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Immunomodulation by Design: A Review of Metal Nanoparticle-induced Macrophage Polarization

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ABSTRACT

Macrophages are pivotal immune cells that exhibit remarkable plasticity, polarizing into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes in response to environmental cues. This process, known as macrophage polarization, plays a critical role in the progression and resolution of various diseases, including cancer, inflammatory disorders, and infections. The emergence of nanomedicine has highlighted the significant interplay between nanoparticles and the immune system, positioning macrophages as a key therapeutic target. This review comprehensively examined the immunomodulatory effects of metal-based nanoparticles—specifically copper, titanium, gold, iron, silver, aluminum, and silicon—on macrophage polarization. We detail how intrinsic nanoparticle properties, such as size, shape, surface chemistry, and composition dictate the polarization outcome by modulating specific molecular pathways, including NF-κB, STAT, IRF, and MAPK signaling. For instance, while iron oxide and certain titanium nanoparticles (TNPs) typically promote M1 polarization, gold and silicon nanoparticles are often shown to induce an M2 phenotype. The effects of other metals, like copper and silver, are highly concentration-dependent or can be tailored through surface functionalization. This analysis underscores the potential of engineered metal nanoparticles to precisely direct macrophage polarization for therapeutic benefit, such as repolarizing tumor-associated macrophages for cancer immunotherapy or promoting M2-mediated tissue regeneration in wound healing. Understanding these intricate interactions is crucial for advancing the application of nanomedicine in immunotherapy and for assessing the safety profile of nanomaterials.

Keywords: Nanomaterials, Human macrophages, Immunotherapy, Polarization

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Highlights

• Metal nanoparticles critically influence macrophage polarization by modulating key immunoregulatory pathways.

• Physicochemical properties of metal nanoparticles determine pro-inflammatory (M1) or anti-inflammatory (M2) macrophage responses.

• Rational nanoparticle design enables targeted immunomodulation with implications for cancer, infection, and inflammatory diseases.

Plain Language Summary

Macrophages are key immune cells that help the body fight infections and repair damaged tissues. They can adopt different roles, either promoting inflammation to defend against threats or reducing inflammation to support healing. When this balance is disrupted, it can contribute to diseases such as cancer, chronic inflammation, and infections. This review study investigates how metal nanoparticles—extremely small materials used in medicine and many everyday products—can influence macrophage behavior. Studies showed that nanoparticles can interact directly with immune cells, and their effects depend on properties such as size, shape, surface features, and metal type. Some nanoparticles stimulate inflammatory responses, while others encourage healing and immune regulation. Overall, it can be said that metal nanoparticles are not inherently harmful or beneficial; their impact on the immune system depends on how they are designed. Understanding these interactions is important for developing safer nanomaterials and designing new medical treatments that guide immune responses in helpful ways. This study highlights the importance of thoughtful design and regulation of nanotechnology to maximize health benefits while minimizing risks.

Introduction

The connection between nanomedicine and the immune system is crucial as many diseases and serious health conditions are linked to inflammation [1]. This includes, but is not limited to, wound healing, heart attack, acute respiratory distress syndrome, and acute lung injury (ALI). Cancer is another well-known disease closely related to the immune system [2]. Understanding the way these conditions work can help create effective treatments. Macrophages, a key component of the immune system, have important impacts on the mechanisms behind these conditions and are therefore a potential target for drugs and medicine. Targeting macrophages can also be useful for diagnostic imaging and testing purposes [3]. In addition to these therapeutic and diagnostic benefits, studying the interaction between nanoparticles and the immune system is critical in determining the safety of nanomedicine-based drugs for clinical use [4, 5].

Macrophages originate from the bone marrow hematopoietic stem cells and exist in the blood as monocytes before migrating to tissues to mature into macrophages. Different environmental factors lead to different differentiation pathways, resulting in different subtypes of macrophages with various roles in inflammation and cancer. These cells can mature into two common phenotypes in response to their microenvironment: M1 or pro-inflammatory, also referred to as classical, and M2 or anti-inflammatory, also referred to as alternative. This maturation process, known as macrophage polarization, is regulated by key transcription factors, like NF-κB, signal transducer and activator of transcription (STAT) protein family, peroxisome proliferator-activated receptor-γ (PPARγ), and interferon-regulatory factor (IRF) family. Research has shown that the activation of STAT1 and IRF5 regulates M1 polarization, while the activation of STAT6/STAT3 and IRF4 leads to polarization of macrophages to the M2 phenotype. M1 macrophages secrete pro-inflammatory cytokines, like TNFα, interleukin-1 beta, and chemoattractant cytokines, like CXCL3, CXCL8, and CXCL10, and play a crucial role in the elimination of microbes, pathogens, and abnormal cells, as well as in recruiting other components of the immune system to the site of inflammation. However, prolonged inflammation can lead to M1 cells promoting a cytotoxic effect, causing harm to nearby tissues through the attraction of $CD8^+$ T and B cells. This is why acute inflammation is beneficial, but chronic inflammation is problematic [6, 7]. M2-like macrophages, on the other hand,

secrete anti-inflammatory factors, like TGFβ, Il-10, and VEGF, to modulate the immune response and promote regenerative processes, like wound healing. However, an excess number of these macrophages has been shown to be linked to poor prognoses in some diseases [8].

