfering with the secretion of cytokines and chemokines, which play an important role in coordinating molecular events between immune cells. Understanding these immunomodulatory effects is extremely important as they can stimulate or suppress immunity.

Table 3 summarizes examples of studies emphasizing the impact of nanosystem physicochemical properties on different components of the innate immune system.

6.1. Phagocytes

Macrophages, DC and neutrophils are characterized by strong phagocytic activity, engulfing pathogens, apoptotic cells and other debris or foreign materials [226]. Most of the currently approved NP were designed to evade phagocytosis to increase their half-life. However, after understanding the role of phagocytic cells in many diseases as cancer, infectious diseases, cardiovascular disease and diabetes, designing NP to target these cells became an interesting approach.

Interaction of NP with phagocytic cells has been extensively studied both *in vitro* and *in vivo*. NP which are not immediately excreted are significantly taken up by these cells, especially in liver, spleen and lungs [227].

In general, size, surface charge, hydrophilicity, composition and concentration are critical factors to target macrophages and DC. Charged and hydrophobic NP are better phagocytosed. Generally, positively charged NP induce higher inflammatory responses, due to macrophages' negative surface charge, which leads to rapid interaction with positive surfaces [228]. For example, after *in vitro* exposure of human macrophages to non-toxic concentrations of silica (SiO_2), zirconium dioxide (ZrO_2), cobalt (Co) and titanium dioxide (TiO_2), increased TLR expression and inflammatory cytokine secretion were observed [228]. TiO_2, a white pigment, is extensively used in many commercial products, such as food, drugs and cosmetics, in the form of TiO_2 NP. TiO_2 NP can induce secretion of important pro-inflammatory mediators, such as Macrophage Inflammatory Protein-1 alpha/beta (MIP-1α and MIP-1β), IL-8 and chemokine growth-regulated protein alpha (Gro-α). MIP-1α and MIP-1β are responsible for attraction and activation of macrophages, DC, NK, lymphocytes and eosinophils, *in vivo*, whereas IL-8 and Gro-α are known to attract neutrophils [229]. In the intestine, TiO_2 induced also an increased secretion of inflammatory cytokines, triggering both Th1 and Th17 pathways, and enhanced CD4+ T cells proliferation, after uptake by M cells at Peyer's patches [230].

Synthetic or subunit vaccines, containing non-living antigens display important advantages to face the classical live-attenuated vaccines drawbacks. However, these antigens, especially purified or recombinant subunit antigens, are often poorly immunogenic and require additional components to help stimulate protective immunity based on antibodies and effector T cell functions. Particulate delivery systems ranging from liposomes, MP and NP, to VLP have been explored to provide the help needed to enhance the immunogenicity of vaccine antigens and consequently, to promote innate immunity and the subsequent right induction of the adaptive immune response [194,214,231,232].

Liposomes containing cationic lipid *N*-(2,3-Dioleoyloxy-1-propyl) trimethylammonium methyl sulfate) (DOTAP) and E7 oncoprotein of human papillomavirus (HPV) type 16 activated APC, resulting in enhanced antigen-specific CD8+ T and antitumor activity in an *in vivo* cervical cancer model [233]. Phosphatidylserine (PS)-containing liposomes encapsulating antigens were efficiently captured by APC, leading to Th cell stimulation, supporting immunological adjuvant activity of PS for peptide vaccines [234]. Similarly, polymeric chitosan NP have demonstrated adjuvant properties *in vivo*, when used as vaccine vehicle to APC, proving their potential benefit for prophylactic or therapeutic schemes [235]. These particles have also been used for the delivery of immunostimulatory adjuvants to achieve enhanced cellular penetration and subsequent cellular activation, avoiding widespread stimulation and potential side-effects, as autoimmunity [217]. NP can also potentiate the cytosolic delivery of biomolecules as siRNA and miRNA, important gene expression modulators, providing their escape from

endolysosomal compartments [236,237]. Accordingly, PLGA particles carrying the synthetic TLR3 ligand poly(I:C) for monocyte-derived dendritic cells (MoDC) targeting, improved its immunostimulatory activity and safety [217]. A liposome complex with poly(I:C) and DOTAP enhanced the interaction between poly(I:C) and TLR3, in DC, enhancing intracellular signaling, leading to enhanced DC maturation and secretion of INF-γ [238]. However, the main advantage of NP as vaccine vehicle is, in fact, the *in vivo* co-delivery, within the same platform, of both antigens and immune stimulators to the same cell, enhancing and boosting the immune response. The delivery of antigens and immunostimulatory adjuvants to phagocytic cells has been thoroughly discussed in several previous reviews [7,239].

