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Influence of physicochemical factors on the interaction of metallic nanoparticles with immune system cells

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Different physicochemical factors, such as size, concentration, shape, exposure time, area, and surface chemistry, influence the interaction between metallic nanoparticles (MNPs) and immune system cells. Particle size is particularly significant, as smaller particles facilitate easier cell internalization, while larger particles exhibit lower immunogenicity. Concentration also plays a critical role; high concentrations may trigger toxic responses, while low concentrations may act beneficially. Additionally, the morphology of nanoparticles affects their affinity for different cell types. It modulates the intensity of immune responses, while exposure time determines whether the immune response manifests as acute or chronic. The material composition of nanoparticles influences the initial interaction with cells, including protein adsorption and recognition by cell receptors. Understanding and controlling physicochemical factors is essential for developing therapeutic applications based on MNPs and minimizing potential adverse effects on the immune system. This paper reviews the reported biological effects of MNPs on various immune cell types, including B and T lymphocytes, neutrophils, monocytes, macrophages, dendritic cells, natural killer cells, mast cells, basophils, and eosinophils.

KEYWORDS

metallic nanoparticles, cell interaction, immunological compatibility, physicochemical factors, immune system cells

1 Introduction

The innate immune system exhibits remarkable capabilities in recognizing and responding to characteristic molecular patterns of pathogens. It can detect subtle chemical differences between pathogens and discriminate between foreign and self-molecules (Tomar and De, 2014). Additionally, it can identify altered self-cells that could potentially lead to cancer. Upon pathogen recognition, the immune system initiates an effector reaction to suppress or neutralize the invader (Punt et al., 2020).

The MNPs have been one of the main topics of study in nanotechnology with biomedical applications (Ramos et al., 2017) due to their remarkable physicochemical properties. These properties include high chemical stability (Auffan et al., 2009),

biocompatibility, which allows it to be customized by altering its shape, size, and surface properties (Harish et al., 2022), and high surface-to-volume ratio, which can easily attach to functional groups of different optical, radioisotopic or magnetic diagnostic and therapeutic agents (Chaturvedi et al., 2019). Their optical properties (Khan et al., 2019) encompass surface plasmon resonance and tunable absorption-scattering profiles, enabling applications in photothermal therapy, biosensing, and bioimaging (Jain et al., 2020). Their magnetic properties (Arruebo et al., 2007) include superparamagnetism and high magnetic susceptibility, crucial for MRI contrast enhancement, magnetic hyperthermia, and targeted drug delivery (Colombo et al., 2022). Their electronic properties (Hoang and Kim, 2022) feature size-dependent conductivity and surface charge characteristics, which are essential for biosensor development and cellular interactions (Wu et al., 2019; Smith et al., 2023). By combining different materials and tuning these physical and chemical properties, the physicochemical properties of MNPs suggest potential in emerging therapeutic applications, but they require thorough clinical validation. They have been applied in research targeting various cancers, autoimmune diseases, inflammatory conditions, and bone regeneration, with several formulations advancing through clinical and experimental trials (Liu J. et al., 2022). The most studied materials include precious metals (gold or silver) and magnetic metals (iron oxide (FeO), cobalt (Co), manganese (Mg), as well as metal oxides (titanium dioxide (TiO_2), cupric oxide (CuO), and zinc oxide (ZnO), which have garnered significant attention due to their unique physical and chemical properties.

Gold nanoparticles (AuNPs) stand out for their nontoxicity, biocompatibility, and negative surface charge, which enable modification with biomolecules (Mody V. et al., 2010). Their surface readily conjugates with ligands containing antibodies, phosphines, thiols, mercaptans, and amines (Alivisatos et al., 1996). Substituted iron oxides (MFe_2O_4) have emerged as potential nanocarriers due to their size, magnetic tunability, ease of synthesis, and adjustable properties (Mokhosi et al., 2022). Gold nanoconjugates with enhanced surface plasmon resonance show promise in diagnostic imaging (Zhou et al., 2013). The nanoscale size of these particles results in an increased surface-to-volume ratio; as the size of the nanomaterial decreases, its surface area increases, expanding possibilities for novel materials and chemical processes (Navya and Daima, 2016).

Studies indicate that nanoparticles readily circulate in the bloodstream, primarily encountering the innate immune system (Mauricio et al., 2018; Stapleton and Nurkiewicz, 2014). Their size, shape, surface coating, and deformability influence cellular uptake and function (Boraschi et al., 2017), though the underlying mechanisms remain partially understood.

Most research on the toxicology of nanomaterials has concentrated on the effects of nanoparticles that enter the body inadvertently (Hoet et al., 2004; Simkó and Mattsson, 2010). However, current studies in nanoparticle toxicology focus on those entering the body unintentionally, and significant efforts are now dedicated to studying the toxicity of nanoparticles designed for biomedical applications, such as drug delivery, immunotherapies, and imaging (Maurer-Jones et al., 2009). Comprehensive toxicity studies have highlighted the critical importance of physicochemical properties—including particle size, material composition, surface chemistry and morphology—and environmental factors such as concentration gradients and exposure duration in modulating immune system responses. The complex interplay between these variables significantly influences cellular uptake, biodistribution, and potential immunological effects (Cai and Chen, 2019; Donaldson et al., 2004). This review examines the primary mechanisms of interaction between different nanoparticles and key cells of the immune system, including neutrophils, eosinophils, basophils, mast cells, monocytes, macrophages, dendritic cells, and lymphocytes (B and T cells), which are involved in the development and progression of immune reactions. Furthermore, we provide an overview of the current understanding of each pathway, along with examples of NPs use in terms of size, shape, surface coating, and deformability.

2 Nanoparticles

Nanoparticles (NPs) are materials with distinctively different properties compared to larger particles or bulk materials (Biswas and Yu Wu, 2005; Royal Society, 2004). These particles, ranging from 10–100 nm in size, manifest in diverse morphologies, including spherical, cylindrical, tubular, cubic, conical, and hollow core structures (Li et al., 2014; Mohanraj and Chen, 2006; Nagarajan, 2008). Their surface characteristics vary from uniform to irregular patterns, while their internal structure can be crystalline or amorphous, existing as either loose particles or agglomerated mono- or multi-crystalline solids (Cho et al., 2013). The exceptional properties of NPs are derived from their nanoscale dimensions, expansive surface area, and customizable surface functionalities, which have led to an increasing use of NPs in various fields (Missaoui et al., 2018).

2.1 Classification and properties

Nanomaterials comprise diverse compounds categorized by distinct characteristics, as shown in Figure 1. They can be classified by origin as natural or anthropogenic, by size into small (1–10 nm), medium (10–80 nm), and large (>80 nm) categories, and by chemical composition as organic/bionanomaterials (proteins, liposomes), inorganic (metals, metal oxides), or carbon-based materials (Klabunde, 2012; Ealia and Saravanakumar, 2017). According to the dimensions of the nanoscale: 0-D (nanoparticles), 1-D (nanorods, nanotubes, nanowires), 2-D (nanofilms, nanocoatings), and 3-D (bulk materials such as powders, nanoparticle dispersions, and assemblies of nanowires and nanotubes) (Kolahalam et al., 2019; Joudeh and Linke, 2022).

Multiple factors, including size, surface area, composition, morphology, surface charge, and crystallinity, determine nanoparticles' properties. These characteristics can be modified for specific applications in medicine, electronics, energy, and industry, with their final properties dependent on synthesis conditions and environmental factors (Mohanraj and Chen, 2006; Nel et al., 2006; Ealia and Saravanakumar, 2017).

Size: Nanoparticles can be engineered to have specific sizes and shapes, which give them unique properties and enable them to adapt to various applications.

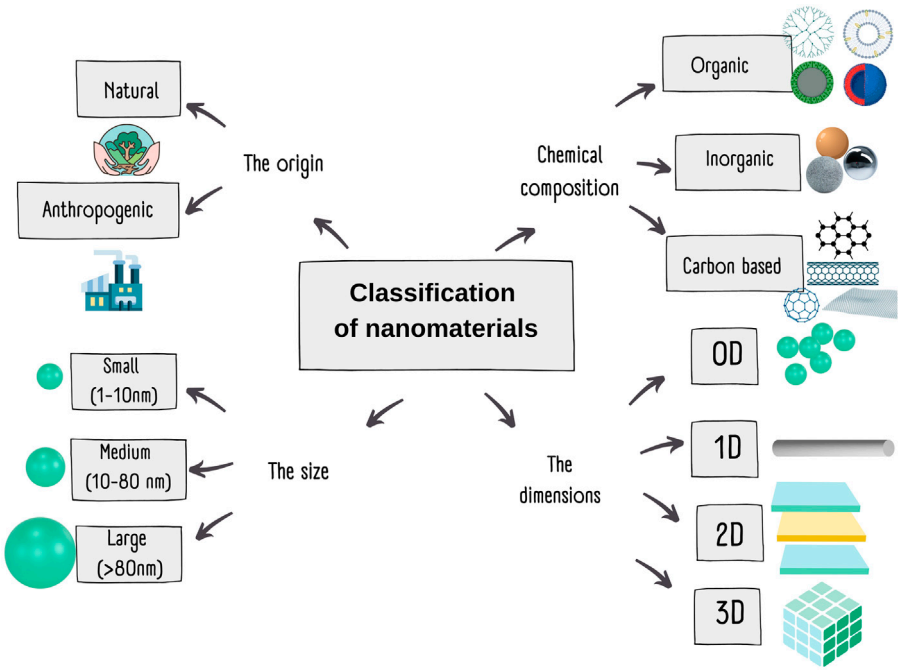

FIGURE 1
Classification of nanomaterials based on origin, dimensions, chemical composition, and size ranges.

Surface Area: The high surface-to-volume ratio of nanoparticles enhances their interaction with surroundings, affecting chemical reactivity, light absorption, heat exchange, and molecular binding capacity.

Composition: This determines purity, performance, and specific properties such as electrical conductivity, optical characteristics, and substance release control. Nanoparticles can comprise metals, oxides, polymers, or ceramics. Impurities can reduce efficiency and trigger unwanted secondary reactions.

Surface Morphology: This variable characteristic encompasses different shapes (spheres, cubes, rods, tubes) and structures (crystalline or amorphous) with uniform or irregular features. These properties influence stability, dispersibility, and material interactions.

Surface Charge: This property affects colloidal stability, molecular binding capacity, and biological interactions. Surface charge can arise from composition or chemical treatment.

Crystallinity: The atomic arrangement pattern influences optical, mechanical, and chemical properties, including catalytic activity. Nanoparticles may exhibit crystalline structures with regular atomic patterns.

2.2 Metallic nanoparticles and their applications

AuNPs represent versatile materials prized for their stability, straightforward synthesis, and unique optical properties, particularly surface plasmon resonance (Mock et al., 2008). Their applications span pre-clinical diagnostics, therapeutics (Fratoddi et al., 2014), gene delivery (Abrica-González et al., 2019), and polymer-functionalized drug/DNA delivery systems (Zamora-Justo et al., 2019).

Silver nanoparticles (AgNPs) are distinguished by their antimicrobial and antibacterial properties (Liang et al., 2015). Their optical, catalytic, and electronic characteristics enable applications in sensing (Manno et al., 2008), protective coatings, and conductive materials (Abou El-Nour et al., 2010).

Copper nanoparticles (CuONPs) combine antimicrobial properties with high electrical conductivity, elevated melting points, and low electrochemical migration, making them cost-effective solutions for catalytic, electronic, and magnetic applications (Dhas et al., 1998; Tamilvanan et al., 2014).

Platinum nanoparticles (PtNPs) excel in catalytic applications due to their high activity and stability. They also serve in sensors, electronic devices, and optical systems (Stepanov et al., 2014).

Zinc oxide nanoparticles (ZnONPs) exhibit diverse catalytic, electrical, optoelectronic, and photochemical properties. Their physical and chemical properties vary depending on their morphology, as they are a wide-bandgap semiconductor with an energy gap of 3.37 eV at room temperature (Kumar et al., 2013; Wang Z. L., 2004).