M1 macrophages have distinctive markers, like CD86, CD80, and CD68, and produce an elevated amount of inflammatory cytokines, including TNF-α, IFN-γ, IL-1, IL-6, IL-12, IL-23, nitric oxide (NO), and reactive oxygen species (ROS). M2 macrophages are known to secrete high levels of IL-10 and TGF-β, express surface markers, such as the mannose receptor (CD206), CD163, and dectin, and are triggered by IL-4 and IL-13. An imbalance between macrophage types is connected to many immunity-related illnesses; therefore, restoring the balance between macrophage types can be a potential solution to treat these diseases [9, 10].

Materials that come into contact with the body can trigger an immune response that can impact the surrounding cells and tissues. However, if the material possesses the appropriate qualities, the body's response can be influenced by the nanoparticle and its properties, such as size, composition, and surface features. Decreasing the particle size or adding an inert surface coating can reduce its polarization effects, while increasing macrophage uptake by adding a macrophage-targeting component to the surface can enhance its polarization properties. Macrophages can be exposed to nanoparticles through different methods, such as oral or intravenous administration of nanoparticle-based medications, inhalation of nanoparticles from air pollution or occupational exposure, or from the degradation of metallic implants in the body. Macrophages can identify these particles and internalize them through endocytosis or phagocytosis. The specific type of can trigger an M2-like response, while other types of nanoparticles tend to result in M1-like polarization. In this thorough study, the effects of various metal-based nanoparticles on macrophage polarization were evaluated. The various methods and molecular processes responsible for MP polarization were explored for each type of nanoparticle.

Materials and Methods

This is comprehensive review of studies examined the effects of metal nanoparticles on macrophage polarization and immune modulation. A systematic search was first conducted in online databases including PubMed, Scopus, and Web of Science for articles published from January 2010 to September 2025, using the keywords "metal nanoparticles," "macrophage polarization," "M1 macrophages," "M2 macrophages," "immunomodulation," "nanomaterials," "innate immunity," and "transcription factors", by employing Boolean operators. In addition, the reference lists of eligible articles were manually searched to identify further relevant studies. The studies that investigated metal-based nanoparticles such as gold, silver, iron oxide, zinc oxide, or titanium dioxide and evaluated their effects on macrophage activation, polarization, or immune signaling pathways using in vitro, in vivo, or preclinical models were included. Only those published in English were included. Articles were excluded if they focused exclusively on polymeric nanoparticles, liposomes, or non-metallic nanomaterials, or if they were conference abstracts, editorials, opinion pieces, or non-peer-reviewed publications.

After screening of titles and abstracts, full-texts of articles that met the inclusion criteria were reviewed. The extracted data included nanoparticle type, physicochemical characteristics including size, shape, surface chemistry, experimental model, macrophage phenotype markers, involved signaling pathways and transcription factors, and reported immunological outcomes. The collected findings were synthesized qualitatively and organized thematically to elucidate the relationship between metal nanoparticle design parameters and macrophage polarization profiles. Particular emphasis was placed on mechanistic insights related to inflammatory and immunoregulatory signaling pathways to highlight key principles for the rational design of metal nanoparticle-based immunomodulatory strategies

Results

Copper (Cu)

Cu oxide (CuO) nanoparticles are a type of intelligent transition metal nanoparticles with a narrow energy bandgap. At the nanoscale, they exhibit unique attributes such as excellent electrochemical behavior, a large specific surface area, an appropriate redox potential, and outstanding stability in liquids [11, 12]. These features make them widely used in non-enzymatic analysis of clinically important substances. Additionally, CuO nanoparticles have demonstrated pharmacological activity, particularly in anti-tumor therapy. After being acknowledged as an antimicrobial material by the US Environmental Protection Agency (EPA), there has been increased interest in using Cu and its derivative nanoparticles in biomedical devices to combat bacterial infections [11, 13]. Studies have revealed that the integration of copper nanoparticles in wound healing and bone formation can enhance tissue regeneration [14, 15]. Díez-Tercero et al. [16] aimed to