Alpha-galactosylceramide (αGC), an invariant Natural killer T (NKT) cells (NKT) lipid cell ligand, is a potential new immunostimulator by inducing secretion of INF-γ by those immune cells, leading to a robust immune response. However, the use of αGC in clinic has been limited by several aspects, as the uncontrolled immune response triggered when administered systemically in its free form. As a result, NP carrying αGC represent an interesting alternative for the delivery of this potential immune adjuvant. The incorporation of αGC in liposomes increased its presentation in APC, resulted in expansion of NKT cells and led to enhanced secretion of INF-γ for lower doses of αGC-liposomes [223]. Similarly, polymeric PLGA NP, loaded with a αGC analogue (KRN7000), showed promising results in the activation of NKT cells *in vitro* and *in vivo* [224]. In fact, *in vivo* delivery of αGC encapsulated in DC-targeted NP enhanced the transactivation of NK cells, DC, and γδ T cells. The co-delivery of αGC and protein antigen to DC proved to be a potential strategy for prophylactic and therapeutic vaccination schemes by triggering optimal antigen-specific antibodies and cytotoxic CD8+ T cell activity [108].

6.2. Natural killer cells

NK cells are lymphocytes of the innate immune system with effector functions in controlling infections and tumors. Activation of NK cells relies on inhibitory or activating signals from cell surface receptors, upon contact with target cells or accessory cells. Unlike CTL, NK cells do not require priming, being rapid responders of host immunity [240].

Although many aspects of NK cell activity are still underexplored, the roles of these cells, known to date, establish them as a valuable targeting for immune modulation. For example, *N*-acetyl-D-glucosamine-coated polyamidoamine dendrimer have triggered NK cells, leading to increased secretion of IFN-γ, cytotoxicity and enhanced antigen specific antibody formation. This response was attributed to the presence of *N*-acetyl-D-glucosamine on the surface of the dendrimers, which enabled the lectin-saccharide interaction with NK cell surface receptors [241,242].

As NK cells play an important role in tumor elimination and higher levels of NK infiltrates in the tumor microenvironment are associated to better prognosis, enrichment of target areas with NK cells is a promising approach. Magnetic iron oxide (Fe_3O_4) NP, in very low doses, have shown ability to control the movement of human NK cells by *in vivo* manipulation. Magnetic NP were coated with silica and conjugated with a fluorescence organic dye (Cy5.5) for the *in vivo* evaluation. The movement of NK cells incorporating magnetic NP was guided by an external magnetic field, enhancing NK cell infiltration into the target site [52].

6.3. Basophils, eosinophils and mast cells

Allergen-specific immunotherapy (AIT) is the only cause-oriented therapy for IgE-mediated allergic diseases, such as asthma and rhinitis. It consists of repeated administrations of increasing doses of the allergen, leading to restored tolerance towards it. Allergen immunotherapy reduces infiltration and activation of eosinophils, mast cells and basophils, converts Th2/Th17 to a Th1 response, with induction of Treg, resulting in decreased allergen-specific IgE and increment of protective IgG antibodies [243]. The use of NP for allergen delivery has been proposed as an alternative to subcutaneous or sublingual administration of free allergen, to avoid potential systemic side-effects, which affect therapy safety and patient compliance. NP enable delivery and co-delivery of allergens with other molecules to the target site, allowing high concentrations at the intended region and protecting the allergen from the interaction with IgE on the surface of mast cells or basophils, thus preventing side-effects [244].