Titanium dioxide nanoparticles (TiO_2NPs) demonstrate strong antibacterial activity and excel in photocatalysis and photoelectrochemistry due to their optical transmittance, high refractive index, and chemical stability. Their properties can vary depending on the phase being utilized, as it is a semiconductor with a bandgap energy of 3.37 eV (Tripathi et al., 2013; Allahverdiyev et al., 2011; Zhao et al., 2007).

Iron oxide nanoparticles (FeONPs) feature superparamagnetic behavior, biocompatibility, and the ability for chemical modification

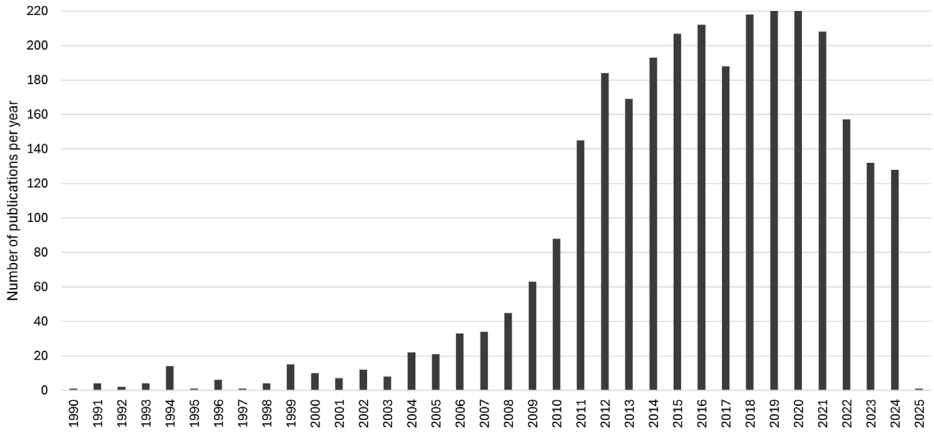

FIGURE 2
Bibliometric analysis (1990-2023) showing annual publication frequency from PubMed database using search terms "metal nanoparticles" AND "immune system", illustrating research trends.

of their surface. They are conveniently applied in photocatalytic processes, antimicrobial agents, magnetic storage media, biodetection, targeted drug delivery, etc. (Harshiny et al., 2017; Issa et al., 2013; Laurent et al., 2008).

While these represent key MNPs, numerous others exist, including palladium, iron, cobalt, nickel, among others. Each offers unique properties and applications across various fields.

2.3 Therapeutic potential of metallic nanoparticles: perspectives in clinical trials

Research on MNPs and their interactions with the immune system has advanced significantly, with several applications progressing through clinical trials. AuNPs have emerged as particularly promising due to their specific immune cell interactions, showing potential in cancer treatment, infectious disease management, and vaccine development. Their applications primarily focus on drug/antigen delivery systems for immune response enhancement and vaccine adjuvant development.

A pioneering human trial evaluated intradermal AuNPs (<5 nm) as carriers for C19-A3 proinsulin peptide in type 1 diabetes treatment. While patients demonstrated good tolerance to AuNP doses without systemic hypersensitivity, mild local skin reactions and delayed gold hypersensitivity were observed. The study revealed no systemic gold retention, though local skin retention persisted (Tatovic et al., 2022).

Clinical advancement of AuNP-based therapies spans multiple therapeutic areas, including cancer (Libutti et al., 2010), type 1 diabetes (Thrower and Bingley, 2009), and infectious disease vaccines (Miauton et al., 2024; Yoosefian and Sabaghian, 2024). AuNPs demonstrate superior stability and efficacy in photothermal therapy and targeted drug delivery, attributable to their distinct optical properties and conjugation capabilities. However, critical challenges remain, particularly regarding organ accumulation and long-term effects, necessitating further research before full clinical implementation.

3 Immune system

The immune system (IS) is an interactive network of lymphoid organs and cells, as shown in Figure 2, from which humoral factors and cytokines are derived. It is a complex biological system whose primary function is the defense of the host through the recognition, prevention, rejection, and eradication of pathogens and other foreign molecules. Low activity of the IS can lead to severe infections and the development of tumors due to immunodeficiency. Conversely, allergic diseases may arise from dysregulated immune responses to harmless antigens, while autoimmune diseases are primarily associated with defects and alterations in immune tolerance toward self-antigens (TeachMePhysiology, 2023; Hocking and Buckner, 2022; Parkin and Cohen, 2001).

There are two types of immune responses: innate responses, which occur to the same extent regardless of how many times the infectious agent is encountered, and adaptive responses, which improve with repeated exposure to a specific infection. Innate responses involve phagocytic cells (neutrophils, monocytes, and macrophages), cells that release inflammatory mediators (basophils, mast cells, and eosinophils), and natural killer cells. At the same time, the adaptive IS includes T and B cells (Delves and Roitt, 2000).

3.1 Interactions of metal nanoparticles with the immune system

The emergence of MNPs has led to their extensive application in medical and therapeutic interventions, attributed to their distinct physicochemical properties relative to micro- and macroscale variants, thus requiring special attention. Primary metals utilized in nanoparticle synthesis include Au, Ag, and Fe (Kharissova et al., 2013), while Pb, Pt, Cu, Cd, and metal oxides such as TiO_2 and ZnO have demonstrated biological applications (Khandel et al., 2018).

Animal cells typically range from 10 to 20 μm in diameter. This microscopic scale enables nanoparticles and other nanoscale

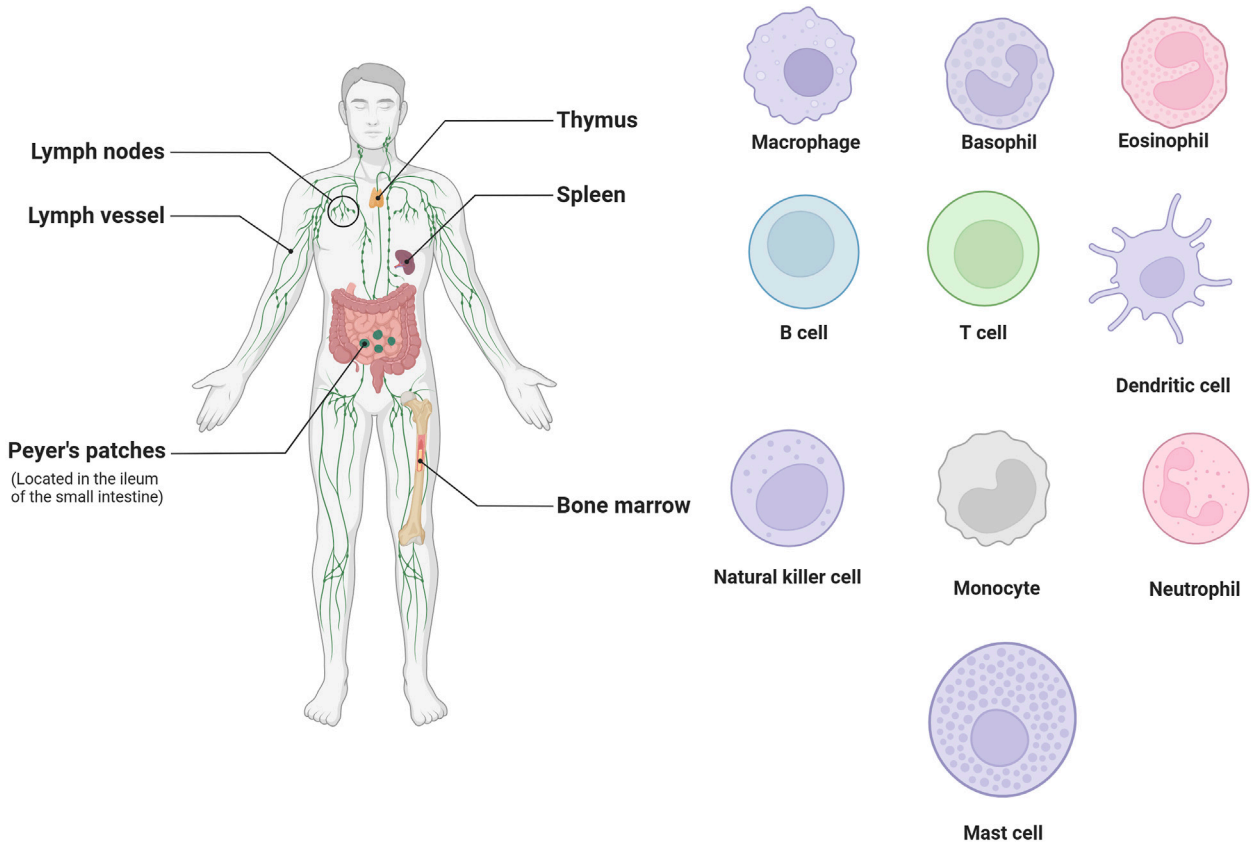

FIGURE 3
Anatomical organization of primary and secondary lymphoid organs and their constituent immune cell populations within the immune system.

materials to readily penetrate and traverse cellular membranes, facilitating their interaction with and potential modification of various intracellular organelles (Dinh, 2021). By modifying these nanoparticles, we can ensure optimal biocompatibility with IS cells and minimize adverse responses (Fulford and Stankiewicz, 2020).

As extensively documented in the research literature, MNPs exhibit complex interactions with immune system components, potentially inducing inflammatory responses and modulating immune function (Zolnik B. S. et al., 2010). Bibliometric analysis of PubMed publications utilizing the keywords "metal nanoparticles" and "immune system" between 1990 and 2023 demonstrate exponential growth in this field (Figure 3).

The generation of reactive oxygen species (ROS) by MNPs is influenced by their physicochemical properties, particularly size and surface charge. Upon cellular internalization through endocytosis, small nanoparticles can initiate ROS production via respiratory bursts in immune cells (Manke et al., 2013) and demonstrate cytotoxicity through oxidative stress induction (Villanueva-Flores et al., 2020; Gutiérrez-Araujo et al., 2021; Pelclova et al., 2016). Surface charge is determinant: positively charged particles interact intensely with cell membranes, activating inflammatory pathways including TLRs and NLRP3, while negatively charged particles can induce oxidative stress through inflammatory protein adsorption (Liu et al., 2021; Schins, 2002; Xiao et al., 2016; Sabourian et al., 2020). The oxidative stress impact is maximized when small, positively charged particles interact with mitochondria and the endoplasmic reticulum, as demonstrated with CeO_2 and TiO_2NPs (Xia et al., 2008). These ROS can trigger inflammatory responses through direct immune cell stimulation or oxidative stress mechanisms (Gao C. et al., 2020; Huang et al., 2010). While acute inflammation facilitates pathogen elimination and wound healing (Landén et al., 2016), its chronic form can be detrimental.

These interactions can affect the function and activity of immune cells in a modulated manner, either by activating or inhibiting certain pathways and mechanisms. For example, by stimulating the production of proinflammatory cytokines or affecting the function of lymphocytes, the adaptive immune response can be altered (Condotta and Richer, 2017). Similarly, the effect can be modulated, as demonstrated by loading multiple immune cells with FeONPs, such as T cells, macrophages, and NK cells, and delivering them to the tumor through an external magnetic field, effectively increasing the population of immune cells and enhancing cancer immunotherapy (Mohapatra et al., 2021).