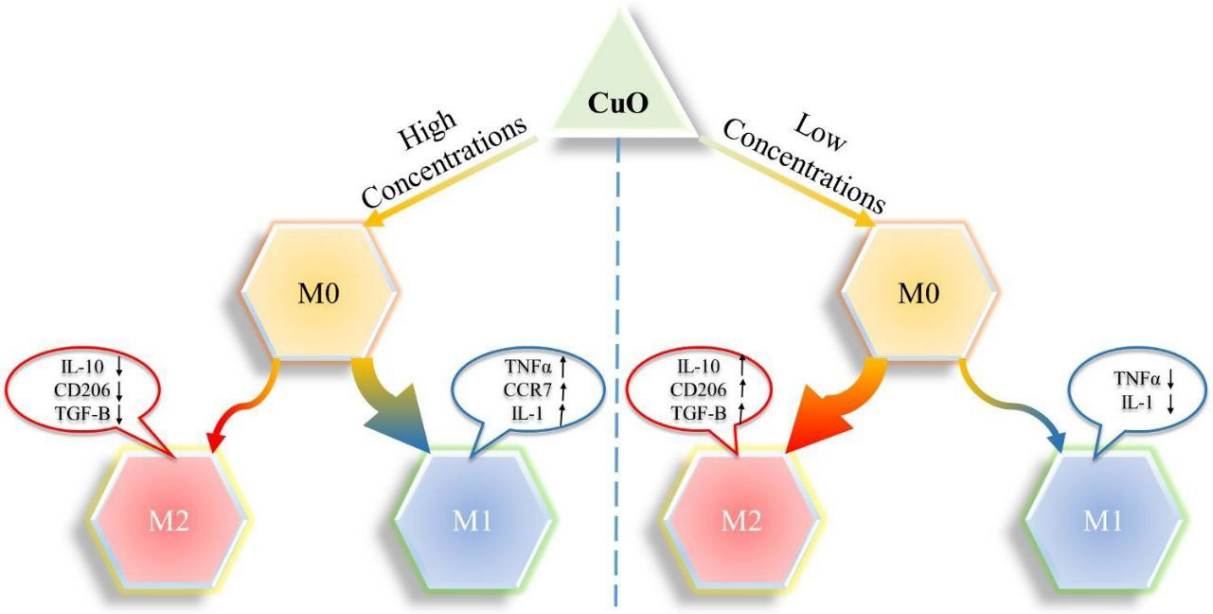

Figure 1. CuO concentration-based interaction with macrophages

examine the immunomodulatory impact of Cu nanoparticles on macrophage polarization. The results showed that low concentrations of Cu^{2+} (less than 10 μM) upregulated *M2* gene expression. In contrast, high concentrations of Cu^{2+} stimulated pro-inflammatory marker expression, demonstrating a correlation between the concentration of the ions and their effect [17] (Figure 1). Another study has shown that administering Cu nanoparticles activates tumor-associated macrophages (TAMs), producing elevated levels of IL-12 and low levels of IL-10, leading to a robust Th1 response characterized by high levels of IFN-γ and reduced T cell death during activation. Most notably, CuNG-treated TAMs were capable of changing TGF-β-producing CD4+CD25+ T cells into IFN-γ-producing T cells [18, 19].

Titanium

Titanium dioxide nanoparticles (TNPs) have a wide range of uses in biomedical devices, including artificial joints, amputation prostheses, dental restorations, and coronary stents. In general, these nanoparticles have been found to activate the pro-inflammatory magnetic polarization (MP) phenotype known as M1. However, Yang et al. [20] showed that TNPs with an irregular shape and an average diameter of 52.59±20.48 nm reduced the production of Arg-1 and IL-4, decreased CD163 and CD206 expression, and increased the production of inflammatory cytokines, such as TNF-α and IL-6, as well as the expression of CD86 and CCR7. At the same time, they also increased IL-10 levels, which is an anti-inflammatory cytokine (Figure 1). The way in which titanium causes M1 polarization was found to be connected to the activation of FAK, mitogen-activated protein kinases (MAPKs), JNK, and ERK. This leads to excessive oxidative stress, DNA damage, and apoptosis. M1 activation caused by TNPs is linked to the dose, with lower doses leading to a partial reduction in inflammation due to increased M2 polarization [21, 22]. Adding other materials to TNPs can also change their effect on MP polarization. Adding Cu to titanium implants increases M1 polarization and promotes osteointegration and bactericidal effects (Figure 2b), while adding lithium chloride (LiCl) and curcumin shifts polarization toward M2 [23, 24]. Yang et al. [20] showed that adding LiCl to TNPs increases the production of Arg-1, IL-4, and IL-10, while decreasing TNF-α and IL-6, and upregulates the expression of CD163 and CD206 while downregulating CD86 and CCR7 [25].

Xu et al. [26] found that the combination of curcumin and TNPs can reduce inflammation by promoting M2 polarization, as indicated by higher levels of Arg-1, IL-4, and IL-10 production. However, they noted that there was no direct link between the size of TNPs and M2 polarization at the nanoscale (Figure 2c). Although increasing the size of TNPs from 65 to 140 nm resulted in a higher number of CD206- positive macrophages, it did not affect the levels of various other markers, such as Arg-1, IL-10, IL-1β, IL-8, TNF-α, iNOS, CCR7, and CD206 [27-29].