Allergen- and allergen-DNA-loaded PLGA polymeric NP led to a Th1 immune response, with reduced allergen-specific IgE, after intranasal or oral immunization, protecting against sensitization [245]. It has been also described the therapeutic effect of these polymeric NP on previously sensitized mice. PLGA NP induced a shift from a Th2 to Th1 response and up-regulation of Treg, resulting in decreased secretion of mucus and lung inflammation, as well as reduced levels of eosinophils in the bronchoalveolar fluid [245,246]. Immunization of mice with peanut protein-loaded spray-dried poly(anhydride) NP enhanced Th1 and Treg-secreted cytokines, whereas those NP lyophilized balanced Th1/Th2 antibodies and cytokine secretion [247].

Carbohydrate-based NP have also shown promising results in prophylactic and therapeutic allergen immunotherapy, decreasing IgE secretion and preventing hyperreactivity and presence of eosinophils in bronchoalveolar fluid. *In vivo*, cat allergens and grass pollen carried by sepharose microbeads did not induce granulomatosus tissue reactions in comparison to alum-adsorbed allergens [248,249]. Chitosan NP induced protection against peanut and house dust mite protein or DNA allergies, by triggering Th1 response [250,251].

Allergen-loaded liposomes have also shown prevention activity in anaphylactic reactions, supporting Th1 over Th2 responses and decreasing eosinophilia [252]. When compared to free allergen, several reports describe the enhanced capacity of allergen- or allergen-DNA-loaded liposomes to decrease allergen-specific IgE and hypersensitivity reactions, after administration in mice [253]. However, results from human clinical trials, have had unclear results. Although a study with asthmatic patients reported reduced symptoms in almost half of the patients immunized with allergen-loaded liposomes, with no side-effects [254], some studies showed only slight increase and less favorable systemic safety for liposomes carrying allergens [255]. Thus, further studies should be performed to clarify the application of liposomes in allergen-specific immunotherapy.

In clinical trials, VLP increased allergen tolerance, reducing allergen-specific IgE and avoiding anaphylactic reactions [256,257].

Even though the effect of CNT on allergen-induced systemic reaction is ambiguous, it has been reported an inhibitory activity of C70 fullerene on mast cells and basophils, preventing the *in vivo* release of histamine and anaphylaxis. Similarly, tetraglycolate fullerenes shifted cytokine secretion profile from Th2 to Th1, with decreased eosinophilia and airway inflammation [258,259].

Intranasal administration of gold NP, before allergen challenge, reduced airway inflammation and decreased accumulation of inflammatory cells in sensitized mice [260].

Treatment of pre-sensitized mice with carbohydrate–coated hydroxyl apatite NP resulted in lower levels of serum histamine and IgE, reduction of symptoms during anaphylactic reactions [261].

7. Nanoparticle-mediated suppression of innate immune system

As described above, innate immunity is the first line of defense against foreign pathogens. It exerts a crucial role in the early recognition, through the specific immune receptors, and consequently the removal of pathogen-infected cells. This capacity to effectively eliminate pathogens makes the immune system essential in the treatment of illnesses. However, a deregulation or imbalance in the immune response (immunosuppression or immune stimulation), triggered by genetic and environmental factors, allows the development of various

inflammatory-driven diseases, namely cancer, heart disease and autoimmune disorders [262–264]. Particularly, immunosuppression may have a dual effect. It can reduce the body defenses against infection or tumor cells, or it may stimulate the treatment of allergies and immune disorders and also prevent the transplanťs rejection [264,265].

7.1. Anti-inflammatory effect – autoimmune disorders

Autoimmunity is considered the most aggressive type of immune dysregulation. Autoimmune diseases, namely rheumatoid arthritis (RA), multiple sclerosis (MS) and inflammatory bowel disease (IBD), result from an aberrant chronic activation of immune cells that are responding to self-antigens and consequently causing tissue inflammation and damage in one or more organs [263,266,267].

In these chronic inflammatory diseases, monocyte-derived macrophages are being constantly recruited to injured tissues where they release high amounts of pro-inflammatory mediators such as TNF-α and IL-1β to maintain an inflammatory state. Specifically, TNF-α is a key cytokine that promotes cell death of intestinal epithelial cells in IBD and stimulates chemokine production to facilitate migration of inflammatory cells to synovium in RA. Likewise, IL-6 and IL-17 contribute extensively to inflammatory chronic state in RA and IBD. In addition, macrophage polarization is deregulated in inflammatory diseases, where M1 phenotype is not converted to M2 phenotype, promoting a constant inflammatory response [268]. Moreover, absence of immature DC promotes tolerance and consequently the development of autoimmune disorders [269].