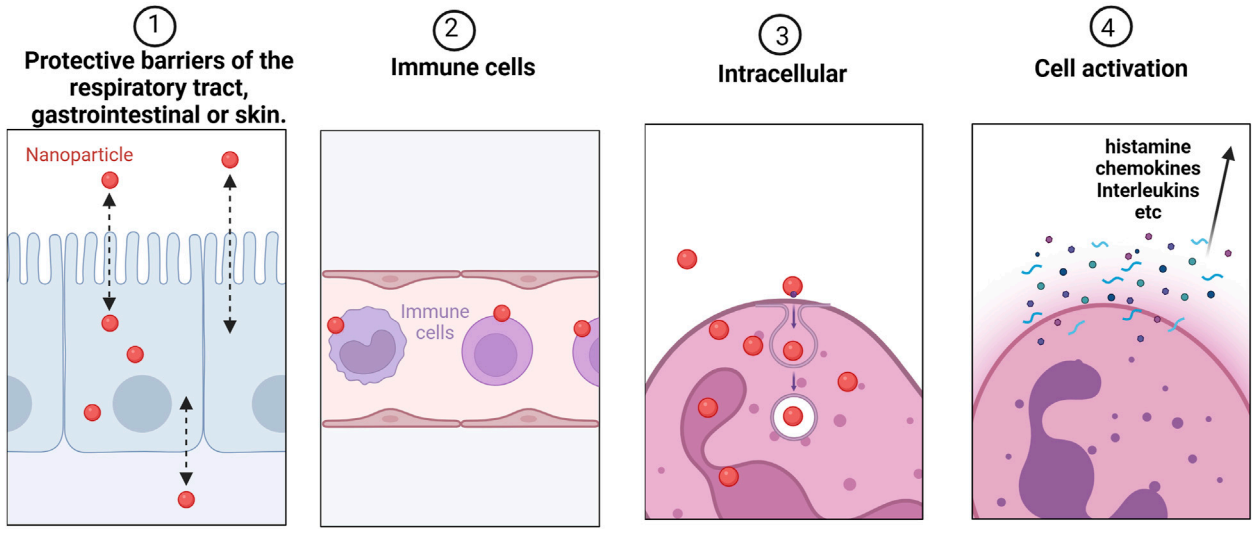

FIGURE 4
Sequential pathway of MNP interactions with the IS: (1) Initial penetration through physiological barriers (respiratory epithelium, gastrointestinal mucosa, dermis, or direct systemic entry); (2) Recognition by immune surveillance mechanisms; (3) Cellular interaction initiation; and (4) Subsequent activation of immune response cascades.

MNPs demonstrate potential adverse effects through systemic migration from administration sites, affecting immune cell function (Crane J., 2020). As illustrated in Figure 4, nanoparticle interaction with immune cells requires traversing respiratory, gastrointestinal, or cutaneous barriers (Elder et al., 2009). Upon immune cell contact, MNPs interact with proteins, polymers, carbohydrates, and lipids, initiating cellular and molecular cascades (Kononenko et al., 2015). Response variations depend on immune cell subtypes and nanoparticle characteristics.

The interaction between MNPs and immune cells has received significant attention in biomedical research, leading to ongoing investigations. Understanding these interactions is crucial for therapeutic optimization and advancing medical applications in immunotherapy.

4 Factors influencing the compatibility of MNPs with the immune system

To understand and categorize the toxicity mechanisms of nanoparticles, information is needed on the response of living systems to the presence of nanoparticles. It has been reported that depending on their physicochemical properties, NPs can interact with cells and proteins to stimulate or suppress the innate immune response, as well as activate or evade the complement system. Size, shape, hydrophobicity, chemical composition, solubility, aggregation, and surface modification of NPs are the main factors influencing the interactions between NPs and innate IS (Liu et al., 2017). IS cells are sensitive to nanoparticles due to their critical role in defending against foreign agents in the body (Zolnik B. et al., 2010). These interactions are influenced by specific nanoparticle characteristics, such as size, composition, and functionalization, which determine the activation of the immune response. When MNPs enter a biological environment, they acquire a "protein corona" that alters their interaction with immune receptors, including TLRs and complement receptors (Ray et al., 2021). Magnetic nanoparticles can interact with various IS receptors, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which detect danger signals or microbial components (Wicherska-Pawłowska et al., 2021). The interaction of these receptors by MNPs can trigger both inflammatory and adaptive immune responses (Vasilichin et al., 2020). Additionally, scavenger receptors play a key role in the phagocytosis of particles, including MNPs, facilitating their internalization by phagocytic cells such as macrophages (Aderem and Underhill, 1999; Zhang et al., 2021). The compatibility of MNPs with IS cells depends on several factors, as shown in Figure 5.

The size and shape of nanoparticles can affect their ability to enter cells and interact with cell membranes. NPs with a size of 10 nm are more likely to be internalized by immune cells (Liu et al., 2010; Zanella et al., 2019; Sokolova et al., 2020).

The chemical composition of nanoparticles can influence their stability and their ability to interact with cells. Reactivity depends on the material, such as Au, Ag, Cu, TiO_2, etc.

The surface charge of nanoparticles modulates cellular internalization, clearance, and uptake mechanisms, and optimization is dependent on the intended therapeutic applications.

Concentration and exposure time: determine cellular particle burden and subsequent toxicological impact. Administration route and dosing frequency represent critical variables.

While current literature provides substantial insight into these parameters, the complexity and multifactorial nature of NP-immune system interactions necessitate continued investigation. This understanding is fundamental for optimizing nanoparticle synthesis in biomedical applications and minimizing toxicological effects. Immune system compatibility directly impacts nanoparticle safety and efficacy profiles, emphasizing the need to develop appropriate safety strategies for their use.

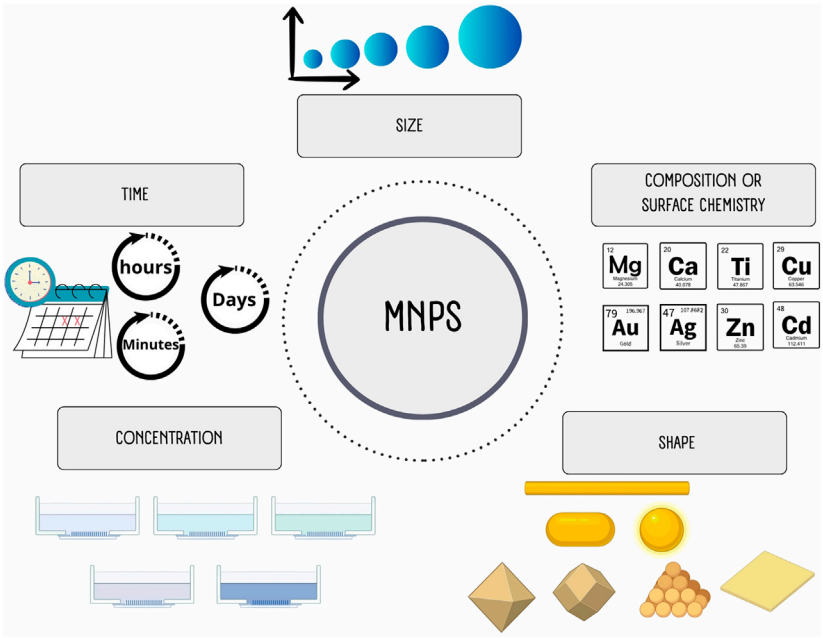

FIGURE 5
Key factors influencing metal nanoparticle-immune cell interactions, including physicochemical properties, biological factors, and environmental conditions.

4.1 Size

Different techniques have been reported in various situations to produce nanoparticles with different dimensions. Reducing the size to the nanoscale level results in a significant increase in the surface-to-volume ratio, which means there are relatively more molecules of the chemical substance present on the surface, thereby increasing intrinsic toxicity (Donaldson et al., 2004).

The size of particles significantly influences their surface area; as the size decreases, a larger proportion of atoms or molecules is exposed on the surface. For instance, when a sphere is reduced to the size of nanoparticles, the material has more atoms on its surface, facilitating interactions with other substances and enhancing its effectiveness in applications such as medicine and chemistry (European Technology Platform on Nanomedicine, 2005).

The increase in surface area impacts the number of reactive groups on the particle's surface, which can determine biological effects, such as acute pulmonary inflammation induced by TiO_2 nanoparticles, which is more related to surface area than hydrophobicity (Höhr et al., 2002). Additionally, the material's physicochemical properties change, promoting interaction with biological tissues and the immune system, leading to adverse effects that would not occur in its macroscopic form. Depending on their size, certain nanoparticles can travel throughout the body, deposit in organs, penetrate cell membranes, localize in mitochondria, and trigger harmful responses (Nel et al., 2006). The particle size itself can determine the pathway of entry, whether through macropinocytosis, phagocytosis, caveolae-mediated, or clathrin-mediated, as shown in Figure 6. Size also determines the cellular entry pathway: particles smaller than 200 nm enter through clathrin-coated pits, while larger particles (500 nm) predominantly use a caveolae-mediated pathway. Furthermore, size influences subcellular distribution, as observed with quantum dots: larger ones (5.2 ± 0.1 nm) remain in the cytoplasm, while smaller ones (2.2 ± 0.1 nm) localize in the nucleus (Rejman et al., 2004).

Cells regulate their function and state through numerous intracellular signaling events that are typically triggered by the binding of a ligand molecule to cell surface receptors. Receptor-ligand binding and receptor clustering affect the intensity and duration of intracellular signaling and other subsequent events (Dubois et al., 1992). Antibody-coated nanoparticles could potentially function as multivalent ligands capable of cross-linking surface receptors, considering that the physical parameters of size, shape, and material properties of nanoparticles can affect their nonspecific uptake by cells, with the potential to induce cellular responses (Hasan et al., 2020; Chithrani et al., 2006). It has been reported that the overall increase in protein adsorption correlates with particle size. In a study using gold nanoparticles anchored with Herceptin (Her-GNPs), it was observed that the internalization of Her-GNPs was highly dependent on size, with more efficient uptake observed for NPs ranging from 25 to 50 nm, showing fewer ligand-receptor interactions than NPs ranging from 50 to 100 nm. Thus, larger NPs have a higher protein-nanoparticle ratio, allowing them to act as cross-linking agents for surface ErbB2 receptors, promoting receptor clustering and uptake (Jiang et al., 2008).

Research by Jiang et al. (2010a) and Shang et al. (2013) documented cellular uptake of 3.3–100 nm particles in HeLa cells, with sub-10 nm Au nanoclusters demonstrating initial membrane accumulation before cellular entry. Oh et al. (2011) established size-dependent intracellular targeting of peptide-functionalized AuNPs: 2.4 nm particles exhibited nuclear localization, 5.5–8.2 nm particles remained cytoplasmic, and

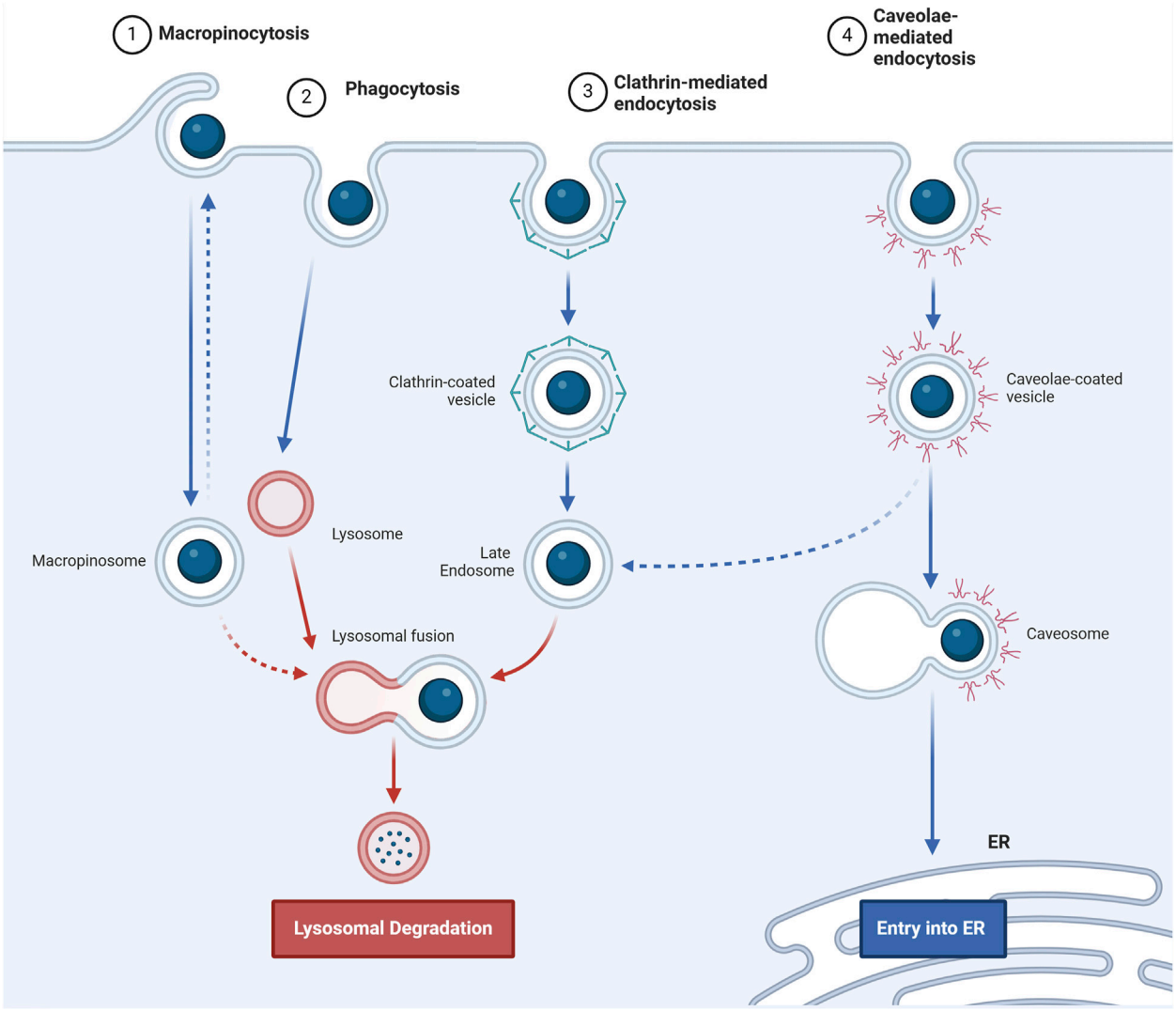

FIGURE 6
Primary cellular internalization mechanisms for nanoparticles: macropinocytosis, phagocytosis, caveolae-mediated, and clathrin-mediated endocytosis.

particles ≥16 nm showed minimal cellular entry. These findings align with studies showing preferential uptake of 2–6 nm particles in both cytoplasm and nucleus, while 15 nm particles remained cytoplasm-restricted (Huang et al., 2012).