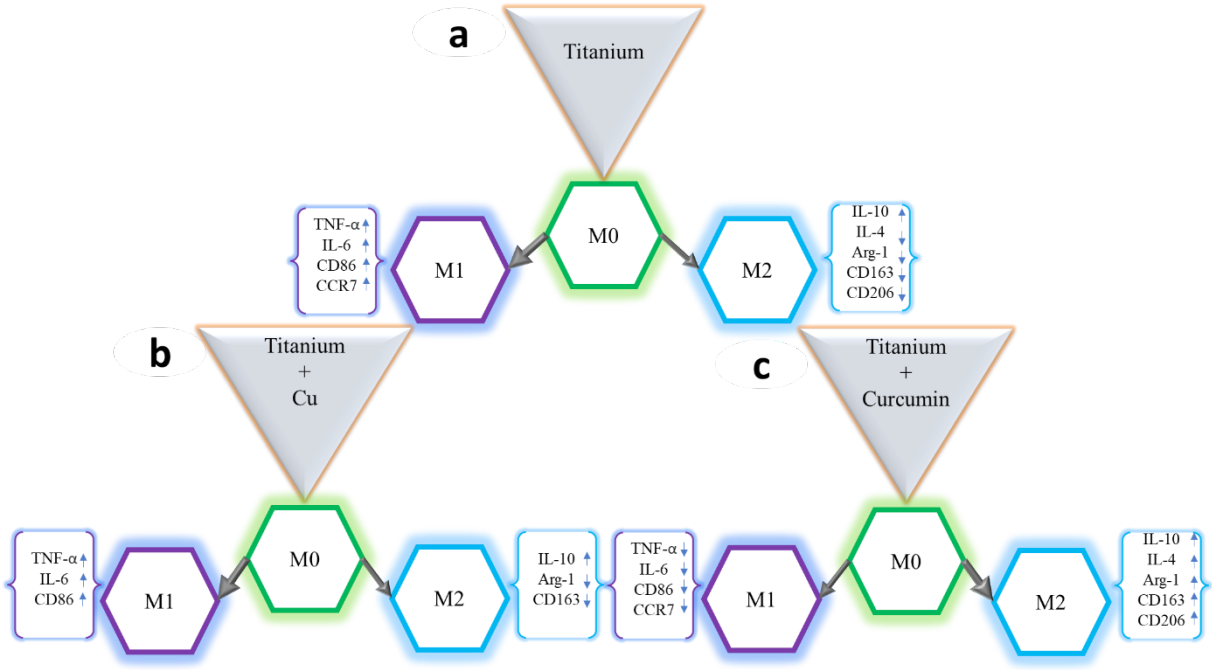

Figure 2. Interactions of titanium and its combinations with other elements with macrophages

Note: a: Titanium; b: Titanium + Cu; c: Titanium + curcumin.

Gold

Gold nanoparticles (AuNPs) have many potential applications in the medical field, including in diagnosis and treatment. They can be easily created and modified with various large molecules, such as proteins, antibodies, carbohydrates, and lipids. Bella et al. [30] found that spherical AuNPs with a diameter of 20 to 30 nm were effective in actively and passively targeting MPs and changing their phenotype to the anti-inflammatory M2 type. This property has been used to treat serious conditions, such as sepsis and lung diseases [31, 32].

Taratummarat et al. [31] conducted a study in which they co-administered spherical 21 nm AuNPs and antibiotics to mice at a concentration of 7.85 μg/g. The results showed that this combination reduced bacterial sepsis and the overall mortality rate in the mice, while improving kidney function and reversing liver injury. The analysis of cytokine levels in the serum and bone marrow showed a decrease in TNF-α, IL-6, and IL-1β, but not IL-4. Additionally, the expression of CD86 decreased, while CD206 expression increased in the spleens of the septic mouse models. Wang et al. [32] found that by coating AuNPs with hexapeptides, they developed bioactive nanoparticles that reduced inflammation in ALI. The results indicated that these nanoparticles significantly polarized MPs toward the anti-inflammatory M2 phenotype, and reduced the levels of M1-related markers, such as IL12, iNOS, and CD80, while increasing the levels of M2-related markers, including IL-4, IL-10, Arg-1, and CD206 in the lung, bone marrow, and bloodstream (Figure 3b).

To tailor the anti-inflammatory effects of AuNPs for different medical applications, researchers have explored the modifications that can be made to their physical/chemical properties. For example, Kang et al. [33] prepared gold nanorods (GNRs) with different anisotropies and found that highly anisotropic nanorods promoted M2 polarization by activating the Rho-associated protein kinase pathway. Cheng et al. [34] studied the impact of AuNP size on MP polarization and found that larger AuNPs induced stronger anti-inflammatory responses. To reduce both M1- and M2-related inflammation and pro-fibrotic effects in systemic sclerosis, Codullo et al. [35] developed AuNPs functionalized with a half-chain of a monoclonal antibody against CD44 and loaded them with Imatinib. This led to a decrease in both M1 and M2 markers, as well as a reduction in fibroblasts and collagen deposition in the lung tissue.

Iron

Iron nanoparticles (IONPs) have gained popularity in the field of biomedical research, both in preclinical and clinical settings. These nanoparticles have been shown to stimulate the polarization of MPs toward the M1 phe-