As result, immunosuppressive therapies for the treatment of autoimmune disorders and transplant rejection are the main therapeutic options. These are based on the inhibition of immune responses, namely through the deletion or inactivation of T and B cells, as well as minimization of antigen presentation and proinflammatory cytokine production. The treatment based on glucocorticoids and anti-metabolites are being largely used to relief and slow the progression of the disease [267]. However, due to its toxic effects, alternative therapeutics are needed.

Nanotechnological approaches are promising tools to improve the treatment of autoimmune diseases. The affinity of some immune cells, such as macrophages and DC to particular materials allows a specific delivery of immunomodulatory drugs [270]. Various studies showed that NP with immunosuppressive effects could be used as therapeutic agents for anti-inflammatory or autoimmune disorders, through the presence of specific cytokines, donor antigens or anti-inflammatory drugs [266,271].

Various strategies have been used to neutralize inflammatory cytokines (*e.g.* TNF-α and IL-1), namely through the entrapment of proinflammatory cytokines (*e.g.* IL-4, IL-10 and transforming growth factor (TGF)-β) or using silencing RNA (siRNA) in NP to decrease the inflammatory state [267]. Howard et al. [272] tried to silence the TNF-α expression in systemic macrophages by intraperitoneal injection of chitosan/siRNA NP in a mouse model of RA. Effectively, the NP system has reduced the expression of this cytokine in peritoneal macrophages. Additionally, a combination of glucocorticoids (dexamethasone) and anti −COX-2 siRNA were co-delivery in PLGA NP to inhibit the expression of genes and proteins involved in RA model cell line. Results showed a reduction of inflammatory and apoptosis-related factors produced in C28/I2 cells, after induction of an inflammatory state by TNF-α [273].

For MS treatment, Cappellano et al. [274] developed a different approach using PLGA-NP loaded with the myelin oligodendrocyte glycoprotein $(MOG)_{35–55}$autoantigen and recombinant IL-10 to inverse vaccinated mice with MS. Results demonstrated that subcutaneous prophylactic and therapeutic inverse vaccination with this NP system significantly improved the MS with reduction of lesions in central nervous system and secretion of IL-17 and IFN-γ in C57BL/6 mice.

Using the strategy to repolarize macrophages from M1 to M2 functional sub-type in RA, Jain et al. loaded alginate tuftsin NP with IL-10 DNA −encoding plasmid to achieve active macrophage targeting. It was achieve the successful reprogramming of macrophage phenotype, as 66% of total synovial macrophages treated rats were in the M2 state compared to 9% of M2 macrophages found in untreated rats. Moreover, alginate tuftsin NP with IL-10 DNA plasmid significantly reduced the expression of systemic and joint tissue pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) [275].

7.2. Transplant rejection – a tolerogenic response

The process of transplant rejection is triggered by recognition of donor antigens of the implant by the immune system of the receiving entity. To enhance the survival of the graft, immunosuppressive therapies that induce antigen-specific tolerance are needed. Tolerance implies modulation of immune cells that respond to allo-antigens [276,277].

Particularly in transplantation, the incorporation of specific ligands for receptors (*e.g.* lectins and scavenging receptors) and immunosuppressive drugs (*e.g.* rapamycin and tacrolimus) in NP allows the interaction with APC subsets and consequently an enhancement of internalization, Ag presentation and production of regulatory cytokines to a proper tolerogenic response [277,278].

Haddadi et al. [279] evaluated the effect of rapamycin entrapped in PLGA NP on the maturation of DC and verified high levels of TGF-β and reduced levels of IL-10 and IL-12 cytokine production after with lipopolysaccharide. Using an isogenic orthotopic rat model of single left lung transplant, Bayer et al. [280] administered by inhalation, tacrolimus NP to evaluate the early immunosuppressive/anti-inflammatory effect. The cytokines levels (IL-6, IL-10 and TNF alpha) showed a tendency to reduce.