Shan et al. (2011) demonstrated that AgNPs of 5 nm efficiently traversed the plasma membrane, achieving uniform distribution in both cytoplasm and nucleus within 30 min. In contrast, 100 nm AgNPs exhibited limited membrane penetration, with delayed detection occurring 12 h post-incubation. The internalized AgNPs were predominantly localized within membrane-bound compartments, specifically intracellular vesicles and late endosomes.

4.2 Chemical composition and surface chemistry

Particle chemical composition and surface chemistry significantly influence toxicity through surface-adsorbed chemicals that modulate cellular responses (Donaldson et al., 2004). Notably, AuNPs and purified FeONPs exhibit negligible cytokine secretion induction. Subsequently, Dobrovolskaia and McNeil (2007) established that PEG coating diminishes particle surface charge, thereby reducing aggregation and platelet activation.

A critical consideration in nanoparticle-biological interactions is their degradation kinetics, particularly regarding protein corona (PC) dynamics. The PC forms spontaneously upon exposure to biological media, conferring novel biological identity and influencing cellular uptake, immune recognition, biodistribution, clearance, and toxicological profiles (Bai et al., 2021; Cai and Chen, 2019). This protein envelope mediates nanoparticle-biological interactions and can modulate colloidal stability through stabilization or destabilization mechanisms, including protein-mediated bridging, charge compensation, and surface charge heterogeneity introduction (Docter et al., 2015).

Exposure of the NP's core to the corrosive intracellular environment can result in its degradation and eventually

complete dissolution (Treuel et al., 2013). While metals with redox activity, such as iron (Fe) and copper (Cu) undergo redox cycling reactions, for a second group of non-redox inactive metals like arsenic (As) and cadmium (Cd), the main route of their toxicity is glutathione depletion (Valko et al., 2005) and their chemical affinity for binding to protein sulfhydryl groups and non-protein thiols, leading to cellular oxidative stress (Rubino, 2015). It has been suggested that metal ions can increase the production of tumor necrosis factor-alpha (TNF-α), activate protein kinase C, and induce the production of proteins that may be involved in basic cellular defense mechanisms. The release of molecular waste and/or metal ions (e.g., Ag, Cd, or In) will result in cytotoxic effects, and some mechanisms associated with the toxicities of metal ions are very similar to the effects produced by many organic xenobiotics (Stohs and Bagchi, 1995).

In contrast, surface modification of nanoparticles can also result in decreased cytotoxicity. As reported by Liu et al. (2018), cationic particles (positively charged) are more likely to induce inflammatory reactions than anionic (negatively charged) and neutral species. Compared to neutral or negatively charged nanoparticles, positively charged nanoparticles are absorbed faster (Thorek and Tsourkas, 2008; Slowing et al., 2006). It is recognized that the surface charge of nanoparticles is an important factor for complement system activation. Charged nanoparticles are more efficient activators of the complement system than their neutral counterparts (Dobrovolskaia et al., 2008). Hühn et al. (2013) modified colloidal AuNPs with amphiphilic polymers to obtain NPs with identical physical properties except for the charge sign (positive/negative) and demonstrated that the absorption rate by cells was higher for positively charged NPs than for negatively charged ones. It was observed that small positively charged NPs could penetrate cell membranes, leading to membrane rupture and notable cytotoxic effects. It is well known that cell membranes typically have a net negative charge, and cellular uptake is driven by electrostatic attractions (Leroueil et al., 2008; Cho et al., 2009). Augustine et al. (2020) demonstrated that this electrostatic attraction between the membrane and positively charged nanoparticles promotes adhesion to the cell surface, leading to uptake. For small nanoparticles (2 nm), a positive charge can disrupt the potential of the cell membrane, resulting in membrane depolarization and the entry of Ca^{2+} into cells and inhibiting cell proliferation compared to neutral, negative, and zwitterionic AuNPs (Arvizo et al., 2010).

In physiological environments, nanoparticles acquire a coating of extracellular molecules from body fluids, including proteins, sugars, and lipids, forming distinct hard and soft coronae prior to cell membrane interactions, collectively termed the protein corona (Jiang et al., 2010b). Specific protein adsorption, particularly immunoglobulin and complement factors, enhances phagocytic recognition while potentially triggering innate immune responses or organ-specific immunotoxicity. These protein coronae establish dynamic, bidirectional interactions with nanoparticles (Huang M. et al., 2021). The characteristics of the adsorbed protein layer depend on nanoparticle surface properties, exposure duration, protein concentration, and binding affinity. Proteins exhibiting high affinity, rapid binding kinetics, and irreversible adsorption constitute the hard corona, whereas those displaying low affinity and reversible binding form the soft corona (Capjak et al., 2017).

4.3 Shape

It has been described that interactions between ligands attached to nanoparticles and cell receptors depend on the designed geometry and ligand density of a nanomaterial (Albanese et al., 2012). The nanoparticle acts as a scaffold, and its design dictates the number of ligands interacting with the target receptor. A multivalent effect occurs when multiple ligands on the nanoparticle interact with multiple cell receptors. The binding strength of the ligands is greater than the sum of their individual affinities and is measured as the overall avidity of the complex, as seen in antibodies that possess at least two antigen-binding sites (Jiang et al., 2008). Similarly, a study by Kumarasamy et al. (2022) investigated the role of shape (spheres, cubes, triangles, and rods) of silver nanoparticles and their interactions with plasma cells. They reported that all 50 nm AgNPs exerted toxic effects, with rods and cubes showing greater toxicity than spheres and triangles, indicating that the edges of AgNPs enhance toxicity, presumably due to increased ion dissolution at the edges. A morphology-dependent cellular adhesion hierarchy was established (elongated > flattened > spherical), while internalization efficiency followed a distinct pattern (oblate > spherical > prolate) (Kinnear et al., 2017). Additionally, antimicrobial studies demonstrate shape-dependent AgNPs interactions with pathogenic organisms, where smaller spherical AgNPs exhibit superior antibacterial efficacy compared to larger spherical or triangular variants (Raza et al., 2016; Galdiero et al., 2011).

4.4 Concentration (dose – response)

Dose-response relationships constitute fundamental determinants in nanoparticle toxicological profiles. Elevated particle concentrations potentially amplify cellular damage mechanisms. Dosimetry considerations extend beyond physicochemical parameters (morphology, chemistry, surface characteristics) to dose-level relevance, particularly regarding in vitro-in vivo dose correlations. Enhanced particle concentrations increase cellular uptake probability, amplifying particle-cell interactions and subsequent structural and functional perturbations, correlating with cellular response mechanisms (Behzadi et al., 2017). Furthermore, elevated nanoparticle concentrations can initiate oxidative stress cascades, enhancing cellular damage. Iron oxide variants demonstrate concentration-dependent cytotoxicity profiles: magnetic iron oxide nanoparticles exhibit toxicity at 300 μg/mL while maintaining biocompatibility at 20 μg/mL, suggesting therapeutic potential in orthopedic applications (Loomba and Scarabelli, 2013).

AgNPs bactericidal efficacy demonstrates morphology, dimension, concentration, and colloidal stability dependence (Shaikh et al., 2019). At 50 μg/mL, AgNPs induce significant bacterial wall structural modifications, including multiple perforations, while 10 μg/mL concentrations promote membrane

vesicle solubilization and component disorganization, indicating concentration-dependent membrane integrity disruption.

Concentration-dependent effects demonstrate biphasic characteristics, with differential impacts at varying concentration ranges. Rosas et al. (2009a), Rosas et al. (2009b) investigated the concentration-dependent effects of 45 nm AgNPs on coronary endothelial cells, examining proliferation dynamics and nitric oxide production. Results revealed biphasic proliferation responses: inhibition at low concentrations *versus* stimulation at elevated concentrations. Similarly, 5.7 and 20.4 nm AgNPs demonstrated dose-dependent macrophage toxicity up to 250 μg/mL, with enhanced toxicity correlating with increasing concentration (Zhang et al., 2016).

These findings emphasize the critical nature of comprehensive concentration-effect evaluation, which considers multiple variables, including cell type specificity, material characteristics, medium composition, and protein interactions.

4.5 Time

The duration of exposure to nanoparticles can have an impact on cellular damage. Studies have suggested that prolonged exposure to nanoparticles can increase the number of particles that enter cells and, therefore, increase the potential for cellular damage (Wang and Tang, 2021; Shang et al., 2014). Additionally, the cellular response to nanoparticle-induced damage may depend on the duration of exposure. For example, a brief exposure to certain nanoparticles may not have an observable effect on cells, but a longer exposure may result in significant cellular damage, as reported by Armand et al. (2016) in a study where NPs did not affect cell viability but caused DNA damage, particularly oxidative DNA damage, and an increase in 53BP1 foci count, correlated with higher intracellular accumulation of NPs.

There is a kinetics of absorption shown in the internalization of NPs that begins during the first few minutes of incubation and reaches completion after 48 h of incubation; as this absorption levels off, it results in saturation of these NPs in the cell. Setting 48 h as the maximum value, the average maximum value is reached after 1 h for HeLa cells, and for Jurkat cells, the average maximum time is even less than 1 h (Mailänder and Landfester, 2009).

It is also mentioned that once nanoparticles enter the cells, the damage generated to the cells is not permanent, and the cells can fully recover over time (Mironava et al., 2010). According to Munger et al. (2014), colloidal AgNPs in clinically healthy volunteer patients conducted two studies, one with 10 ppm colloidal silver for 3, 7, and 14 days, and the second used 32 ppm for 14 days. When conducting hemoglobin studies, the exposure time was not associated with changes in blood cell counts, as there were no clinically significant changes in any hemogram values.

5 Immune system cells and their interactions with nanoparticles

5.1 B and T lymphocytes

B and T Lymphocytes are fundamental cells of the adaptive IS. They are responsible for producing antibodies and cytokines and inducing apoptosis and possess the ability to release various inflammatory mediators upon cellular activation. These functions orchestrate the body's response to infections and diseases (Hans, 2014; Luster et al., 2005). MNPs have been extensively studied for their ability to modulate lymphocyte function. Due to their physicochemical properties, such as size, shape, and surface charge, MNPs can influence immune responses, indirectly promoting oxidative stress through the generation of ROS (Sarkar et al., 2014; Ercal et al., 2001). These properties affect cellular interactions and pathways, such as the activation of NADPH oxidase or mitochondrial dysfunction, which can lead to the release of pro-inflammatory cytokines and, in severe cases, cell apoptosis (Abdal Dayem et al., 2017). AgNPs have shown cytotoxicity at high doses in peripheral blood mononuclear cells (PBMC) (Shin et al., 2007) and T cells (Greulich et al., 2011), underscoring the need for biocompatibility assessment in therapeutic applications. Studies have shown that silver and copper ions generated from AgNPs and CuNPs can interact with nitrogen, oxygen, or sulfur-containing cell membrana components, causing damage (Ameh et al., 2022).