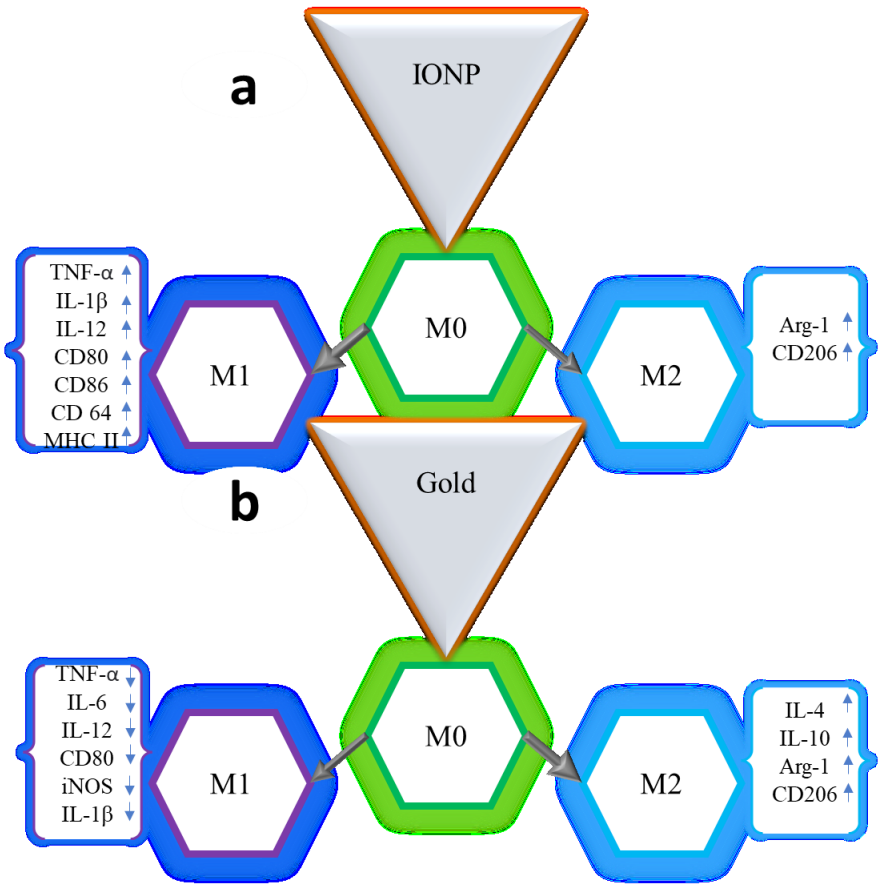

Figure 3. Interactions of iron (a) and gold (b) nanoparticles with macrophages

notype, which is pro-inflammatory in nature. In a study by Mulens-Arias et al. [36], IONPs were found to significantly increase the production of pro-inflammatory cytokines, like IL-1β, IL-12, and TNF-α. The expression of CD80, CD86, and CD64 was also found to increase. In another study, IONPs upregulated M1-related markers, like CD80, CD86, and MHC II, while downregulating M2-related markers, like CD206 and Arg-1. The main regulatory pathway for iron is the NF-κB pathway, which controls the polarization of MPs through different pathways, like MAPKs and STATs. Iron has been shown to target the OXPHOS pathway and regulate various other factors, like miRNAs and Jumonji domain-containing protein D3 (JMJD3). The stimulation of glycolysis by iron has been linked to the upregulation of glycolysis-dependent genes and the promotion of M1 MP polarization [37-39].

Gu et al. [40] conducted a study to examine the intracellular effects of magnetite (Fe_3O_4) on MP polarization. The results showed that the MP polarization induced by IONPs is more closely related to its intracellular accumulation and the activation of the IRF5 signaling pathway. The study found that while IL-23 production was significantly increased in MPs treated with IONPs, the upregulation of iNOS was relatively low. This suggests that the M1 polarization depends on the IRF5-IL23 pathway instead of the ROS-induced NF-κB-iNOS pathway, likely due to the suppression of iNOS expression by iron. Gu et al. [40] also noted that several factors related to IONPs can influence MP polarization, such as iron oxidation and the superficial charge of super-paramagnetic iron oxide NPs (SPIONs). The study showed that positively and negatively charged SPIONs led to M1 polarization, while the neutral SPIONs had the least polarization effect. The results indicated that the administration of both positively and negatively charged SPIONs increased M1-related markers, such as CD80 and decreased M2-related markers, like CD206, with negatively charged SPIONs exhibiting greater potency.

Recently, numerous studies have been conducted on the use of iron-based NPs with multiple functions for cancer therapy. These NPs have been demonstrated to induce M1 MP polarization and trigger either immunogenic or heat/laser-induced death of tumor cells, some-