7.3. Allergenic inflammation – inhibition of the reaction to allergens

Anaphylaxis, hay fever and asthma are the most common allergic disorders. In allergic people, a constant or frequently exposition to allergens (non-infectious environmental substance that can induce IgE production) leads to the development of a chronic allergic inflammation and consequently long-term changes in structure and function of affected organs [281,282]. This is characterized by the extensive presence of innate and adaptive immune cells, namely leukocytes, in the affected tissues. An inappropriate activation of DC by allergens can be responsible for an exacerbation of allergen-induced airway disease [283]. Also, mast cells contribute to pathology of allergic inflammation independently of IgE. In asthma, mast cells present in airway epithelium are activated by viral components, through TLR [284]. However, the production of IL-10 by mast cells stimulates the inflammatory state in the affected tissues. Thus, reduction of differentiation, maturation and proliferation of mast cells as well as reduction of cytokine production that causes inflammation leads to the relief or treatment of allergic inflammation [285,286]. For other side, immune cells such as eosinophils could produce mediators and cytokines (IL-4, TGF-beta, Il-10 and IL-35) that are able to reduce inflammation and repair the affected tissues [287].

NP are being used to inhibit the reaction of allergens. Hardy et al. [288] developed a polystyrene NP coated with the neutral amino acid glycine (PS50G NP) to test its effects on pulmonary DC function and the development of acute allergic airway inflammation. Results showed that PS50G NP inhibited allergic airway inflammation reducing serum allergen-specific IgE and allergen-specific Th2 cytokines in the lung-draining lymph node after allergen challenge during 1 month. Moreover, TiO_2 NP were inhaled by ovalbumin-sensitized mice during four weeks and a suppression of allergic pulmonary inflammation, especially in the levels of leucocytes and cytokines (TNF-alpha and IL-13) was verified [289]. Polymeric NP, namely PLGA itself, showed to inhibit allergic responses mediated by reduced histamine levels released by

mast cells, either *in vitro* and *in vivo* studies [290].

Wang et al. [291] developed curcumin-solid lipid NP to improve the therapeutic efficacy in an ovalbumin-induced allergic rat model of asthma. By delivering this anti-inflammatory compound, NP effectively suppressed airway inflammatory cell infiltration, through reduction of eosinophil number and inhibition of the Th2 cytokines expression (IL-4 and IL-13).

8. Conclusions and future perspectives towards translational nanomedicines

Despite being in the forefront of the development of efficacious medicines to improve the health care and quality of life of patients, advances on biomaterials and complex drug development tools also brought new challenges to the scientific and regulatory communities. The innate immune system is among the first compartments to interact with those nanosystems having thus a profound impact on the way they will be recognized, processed and consequently trigger a particular immune response. It is becoming evident that by improving the knowledge on the mechanisms of interaction between nanomaterials and cellular and soluble components of the immune system, it will be possible to predict and therefore better control the overall effect on biological systems. This improved understanding will be of utmost importance not only to prevent the immunological reactions that may unexpectedly limit the biocompatibility of those nanoparticulate systems considered safe at preclinical settings, but also guide the design of nano-based tools which interaction with immune cells will be used to therapeutically address immunological-associated dysfunctions. Multiple studies have already addressed how the physicochemical and surface properties of nanoparticles influence their interaction with complement proteins, innate immune cells, including the activation of PRR and subsequent production of soluble factors. However, despite the variety of nanotechnology-based systems and methodologies used to understand those interactions at the molecular level and consequent heterogeneous evidences, it is widely agreed that it is fundamental to perform those immunopharmacological studies to fill the gap between the undoubted efficacy obtained at preclinical level and the limited translation of nanomedicines into the market. As a summary, the use of controlled experimental methodologies to study of the mechanisms under the modulation of immune cell function and activity by nano-based systems at clinical levels, will definitely clarify the nanomaterial structure-activity correlation, which will certainly have an impact on their future as drug delivery, imaging and diagnosis tools by anticipating the ideal properties to fulfill a predominant therapeutic effect without any associated toxicity.

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