Recent studies have reported the interaction between gold nanoparticles (NpAu) and lymphocytes, with approximately 90.4% ± 8.5% of the lymphocytes internalizing the NpAu intracellularly, without significant morphological changes detected (Wiwanitkit et al., 2009). Furthermore, controlled doses of AuNPs and TiO_2 can enhance T cell activation and proliferation. This effect is more pronounced in 8 nm AuNPs synthesized in citrate buffer than in negatively charged coated AuNPs, and it is also associated with increased proliferation and cytokine release, such as IL-10, IFN-γ and IL-2 in a PBMC culture (Liptrott et al., 2014). Meanwhile, CuNPs may reduce lymphocyte viability by increasing ROS production in a concentration-dependent manner and loss of mitochondrial membrane potential and lysosomal membrane leakiness (Assadian et al., 2018). Małaczewska demonstrated that oral administration of AuNPs in mice increased CD4+/CD8+ B and T cell percentages. While a high dose of AuNPs decreased lymphocyte proliferation, suggesting an immunotoxic effect (Małaczewska, 2014). Fullerene nanoparticles containing cadmium do not decrease the viability of T and B lymphocytes and induce an immunomodulatory effect by shifting T cell cytokine profiles toward a Th1 response, with reduced Th2 cytokine production and increased Th1 cytokine production (Liu et al., 2009).

For B lymphocytes, *in vitro*, *ex vivo*, and *in vivo* evidence suggest that AuNPs activate B cells and enhance IgG secretion through the blimp1/pax5 pathway, with optimal stimulation observed with AuNPs sized between 2 and 12 nm and dependent on exposure time (Lee et al., 2014). Citrate-stabilized 10 nm AuNPs in murine B cells (CH12.LX cell line) activated an NF-κB-controlled luciferase reporter, correlating with increased antibody expression. TEM images indicate that AuNPs can penetrate the cell membrane and interact with intracellular components of the NF-κB pathway, suggesting a direct impact on B cell function (Sharma et al., 2013). While limited data exists on direct interaction between MNPs and B lymphocytes in physiological conditions, preliminary studies suggest that polymer-coated AuNPs do not affect cell viability or adaptive immune responses in these cells (Hočevar et al., 2022).

However, PEGylated nanomaterials face the significant challenge of rapid clearance from the bloodstream after repeated

systemic injections, reducing their efficacy and requiring solutions to enhance their circulation stability—a phenomenon known as accelerated blood clearance (ABC) (Abu Lila et al., 2013). For instance, repeated doses of PEG-coated AuNPs have affected B cell counts (Abu-Dief et al., 2022).

Studies show that MNPs can modulate T and B lymphocyte functions depending on their physicochemical properties, such as size, charge, and coating. AuNPs have shown positive effects on T and B cell proliferation and activation, increasing cytokine and antibody production, while other nanoparticles, such as AgNPs and CuNPs, may induce cytotoxicity and oxidative stress at high concentrations. These findings highlight the therapeutic potential of MNPs in immunotherapy, though challenges remain regarding biocompatibility and bioavailability. Continued research on how different types of MNPs and their physicochemical properties influence human lymphocyte responses is essential to design nanoparticles that maximize therapeutic effects and minimize associated risks, establishing an adequate safety framework for clinical applications.

5.2 Neutrophils

Neutrophils are the most abundant leukocytes and are noted for their phagocytic and microbicidal functions and their ability to migrate to infection sites (Springer, 2004). The interaction of MNPs with neutrophils can activate these cells and trigger an inflammatory response, such as the metal fume fever (MFF) syndrome observed after inhalation of metal oxide particles like zinc and copper. In this context, studies have demonstrated that exposure to metal oxides (ZnO, CuO, Al_2O_3, SnO_2, and TiO_2) increases serum amyloid A (SAA) levels in the blood and induces a dose- and time-dependent acute phase response (Gutierrez et al., 2023). The pathophysiological mechanisms of MFF are expressed through the release of proinflammatory cytokines, neutrophil activation, and the production of oxygen radicals (Greenberg and Vearrier, 2015).

As professional phagocytes, Neutrophils internalize nanoparticles via endocytosis (Conner and Schmid, 2003). Upon interaction with MNPs, neutrophils exhibit responses such as respiratory burst, degranulation, and forming extracellular traps (NETs) (Lin et al., 2018). For instance, cetyltrimethylammonium bromide (CTAB) and polyethylene oxide (PEO)-NH-coated gold nanoparticles (AuNPs) with a positive charge of 15–50 nm have been shown to activate NETosis in neutrophils after just 15 min of exposure. Their positive charge facilitates entrapment in NETs due to electrostatic forces (Bartneck et al., 2010; Yang et al., 2019). AuNPs may also alter the membrane charge of neutrophils, leading to cell activation (Chekanov et al., 2013). Certain nanoparticles also affect the ability of neutrophils to migrate to infection sites, thereby altering the immune response (Yang et al., 2019). For example, AuNPs of 20 and 70 nm have been shown to induce apoptosis in neutrophils, while TiO_2 and ZnO affect cell function without generating ROS. AgNPs, on the other hand, induce apoptosis by quickly interacting with and penetrating the cell membrane (Noël et al., 2016; Gonçalves et al., 2010; Goncalves and Girard, 2014; Poirier et al., 2014).

Various MNPs have demonstrated cytotoxic effects on neutrophils, which vary according to specific particle properties, including concentration, exposure time, and size. For example, polyvinylpyrrolidone (PVP)-coated AgNPs were found to be toxic to human neutrophils, with 10 nm AgNPs causing greater membrane damage, lysosomal activity disruption, and oxidative burst than 50 nm AgNPs (Soares et al., 2016). AgNPs have also been shown to induce apoptosis by rapidly interacting with and penetrating the cell membrane. In an **in vivo** study with Sprague Dawley rats, hematological, biochemical, and histopathological results indicated that AgNPs were well tolerated up to a dose of 1.7 mg per 10 mL/kg body weight per day, administered orally for 28 days (Srisrimal et al., 2023). MNPs can also interfere with the antimicrobial function of neutrophils. For example, certain silver nanoparticles have been used to enhance the antimicrobial activity of neutrophils against antibiotic-resistant bacteria, where AgNPs of 17.9 ± 7.8 nm were found to reduce phagocytosis and inhibit the production of ROS and superoxide, thus inhibiting the antibacterial capacity of neutrophils (Huang W. et al., 2021).

In summary, the interaction between MNPs and neutrophils and the resulting biological effects are crucial for understanding the risks and applications of MNPs in medicine and immunology, as effects vary depending on nanoparticle characteristics and the experimental conditions of each study.

5.3 Monocytes

Monocytes are a type of white blood cell integral to the human IS. Originating from hematopoietic stem cells in the bone marrow, monocytes circulate briefly in the blood and serve as a fundamental part of the innate immune response, defending the body against infections and diseases. Once released into the bloodstream, human monocytes differentiate into two main subsets: classical $CD14^+CD16^-$and non-classical $CD14^-CD16^+$ monocytes (Ziegler, 2015). Upon reaching tissues, monocytes can further differentiate into macrophages or dendritic cells, depending on environmental conditions and specific stimuli (Menezes et al., 2016).

MNPs are also capable of being internalized by monocytes, with uptake influenced by factors such as size, shape, and surface charge. Studies report that monocyte uptake of SnO_2NPs was lower for particles ≤100 nm, whereas TiO_2NPs <25 nm were highly internalized. TiO_2NPs caused more alterations in protein and nucleic acid patterns and the formation of large vacuoles unique to monocytes (Ispanixtlahuatl et al., 2021). Similarly, dextran-coated FeONPs were observed within vesicles or freely in the cytoplasm of human monocytes, prompting the formation of autophagosomes and increased expression of LC3II, a key autophagy marker. This cellular process plays roles in homeostasis, cell survival, and death and is implicated in neurodegenerative diseases and cancer (Wu et al., 2017).

Certain MNPs can activate monocytes, impacting their inflammatory response and cytokine production. Some nanoparticles stimulate the release of proinflammatory cytokines, including tumor TNF-α and interleukin-6 (IL-6). For instance, a study investigating CuO, CeO_2, and combined NPs found that none of the nanoparticles affected IL-6 concentrations in THP-1 monocyte cell lines. However, the dose-dependent effect of CuONPs increased IL-8 and TNF-α production, while CeO_2NPs did not significantly increase these cytokines unless at higher concentrations (Kaur et al., 2019).

MNPs have also demonstrated immunomodulatory and proinflammatory effects on monocytes. In a study using THP-1 monocytes, CdTeNPs elicited a proteomic response comparable to anticancer drugs like camptothecin and doxorubicin, suggesting toxicity mechanisms involving DNA alkylation or chromatin effects. CuO-core NPs, less toxic than CdTe, led to structural changes by replacing essential ions (Fe^{2+}, Mn^{2+}, Mg^{2+}) in proteins, although they induced extracellular matrix reorganization likely due to monocyte activation and ROS-related cellular responses. In contrast, Au-NH_2 NPs caused around 50% cell death in THP-1 cells but showed a weak proteomic response, suggesting immune cells may recover more readily after exposure to 15 nm AuNPs. Notably, positively charged nanoparticles, such as amino-functionalized ones, are more readily taken up by cells (Tarasova K. et al., 2017). Although AuNPs induce cell death in specific conditions, their cytotoxicity varies based on size, surface chemistry, and charge (Goodman et al., 2004).

The interaction of MNPs with monocytes carries potential implications for pathological processes like inflammation, cardiovascular disease, and immune response modulation. It is essential to recognize that these effects depend on nanoparticle characteristics such as type, size, shape, concentration, and surface treatment.

5.4 Macrophages

MNPs can stimulate the activity of specific immune cells, such as macrophages, which are phagocytic cells derived from monocytes and play crucial roles in pathogen elimination (Kawauchi, 2013; Springer, 2006). M1 and M2 macrophages are two subtypes with distinct roles in the immune response. M1 macrophages, activated by interferon-gamma (IFN-γ), are pro-inflammatory and effectively eliminate pathogens and tumor cells. In contrast, M2 macrophages, activated by interleukin-4 (IL-4) and interleukin-13 (IL-13), promote inflammation resolution, tissue repair, and adaptive immune responses, contributing to healing and homeostasis (Gordon and Taylor, 2005; Mantovani et al., 2013).

Regarding phagocytosis, it has been observed that AuNPs and SiO_2 nanoparticles (10 nm) reduce this capacity by 50%, while larger sizes show comparatively less impact. These smaller nanoparticles also alter cell proliferation and morphology, although AuNPs do not affect the cell cycle or cytokine production, nor do they reduce the phagocytic capacity in the murine macrophage cell line Raw 264.7 (Bancos et al., 2014). However, the J774.1A cell line did not show a reduction in phagocytosis after 24 h of exposure to AuNPs, suggesting that factors such as cell line and NP size influence this process (Pan et al., 2007).

The toxicity of MNPs in human macrophages primarily depends on factors related to AuNPs, such as size and concentration. Concentrations of 1 ppm of AuNPs do not affect macrophage viability, but at 10 ppm, cell numbers decrease significantly; smaller particles under 2 nm are toxic, whereas particles of 15 nm do not show this effect (Yen et al., 2009). Iron oxide (FeO) nanoparticles at concentrations of up to 10 μg/mL do not reduce viability but affect phagocytic function and stimulate other immune functions. It has also been observed that these NPs incorporate into the cytoplasm and accumulate in membrane-bound organelles without causing cytotoxicity. At higher concentrations (100 μg/mL), migration, TNF-α production, and nitric oxide increased (Hsiao et al., 2008). Additionally, AuNPs did not show cytotoxic effects or induce ROS or proinflammatory cytokine production (Shukla et al., 2005). Differences in these results may be attributed to using various cell lines and nanoparticle formulations, as size, morphology, and composition can influence phagocytosis efficacy. It has been observed that some J774A1 cells internalize 15 nm AuNPs (Pan et al., 2007).