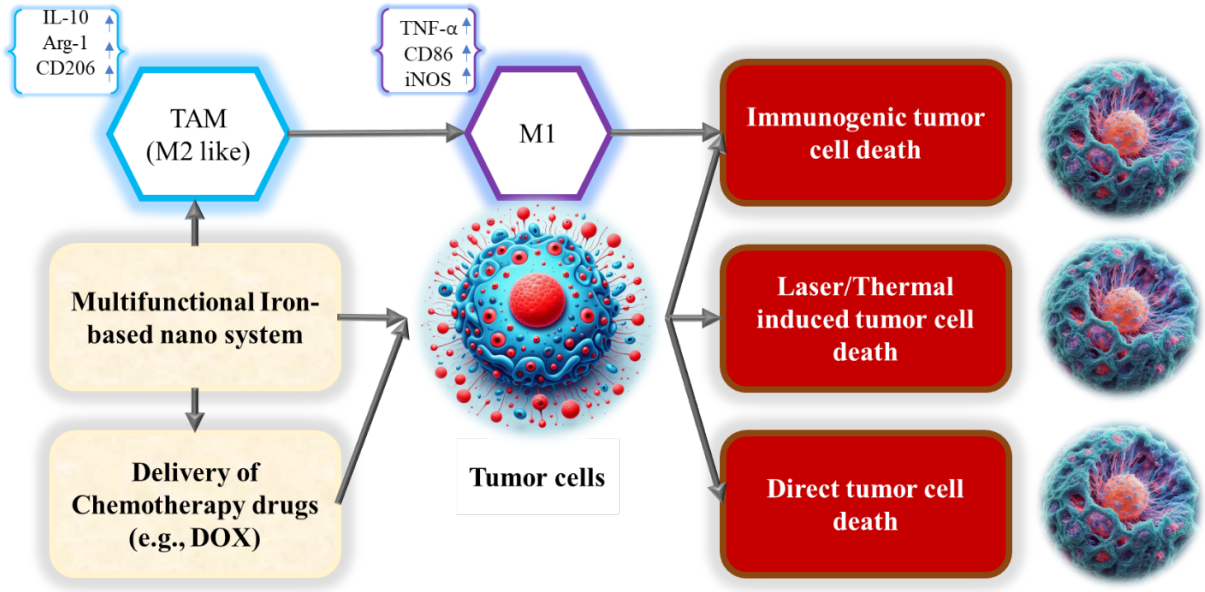

Figure 4. Interactions of multifunctional iron-based nano-systems with tumor cells

times also serving as carriers for drug delivery. The following section provides an overview of some of these multifunctional iron-based systems [41, 42] (Figure 3a).

Recently, Li et al. [43] conducted a study on the use of porous hollow iron oxide nanoparticles (PHNPs) for delivering a small molecule inhibitor of phosphoinositide 3-kinase gamma (P13K γ) to shift tumor-associated macrophages (TAMs) to the pro-inflammatory M1 phenotype. This system was found to have anti-tumor properties in vivo by activating the NF-κB p65 inflammatory factor in TAMs and repolarizing them to M1 MPs. Another study by Chen et al. [44] developed iron oxide-embedded large-pore mesoporous organosilica nanospheres (IO-LPMONs) for NP-based immunotherapy. These nanospheres could suppress tumor growth by activating antigen-specific CD4+ and CD8+ effector T cells and repolarizing TAMs to M1, as indicated by the upregulation of iNOS, TNFα, and CD86 and the downregulation of IL-10, Arg-1, and CD206.

Yu et al. [45] developed a type of iron oxide magnetic NP that is coated with the membrane of myeloid-derived suppressor cells (MDSCs) to target and eliminate cancer cells. These nanoparticles showed good tumor-targeting abilities, magnetic resonance imaging (MRI) compatibility, and photothermal (PTT)-induced tumor cell death. The study also found that MNP@MDSC increased M1 polarization and decreased M2 MP phenotypes. In a separate study, Liu et al. [46] designed ferrimagnetic vortex-domain iron oxide nanorings (FVIOs) that induced mild magnetic hyperthermia. This led to the expression of calreticulin (CRT) on the surface of cancer cells, making them easier to be phagocytosed by MPs and increasing the recruitment of cytotoxic T-lymphocytes near tumor cells. The research also showed that the use of FVIOs increased M1 polarization. To combine the magnetothermodynamic therapy of cancer with the ROS-induced immune response, Liu et al. [47] created FVIOs that were grafted with graphene oxide (FVIOs-GO). In an effort to target breast cancer with greater efficiency, Liu et al. [46, 47] combined FVIOs-GO with a short peptide called Cys-Arg-Glu-Lys-Ala (CREKA). The result was an MTD system that combined the heating effect of FVIOs-GO with the ROS-related M1 MP polarization to effectively kill tumor cells at temperatures that are safe for the body. In another study, Xiao et al. [48] created BSO-FeS_2 NPs that increased ROS generation under laser irradiation at a single wavelength of 808 nm, leading to tumor cell death. This system was also considered a form of immunotherapy, as the NPs induced M1 polarization by boosting the expression of CD86 and reducing CD206 expression in MPs [40, 49].

In a study by Gong et al. [50], iron oxide (Fe_3O_4) was utilized to transport the chemotherapy drug doxorubicin (DOX) to cancer cells. The researchers combined Fe_3O_4 nanoparticles with DOX and hyaluronic acid (HA) nanoparticles (Fe_3O_4-DOX+HA) to develop a multifunctional iron-based cancer treatment system. Fe_3O_4-DOX+HA was found to extend the circulation time of DOX and improve its accumulation in tumor cells through passive targeting. Additionally, this system in-