MNPs can modulate the production of inflammatory cytokines such as IL-1β, IL-6, IL-12p70, and TNF-α. For example, AgNPs affect IL-6 secretion without significant inflammatory effects (Haberl et al., 2013; Castillo et al., 2008). Macrophage activation can benefit pathogen clearance, depending on metal type and synthesis mechanism (Yao et al., 2018; Lin et al., 2014; Heckman et al., 2013), and has shown immunotherapeutic potential; however, prolonged activation can be associated with chronic inflammation and disease (Dukhinova et al., 2019).

MNPs can induce apoptosis in M1 macrophages and promote their repolarization to the M2 phenotype by eliminating ROS, reducing inflammation, and suggesting applications in inflammatory diseases such as rheumatoid arthritis (Yang et al., 2021). These effects may also be beneficial in cancer, infection, and wound healing, although it is crucial to understand how MNP properties impact macrophages to optimize their therapeutic use (Laviron and Boissonnas, 2019; Yao et al., 2018; Seisenbaeva et al., 2017). The supplementary files summarize the articles analyzed in the text in tables, highlighting the most relevant aspects covered in each.

5.5 Dendritic cells

Dendritic cells (DCs) are immune cells essential for antigen presentation and activating specific immune responses. There are two primary types: myeloid and plasmacytoid dendritic cells (Springer, 2012). DCs constantly scan their environment for pathogens, which they detect directly or indirectly through endogenous factors like cytokines and chemokines. Direct activation of DCs via pathogen-associated molecular patterns (PAMPs) is critical for initiating primary T cell responses (Lombardi and Vásquez, 2008).

Certain MNPs can activate DCs and trigger immune responses. For example, titanium dioxide nanoparticles enhance DCs functionality by promoting inflammatory cytokine production and facilitating the maturation of naive $CD4^+$ T cells, which initiates lymphoproliferation (Schanen et al., 2009). TiO_2NPs doped with 33% copper have also demonstrated high efficiency in DC activation (Hesemans et al., 2023). MNPs can influence various DC functions, including maturation, migration, and antigen presentation. For instance, TA-Fe/Mn-OVA@MB nanoparticles promote DC maturation and antigen presentation by activating the cGAS-STING pathway, mediated by manganese (Gong et al., 2023).

Different types of nanoparticles exhibit varied effects on DCs. For instance, ZnONPs at 30 μg/mL increase the expression of costimulatory molecules CD80 and CD86 and the secretion of IL-6 and TNF-α, while at lower concentrations (10 μg/mL), these

effects are not observed (Heng et al., 2011). AuNPs generally have a minimal impact on DC functions; however, they can alter the secretion of inflammatory molecules like cytokines (IL-6, TNF-α), chemokines (MCP-1), and ROS. AuNPs enhance antigen presentation to T cells, resulting in stronger Th1, Th2, and Th17 responses (Dey et al., 2021). Similarly, 2-nm gold nanoparticles showed no toxicity in DCs while increasing the expression of CD80 and CD86 and the secretion of IL-12, IFN-γ, and IL-10, which boosted the proliferation of T cells, Th cells, and NK cells (Le Guével et al., 2015).

MNPs can be taken up by DCs via various endocytosis pathways, depending on their physicochemical properties. Small nanoparticles, for instance, often utilize clathrin-dependent pathways and scavenger receptors, while larger particles (diameters >250 nm) generally enter DCs through clathrin-independent routes (Jia et al., 2018). Studies also indicate that AuNPs coated with zwitterionic ligands (<3 nm in size) are taken up more efficiently by DCs than those coated with PEGylated ligands (Fernández et al., 2015), and positively charged AuNPs show higher uptake efficiency in human monocyte-derived DCs (Fytianos et al., 2015). MNPs can further influence immune polarization by promoting either proinflammatory or anti-inflammatory responses, depending on their properties. Gold nanoparticles are particularly biocompatible with low toxicity for DCs, yet they can impact DC maturation, cytokine secretion, and T cell priming, effects partly linked to the internalization of AuNPs within DCs (Ahmad et al., 2017).

5.6 Natural killer cells

Natural killer (NK) cells are innate immune lymphocytes that express CD56 and lack CD3 surface antigens. When activated, they play a crucial role in defense against tumor cells and virus-infected cells (Childs and Pantin, 2017). NK cell-based immunotherapy is emerging as an attractive approach for cancer treatment (Gangadaran and Ahn, 2017). It has been observed that certain MNPs can activate NK cells and enhance their cytotoxic capacity against tumor cells. For example, certain gold nanoparticles have been shown to induce cytokine release and increase the cytotoxic activity of NK cells. NK92 cells loaded with AuNP were found to secrete IFN-γ and TNF-α, functioning as NK cell activation markers without affecting their biological function, as evaluated both *in vitro* and *in vivo* (Shamalov et al., 2021).

However, information regarding MNPs in NK cells is still limited. Exposure to selenium nanoparticles (SeNPs) has been observed to enable simultaneous treatments of immunotherapy, chemotherapy, and radiotherapy, releasing doxorubicin (DOX) in response to 5 Gy radiation, which enhances chemotherapy efficacy. Radiation oxidized diselenide to seleninic acid, blocking the expression of HLA-E in tumor cells and improving NK cell cytotoxicity while increasing the production of IFN-γ and granulysin (Pan et al., 2022). SeNPs, approximately 100 nm in size, have been used to improve pemetrexed (Pem)--based chemoimmunotherapy and NK cells against cancer. At a concentration of 10 mg/kg, these nanoparticles selectively delivered Pem to tumor sites, where high levels of ROS in cancer cells converted selenium into seleninic acid. This acid blocked HLA-E expression, sensitizing tumor cells to NK cell attacks and increasing the release of pro-inflammatory cytokines such as IFN-γ and TNF-α, thereby enhancing both chemotherapy and immunotherapy in animal models without significant adverse effects (Gao S. et al., 2020).

A previous review concluded that selenite, a derived form of selenium, could increase the sensitivity of mesothelioma cells to NK cells by reducing HLA-E expression, indicating an activation of immune activity and enhancing NK cell potency for antitumor treatments (Chen et al., 2022). In experiments, these selenium nanoparticles could deliver the chemotherapeutic drug doxorubicin to tumor sites via systemic administration with radiation stimuli, thus improving the efficacy of chemotherapy. Additionally, iron oxide nanoparticles coated with gold and radiolabeled have been investigated to enhance the efficacy of NK cells in attacking tumors. These nanoparticles can be monitored through PET/MRI/PA imaging and combined with photothermal therapy to potentiate anticancer effects. *In vivo* studies showed that combining these nanoparticles with NK cells resulted in complete tumor elimination following laser irradiation, achieving more effective results than treatment with NK cells alone (Jung and Chen, 2018).

Furthermore, ferumoxytol nanoparticles have been tested to induce ferroptosis in cancer cells, which increases the levels of molecules that activate NK cells, thereby enhancing their cytotoxic function. In prostate cancer models, this combination improved NK cell activation and intensified the secretion of IFN-γ, a key cytokine in the immune response (Kim et al., 2022).

5.7 Mast cells

Mast cells are immune cells essential for the body's response to injury, especially in the skin. Present in most tissues, they release pro-inflammatory mediators like nerve growth factor (NGF) upon activation, initiating allergic inflammation and orchestrating the early immune response (Springer, 2007). Activated mast cells release mediators that recruit and activate eosinophils (Puzzovio et al., 2023). Both basophils and mast cells act as effector cells, producing bioactive molecules, including histamine, cytokines, chemokines, lipid mediators, and proteases, in response to IgE-bound antigens. This functionality positions mast cells as crucial mediators of allergic inflammation, where they serve as critical effector cells bridging innate and adaptive immune responses in combating pathogenic infections (Yamanishi and Karasuyama, 2016; Stone et al., 2010). In nanoparticle exposure, certain MNPs, particularly TiO_2, have demonstrated the capacity to induce RBL-2H3 mast cell line activation under *in vitro* conditions. This activation triggers the consequent release of inflammatory mediators, specifically manifesting in elevated histamine secretion levels through degranulation processes (Garnica et al., 2012). The observed cellular response underscores the potential immunomodulatory effects of engineered nanomaterials on mast cell function.

Recent research explores MNPs for anti-inflammatory applications and controlled mast cell response modulation. Gadolinium fluoride nanoparticles (GdF3), modified with poly (styrene sulfonic acid-co-maleic acid) paramagnetic (PSSMA) and poly (2-(dimethylamine) ethyl styrene) acrylate marked with Atto

488, demonstrate effects on mouse-derived mast cells and rat RBL-2H3 cell line. These nanoparticles alter mast cell morphology and tyrosine-protein phosphorylation, inhibiting calcium mobilization and degranulation (Shapoval et al., 2021).

Research indicates variable outcomes in nanoparticles and mast cell interactions depending on specific conditions. Some studies suggest immunomodulatory effects that could be leveraged for therapeutic purposes. For example, it was reported that 60 nm AuNPs did not induce cytotoxicity or pro-inflammatory mediators in human mast cells (HMC-1) at any concentration. Although the AuNPs reduced HMC-1 viability by ~5% within the first 4 hours, they did not affect cell proliferation, TNF-α production, or ROS. However, the higher concentrations increased cell granularity, and fluorescence confocal microscopy showed AuNPs inside the cytoplasm (Gutiérrez-Calleja et al., 2021).

Inflammation underlies numerous diseases. ZnONPs show promise in biomedicine through wound healing, bioimaging, and antibacterial and anti-inflammatory properties (Dutta and Sugumaran, 2021). ZnO nanoparticles, particularly those synthesized through green chemistry, are highly valued in biomedical applications due to their significant action against inflammatory mechanisms. They inhibit the expression of inducible nitric oxide synthase, the release of proinflammatory cytokines, myeloperoxidase activity, the NF-kB pathway, and mast cell degranulation (Agarwal and Shanmugam, 2020). Additionally, ZnONPs regulate MDM2 and p53 protein levels, potentially aiding in mast cell-mediated disease treatment (Kim and Jeong, 2016). Exposure of mouse bone marrow-derived mast cells to ZnONPs significantly inhibited histamine and β-hexosaminidase release, with the effect depending on particle size and dispersion. In contrast, TiO_2NPs did not inhibit the allergic response. These effects were independent of cytotoxicity, observed only at high ZnONPs concentrations and absent for TiO_2NPs (Feltis et al., 2015).

In contrast, AgNPs can influence mast cell degranulation and osteopontin production. AgNP effects vary by physicochemical properties, such as size, shape, and coating. For instance, 20 nm AgNPs with polyvinylpyrrolidone (PVP), citrate, and larger nanoplates (550 nm and 850 nm) induced significant degranulation, whereas 110 nm AgNPs did not. Nanowires induced degranulation dose-dependently, and AgNPs interacted with scavenger receptor B1, which is crucial for degranulation. Though degranulation does not depend on AgNPs dissolution, exposure to these particles may provoke adverse mast cell responses, potentially worsening allergic conditions (Aldossari et al., 2015).

5.8 Basophils

Basophils are blood granulocytes derived from bone marrow progenitors, distinct from mast cell precursors. Unlike mast cells, which mature in the tissues, basophils mature in the periphery. Consequently, mature mast cells rarely occur in circulation (Abbas, 2018). Basophil progenitors migrate to peripheral tissues as immature cells and undergo differentiation in response to local biochemical signals, including stem cell factor produced by tissue cells. This factor binds to the c-Kit receptor on the mast cell precursor.

Basophils and mast cells share several structural and functional similarities. Both contain granules capable of synthesizing many of the same mediators, such as histamine and cytokines. Moreover, like mast cells, basophils express the Fcε receptor (FcεRI), which binds to IgE, and they can be activated by antigen binding to IgE (Gibbs and Falcone, 2020).

Certain MNPs, such as AuNPs, activate basophils and trigger proinflammatory mediator release, including histamine and cytokines, through specific signaling pathways. Cheung et al. (2012) investigated the adverse effects of approximately 15 × 64 nm gold nanorods (Au-NR) coated with cetyltrimethylammonium bromide (CTAB) and polyethylene glycol (PEG) on the human IS. This research specifically focused on non-IgE-mediated allergic responses at 4 and 25 h.