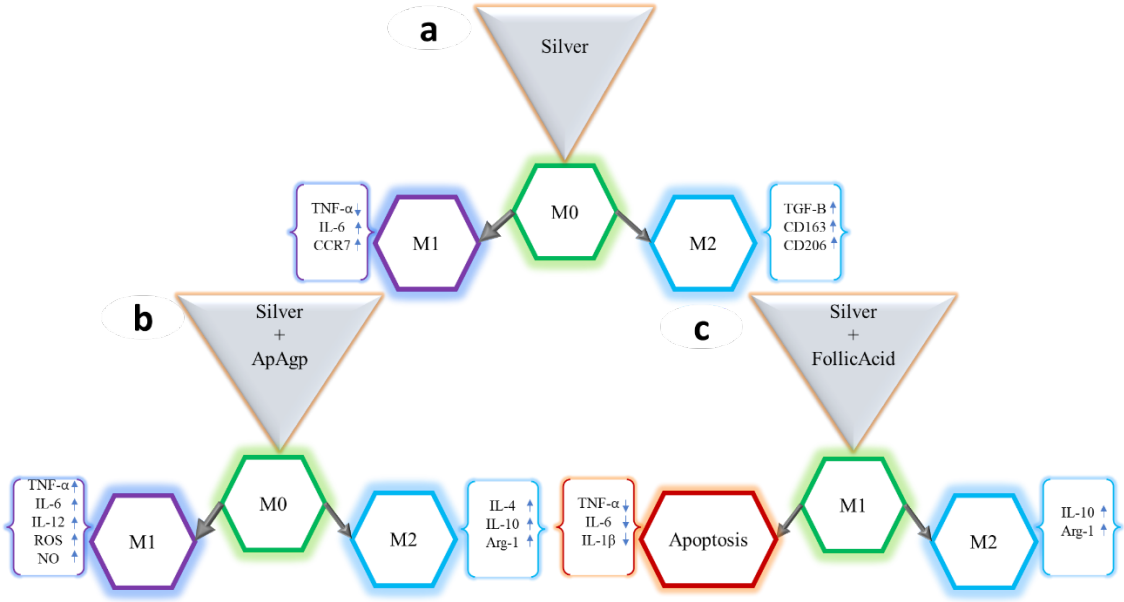

Figure 5. Interactions of silver-based nanoparticles with macrophages

Note: a: Silver; b: Silver + ApAgp; c: Silver + follic acid.

creased the polarization of macrophages toward the M1 phenotype, leading to enhanced anti-tumor effects [51].

The M1 polarization of macrophages induced by iron NPs also presents a new approach for treating infectious diseases. When combined with a reducing agent that converts Fe^{3+} to Fe^{2+} and catalyzes the Fenton reaction, iron oxide NPs can significantly enhance the antibacterial effects of macrophages against intracellular *Staphylococcus aureus* by inducing M1 polarization and stimulating the production of ROS. The mechanisms are summarized in Figure 4.

Silver

Silver nanoparticles (AgNPs) are widely used in biomedical applications because of their simple synthesis, ability to be modified easily, and broad range of biological activities. They are utilized for several purposes, including antimicrobial and antifungal applications, cancer therapy, promotion of wound repair, bone healing, vaccine adjuvants, anti-diabetic agents, and biosensors [52-54].

AgNPs have been shown to promote the M2 phenotype, but the size-dependency of the effect is still unclear. Roszak et al. [55] found that AgNPs with sizes of 15 nm or 45 nm did not differentiate M0 macrophages into M1 or M2. However, other studies, such as those by Saleh et al. [56, 57] and Yilma et al. [58], have reported that AgNPs can alter the host's inflammatory response, downregulate certain markers, and suppress the secretion of inflammatory mediators, indicating the promotion of M2 polarization. For example, Saleh et al. [57] found that AgNPs with a size of 100 nm reduced the host's inflammatory response by downregulating CCR7 and upregulating CD206 in subcutaneously implanted decellularized porcine liver slices in mice. In the study by Yilma et al. [58], Ag-PVP nanoparticles reduced the secretion of IL-6 and TNF-α by infected macrophages in burn wound models by disrupting inflammatory signaling pathways and downregulating certain genes involved in the immune response. Varela et al. [59] conducted a study to assess the effect of AgNPs on wound healing by comparing the modulation of macrophages by wound dressings with and without AgNPs. The wound dressings had different compositions and were found to affect the metabolism and phenotype of macrophages after just one day of the experiment. AgNPs exhibited anti-inflammatory effects by inducing M2 polarization, as evidenced by increased levels of CD163 and CD206 expression and TGF-β production. These effects are believed to aid in the wound healing process, as demonstrated in Figure 5a [60, 61].

Research has demonstrated that AgNPs can display immunomodulatory properties when combined with pro-inflammatory nanoparticles. Chen et al. [44, 53, 62] conducted a study aimed at improving the success of endosseous implants and found that loading AgNPs on the surface of titanium dioxide nanotubes decreased lo-