Their study assessed allergic degranulation in KU812 cells through histamine and β-hexosaminidase release assays after Au-NR treatment. CTAB-coated Au-NR induced greater allergic mediator release from KU812 cells dose-dependently after 20 min of incubation. Additionally, CTAB-Au-NR caused more apoptosis than PEG-Au-NR in KU812 cells at 24 h, though both showed similar but lesser mediator release (10%–35% of total). CTAB-coated nanorods exhibited stronger cytotoxicity, with an IC50 of 0.15 nM at both time points. These findings indicate that inflammatory mediator release from basophils significantly influences allergic reaction symptoms and contributes to pro-allergic IS tendencies (Sengoku et al., 2000).

Certain AuNPs also modulate basophil allergic responses by inhibiting allergic mediator release. Nanoconjugates for diagnosis and drug delivery were investigated, focusing on human leukocyte targeting for immunotherapy. Using human myeloid leukemia THP-1 cells and primary cultured basophils, they tested nanoconjugates of citrate-stabilized 5 nm AuNPs functionalized with ascomycin-CO-OGSH. Cells incubated with 20 mM HEPES LPS and sensitized with 100 ng/mL human IgE for 24 h bound specifically to low-affinity IgE receptors. Results showed that nanoconjugates containing ascomycin significantly inhibited basophil histamine release, releasing only 12% of histamine and 80% inhibition compared to the drug alone, suggesting specific cell targeting (Gibbs et al., 2014).

A related study conjugated AuNPs with anti-CD203c antibodies and ascomycin to specifically target basophils and LAD2 mast cells. Using purified human basophils and LAD2 mast cells treated with AuNPs conjugates (NCJ) containing CD203c antibodies or stem cell factor (SCF), researchers incubated cells with or without NCJ or ascomycin alone (5 or 100 nM) before anti-IgE, fMLP, or buffer stimulation. NCJ containing ascomycin and anti-CD203c substantially inhibited IgE-dependent histamine release from basophils, comparable to 100 nM ascomycin alone. NCJ without ascomycin showed no inhibition with fMLP but demonstrated stronger effects on histamine release than higher concentrations of ascomycin alone, suggesting specific basophil targeting and enhanced free drug distribution between basophils and mononuclear blood cells (Yasinska et al., 2019).

5.9 Eosinophils

Eosinophils develop from pluripotent hematopoietic stem cells in the bone marrow, differentiating initially into eosinophil/basophil

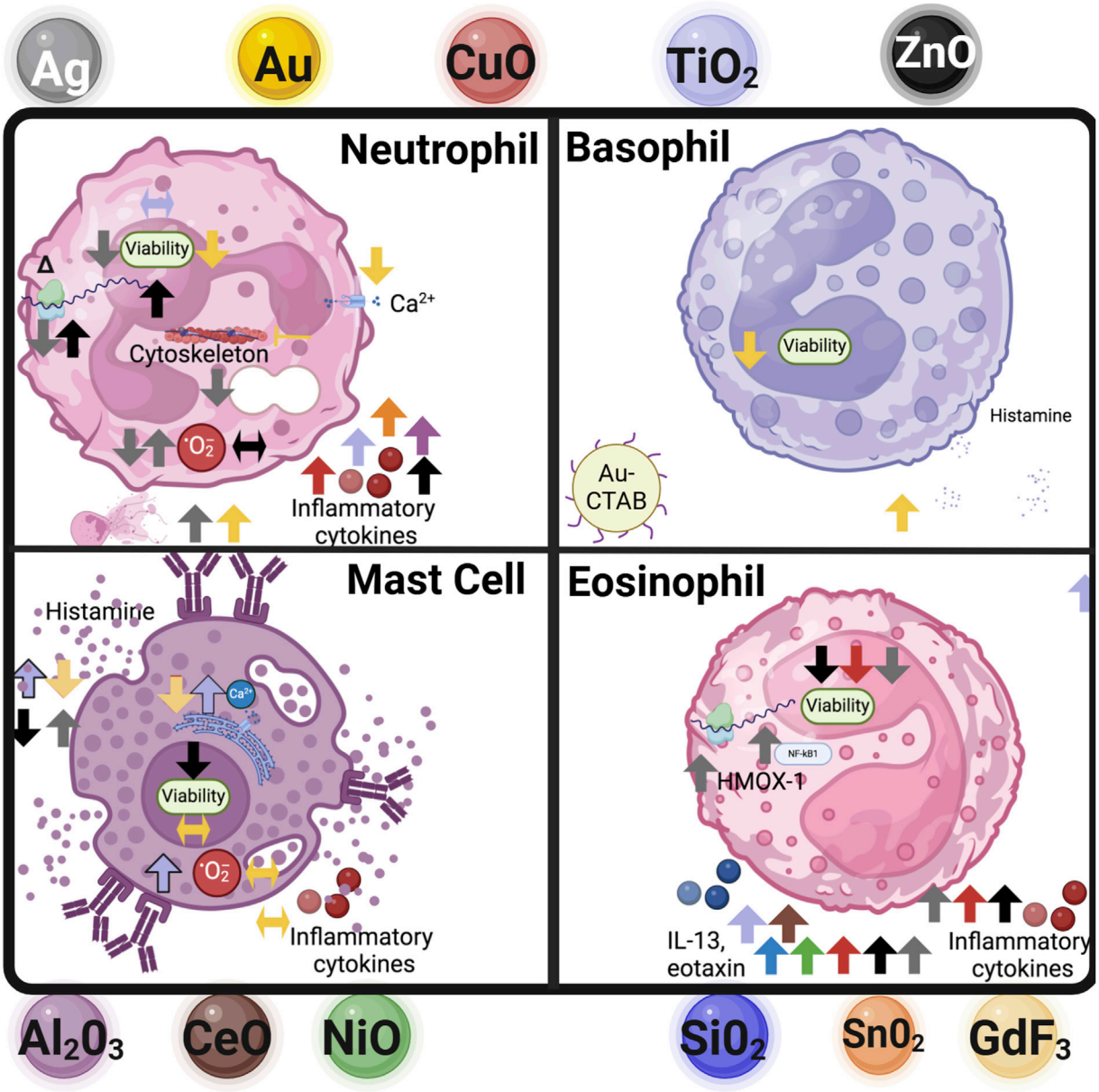

FIGURE 7
Effects of MNPs on polymorphonuclear leukocytes: **(A)** Neutrophil, **(B)** Basophil, **(C)** Mast cell, and **(D)** Eosinophil responses. Arrows (color-coded to MNPs) indicate increased (↑), decreased (↓), or unchanged (↔) function.

progenitors or eosinophil/basophil colony-forming units (Eo/B CFU), which are mononuclear cells expressing CD34, CD35, and interleukin-5 (IL-5) receptors. These progenitors can respond to cytokine signals to differentiate into mature eosinophils and basophils (Tiñana et al., 2010). Eosinophils are blood cells involved in allergic responses, and their accumulation in the blood and tissues is associated with various inflammatory and infectious diseases (Fulkerson and Rothenberg, 2013).

Inflammatory responses in eosinophils are reflected in the release of pro-inflammatory mediators. Certain MNPs have been shown to influence the adhesion of eosinophils to endothelial cells, a crucial step for eosinophils to leave the bloodstream and reach the airways after antigenic stimulation (Rosenberg et al., 2007). For instance, TiO_2NPs have been reported to increase eosinophil adhesion through phosphoinositide 3-kinase/Akt activation (Murphy and Girard, 2018). Additionally, nanoparticles like CeO_2, NiO, ZnO, and CuO have been linked to eosinophilic inflammation associated with elevated IL-13 levels (Cho et al., 2010). IL-13, a key cytokine in allergic asthma, primarily recruits eosinophils, highlighting its role in allergic responses (Wills-Karp, 2004).

Moreover, some MNPs have been shown to be cytotoxic to eosinophils, leading to cell death. For example, exposure to NiONPs, ZnONPs and CuONPs and their aqueous extracts in A549 lung epithelial cells significantly increased eosinophil numbers. LDH and total protein levels, markers of cytotoxicity and vascular

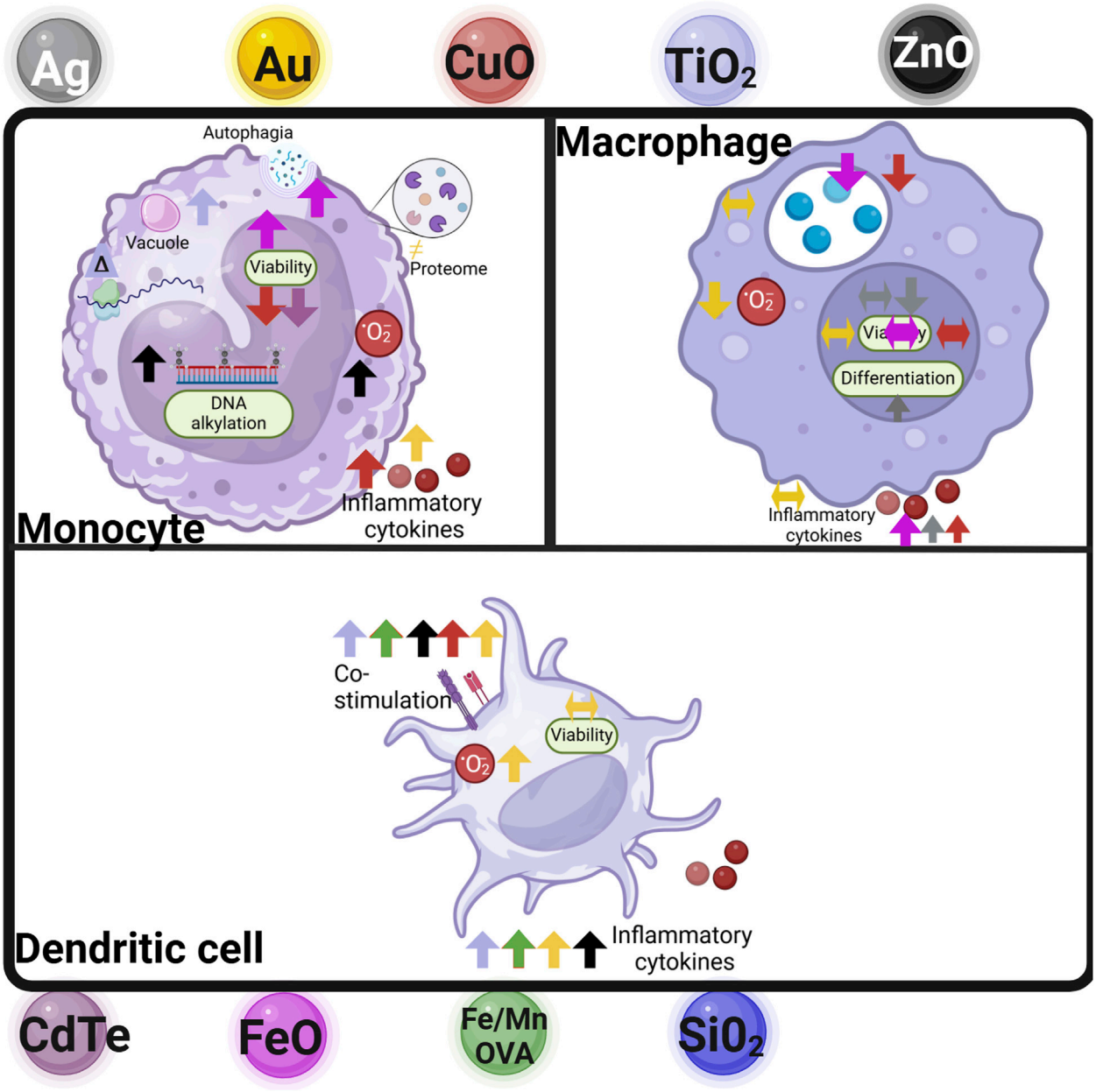

FIGURE 8
Modulation of antigen-presenting cell functions by MNPs in **(A)** Monocytes, **(B)** Macrophages, and **(C)** Dendritic cells. Color-coded arrows correspond to specific MNPs and indicate enhanced (↑), suppressed (↓), or unchanged (↔) cellular functions.

permeability, were significantly elevated 24 h after nanoparticle exposure. However, after 4 weeks, LDH and total protein levels returned to control levels, except for NiONPs, which maintained higher levels, suggesting IS recovery after exposure (Cho et al., 2012). In a 3D alveolar barrier model, uncoated 20 nm AgNPs also decreased cell viability and metabolic activity at 6 h of exposure, with recovery at 24 h (Fizeşan et al., 2019).

Some MNPs also impact eosinophil-associated allergic responses. For instance, 20 nm AgNPs have been shown to induce increased pulmonary resistance and bronchial responsiveness, along with eosinophilic and neutrophilic inflammation and bronchial hyperreactivity, which are characteristic features of asthma. Notably, there was little difference in inflammatory responses between citrate-coated and PVP-coated AgNPs, while the 20 nm particles were more proinflammatory and toxic compared to the 110 nm particles (Seiffert et al., 2015).

6 Discussion

The interaction between MNPs and IS cells is an ongoing and highly important area of research in the field of nanomedicine. In this discussion, we have examined the physicochemical factors that

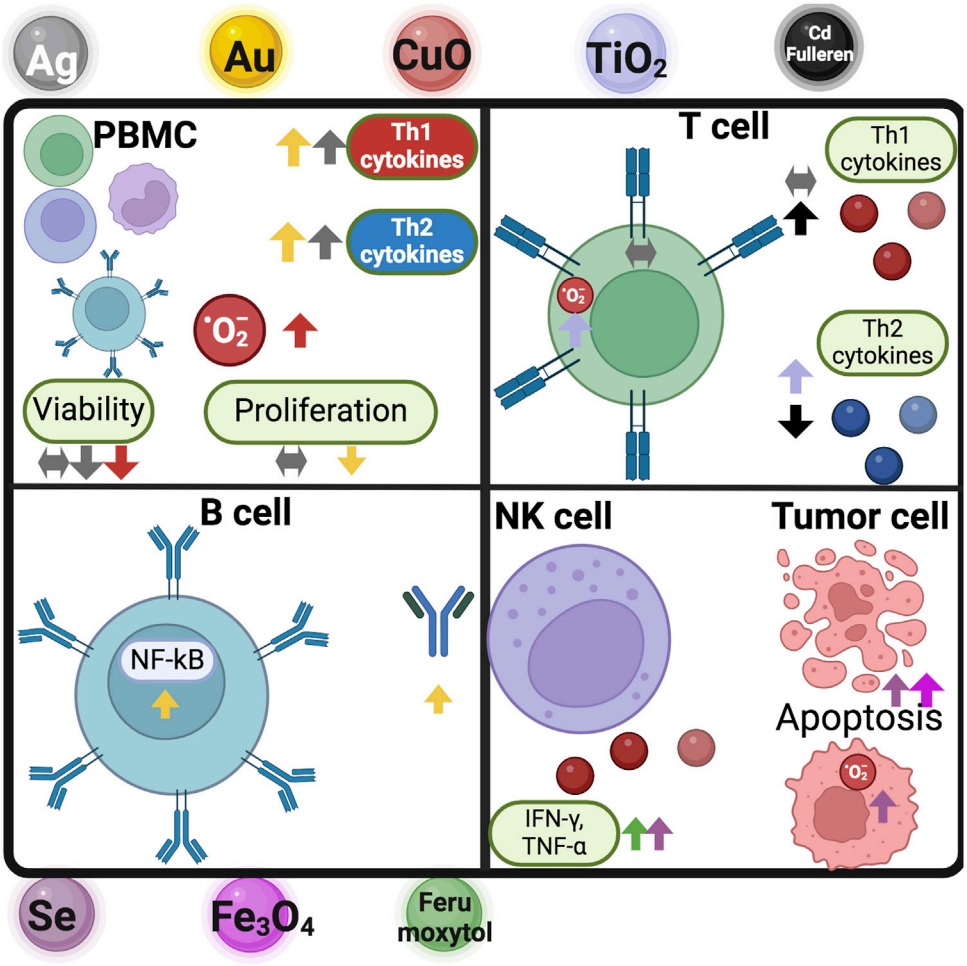

FIGURE 9
MNP effects on lymphocytes: **(A)** PBMC cultures, **(B)** T cells, **(C)** B cells, and **(D)** NK cells. Arrows (color-matched to MNPs) indicate enhanced (↑), suppressed (↓), or unchanged (↔) function. PBMC: peripheral blood mononuclear cells.

influence the compatibility of nanoparticles and the effects generated in specific IS cells. These interactions are crucial for understanding the modulation of both innate and adaptive immune responses, which could have significant implications for the design of nanoparticle-based therapies. The innate immune response involves interactions with cells such as neutrophils, monocytes, macrophages, dendritic cells, Natural Killer (NK) cells, mast cells, basophils, and eosinophils. On the other hand, the adaptive immune response primarily involves B and T lymphocytes, which participate in antigen-specific responses and the formation of immune memory.

Given that most physiological processes occur at the nanoscale, the size of MNPs significantly impacts their interaction with IS cells (Chandrakala et al., 2022). The main function of the cell membrane is to protect cells from their environment, which involves strict regulation of material exchange between the cell and its surroundings (Uzman, 2002). It has been observed that smaller nanoparticles have a greater capacity for cellular internalization compared to larger particles (Shang et al., 2014; Seipenbusch et al., 2008; Panzarini et al., 2018). Additionally, size can influence the immune response, as smaller nanoparticles can activate anti-inflammatory responses (Sumbayev et al., 2013), while others may induce strong pro-inflammatory responses (Park and Park, 2009). Larger nanoparticles may be less immunosuppressive than smaller ones (Luo et al., 2015).

The concentration of nanoparticles also plays an important role in their interaction with immune cells. Higher concentrations can lead to toxic responses, triggering oxidative stress and cellular damage. On the other hand, lower concentrations can beneficially modulate the immune response, promoting the activation of specific IS cells (Peters et al., 2007).

The shape of MNPs also affects their interaction with immune cells. Particles with specific shapes may have a higher affinity for certain cell types and selectively approach them (Chithrani and Chan, 2007). Furthermore, shape can influence uptake and immune response, as elongated or branched particles may be more efficiently internalized (Chithrani et al., 2006).

Another factor to consider is the time of nanoparticle exposure. The duration of exposure can influence the immune response, as acute exposure can trigger intense inflammatory responses, while chronic exposure can have cumulative and prolonged effects on

immune cells (Ortega et al., 2015; Monteiller et al., 2007; Bouallegui et al., 2017).

The surface area and surface chemistry of nanoparticles are factors that determine the initial interaction between particles and cells. The high surface-to-volume ratio of nanoparticles allows for greater cell interaction by increasing protein binding efficiency (Roy et al., 2014). Additionally, the surface chemistry of particles can affect protein adsorption and recognition by cell receptors, influencing subsequent immune responses. Surface charge is another important property that plays a role in cell interaction, as positively charged nanoparticles are often more efficiently internalized than neutrally or negatively charged nanoparticles of similar dimensions (Jiang et al., 2015).

MNPs have the ability to modulate the responses of different immune cell types, which is significant for their therapeutic or immunotoxic potential. These interactions affect both innate and adaptive immune cells, altering specific immune functions. In particular, polymorphonuclear leukocytes (Figure 7), antigen-presenting cells (Figure 8), and lymphocytes (Figure 9) are affected in diverse ways depending on the physicochemical properties of MNPs, which can increase, decrease, or leave their functions unchanged. These effects provide a visual basis to understand how MNPs influence immunity, with important implications for nanomedicine and the development of new therapies.

For instance, MNPs can impact the maturation and activation of B and T lymphocytes, modulating antigen-specific responses and immune memory (Est-Witte et al., 2021; Klippstein and Pozo, 2010). In PBMC cultures and T, B, and NK lymphocytes, MNPs can influence proliferation and cytotoxic activity. Specifically, the cytotoxic activity of NK cells may be altered, affecting the elimination of infected or tumor cells (Evans et al., 2018; Murugan et al., 2022). MNPs can also reduce the release of inflammatory mediators by mast cells and basophils, lowering inflammatory responses in allergic conditions (Yasinska et al., 2019). Additionally, they affect the phagocytic capacity of antigen-presenting cells (APCs) and their role in activating the innate immune response. MNPs can modify the activity of monocytes, macrophages, and dendritic cells, altering their ability to phagocytize and process antigens, which is essential for lymphocyte activation in the adaptive response (Dwivedi et al., 2009; Chen et al., 2018). These responses can be pro-inflammatory or immunosuppressive, depending on the MNP properties. A general point is that it is important to include information reported from cell lines such as human lymphocytes (Jurkat), human monocytes (THP-1), and two murine macrophage lines (RAW and J774), although they are not truly representative of blood lymphocytes, macrophages, or monocytes. However, they are commonly used in research due to their ease of handling, proliferation, and availability despite their differences from primary cells.

Finally, the functions of neutrophils and eosinophils—essential in antimicrobial defense and allergic responses, respectively—are also affected by MNPs (Dwivedi et al., 2009). Neutrophils may experience phagocytic activity and ROS production changes, while eosinophils may show modulations in releasing inflammatory mediators.

In this article, we have focused on the interactions of MNPs with the IS. However, it is also important to consider their potential interaction with other cell types, such as endothelial cells. It has been reported that MNPs can alter endothelial function and cause cytotoxic effects in cellular models (HUVEC) and *in vivo* studies (Gong et al., 2017; Gu et al., 2017; Guo et al., 2016; Freese et al., 2012). Factors such as size, metal type, concentration, and exposure time influence the observed responses. Therefore, when studying the interactions of MNPs, it is essential to consider the target cells and the potential interactions with other cells within the shared microenvironment.

7 Conclusion

The interaction between MNPs and IS cells is determined by their physicochemical properties, including size, concentration, shape, exposure time, and surface chemistry. These properties influence how immune cells internalize and recognize nanoparticles, thus affecting cellular responses. Certain nanoparticles, such as those of CuO, ZnO, and Ni, exhibit high reactivity and toxicity; in contrast, AuNPs stand out due to their biocompatibility and low toxicity. AuNPs show fewer adverse effects and possess a higher capacity for surface modification, a feature particularly advantageous for therapeutic and diagnostic applications, as they have shown good tolerance by immune cells such as lymphocytes, macrophages, and neutrophils.

Sizes between 10 and 50 nm and spherical shape facilitate the internalization of nanoparticles without inducing excessive activation, toxicity, or functional impairment in immune cells. However, excessively small sizes may interact more readily with proteins, triggering heightened inflammatory responses, which should be controlled depending on the application. In comparison, nanoparticles with irregular or edged shapes may induce more cytotoxic effects due to ion release and increased interaction with cell membranes. Additionally, the use of biocompatible coatings, such as polyethylene glycol (PEG), reduces toxicity and enhances the stability of MNPs in physiological environments, minimizing undesired immune responses. Neutral or negative charges also improve biocompatibility, as positive charges often increase toxicity in immune cells. Maintaining low nanoparticle concentrations and controlled exposure times is also essential to avoid toxic effects, particle accumulation, and chronic inflammatory responses.

The effect of MNPs cannot be generalized, as each physicochemical factor may influence their interaction with immune cells differently, depending on the cell type. These effects can vary even within the same cell, especially since many studies are conducted on isolated, cultured cells, limiting the observation of effects in a more complex biological context. Additionally, factors such as the tissue microenvironment must be considered. Therefore, continued research is necessary to better understand these phenomena and ensure the safe and efficient use of MNPs for specific therapeutic objectives.

In conclusion, the design of MNPs for immunomodulation should focus on optimizing their physicochemical properties to enhance interactions with immune cells while minimizing risks. Factors such as size, shape, material, and surface charge influence nanoparticle uptake and the immune response. By carefully considering these parameters, researchers can develop

nanoparticles that balance efficacy and biocompatibility, supporting safer immunotherapy and drug delivery applications.

Author contributions

SG-C: Conceptualization, Methodology, Writing–Original Draft, Writing–review and editing. AM-D: Conceptualization, Methodology, Funding Acquisition, Writing–review and editing. RG-C: Writing–review and editing. OR-C: Methodology, Funding Acquisition, Writing–review and editing. AO-R: Writing–review and editing. RF-M: Conceptualization, Methodology, Funding Acquisition, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnano.2024.1496230/full#supplementary-material

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