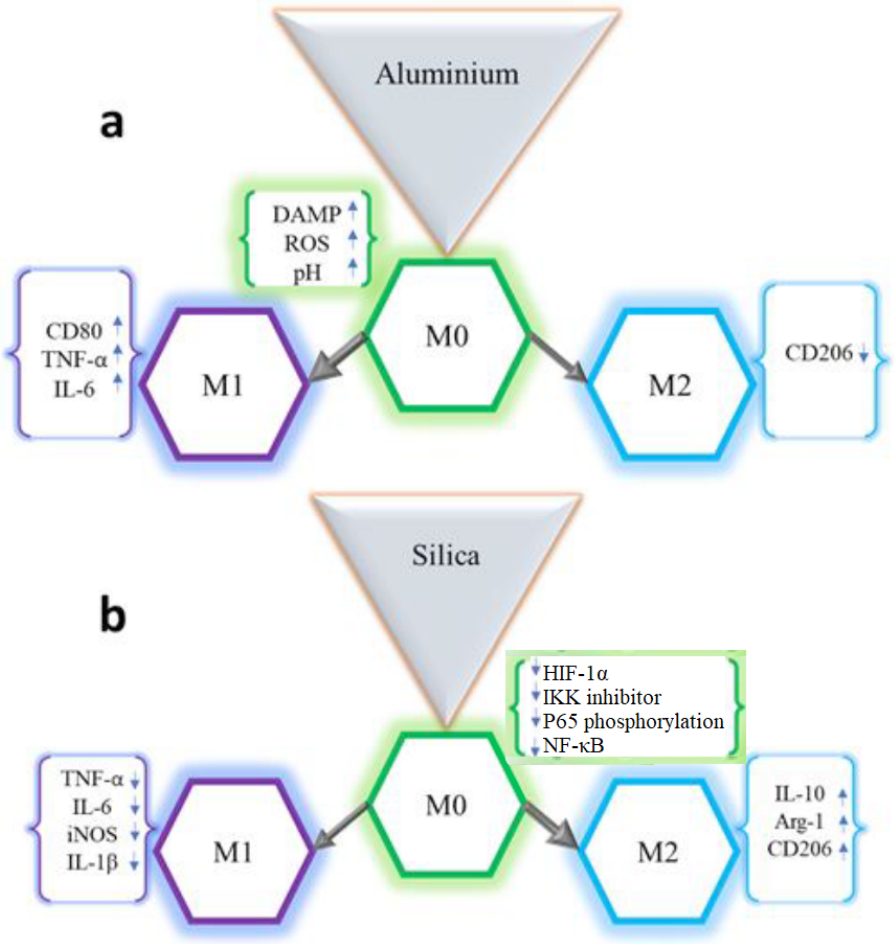

Figure 6. Interactions of aluminum (a) and silicon (b) with macrophages

cal inflammation and improved bone healing. This was due to the induction of M2 polarization and the added antibacterial effects provided by the AgNPs.

Yang et al. [20] conducted a study to explore a potential treatment strategy for rheumatoid arthritis by reducing the M1 macrophage population. They investigated the impact of functionalizing the surface of AgNPs with folic acid (FA-AgNPs) because M1 macrophages overexpress folate receptors on their surface. The folic acid was meant for targeted delivery of AgNPs to M1 macrophages. The results showed that these nanoparticles increased M2-related markers, such as Arg-1 and IL-10, and decreased M1-related markers, such as IL-1β, IL-6, and TNF-α, due to the scavenging of reactive oxygen hydroxyl radicals. The study concluded that the repolarization of M1 macrophages to M2, along with the intracellular release of Ag^{+}, led to the apoptosis of M1 macrophages and a decrease in inflammation (Figure 5c) [63, 64].

Raja et al. [65] examined the effects of combining AgNPs with another macromolecule, the arabinogalactan protein from *Andrographis paniculata* (ApAGP). They made AgNP-ApAGP particles, which were found to increase the production of ROS, NO, IL-12, TNF-α, and IL-6, and decrease the release of anti-inflammatory cytokines IL-4 and IL-10. The study showed that adding ApAGP to AgNPs leads to M1 polarization and promotes an inflammatory environment (Figure 5b) [66, 67].

Aluminum

Aluminum oxide nanoparticles (AlNPs), which are porous nanomaterials, belong to the metal oxide nanomaterial family. Structurally, they are composed of a corundum-like arrangement in which one aluminum atom is surrounded by six oxygen atoms. Similar to other metal oxide nanoparticles, AlNPs are straightforward to work with and readily available. AlNPs have been evaluated as a favorable option for use in the field of biomedical science and biotechnology due to their diverse applicability.

Table 1. The cumulative summary of studies

No.	Nanoparticles [Ref.]	Explanation	Increased/ Upregulated	Decreased/ Downregulated	Process/Operation	Study Type (In Vivo/ In Vitro)	M1/M2 Polarization
1	TNPs [20]	The size of TNPs varies between 30 and 90 nm, with an average diameter of 52.59±20.48 nm.	CR7, CD86, IL-6, TNF-α, and IL-10	CD206, CD163, IL-4, and Arg-1	Activation of the MAPK pathway involves the phosphorylation of extracellular signal-regulated kinase (ERK) and p38	In vivo and in vitro	M1
2	TNPs+LiCl [20]	TNPs undergo modification with the addition of LiCl.	Arg-1, CD206, CD163, IL-4, and IL-10	CD86, TNF-α, CCR7, and IL-6	Suppression of the MAPK pathway involves inhibiting the phosphorylation of ERK and p38.	In vivo and in vitro	M2
3	Cu-Hier-Ti [27]	A titanium surface with micro/nanotopography incorporating Cu elements is described as a Cu-containing micro/nanotopographical titanium surface.	IL-1β, iNOS, D11c, and TNF-α	CD163, Arg-1, and IL-4	Cu transport (↑) Ticam-2(↓) NF-κB (↑) TLR-3 (↓) αM (↓)	In vivo and in vitro	M1
4	Titanium particles + curcumin [81]	Curcumin is applied to titanium particles, characterized by an average diameter of 2.9 µm.	CD206, CD163, Arg-1, IL-4, and IL-10	TNF-α, CD86, CCR7, and IL-6	No answer	In vivo and in vitro	M2
5	AgNPs [56, 59]	Silver nanoparticles (AgNP) exhibit a size of 100 nm. Various commercially available wound dressings feature silver ions, including metallic silver, patented ion silver complex salt, and nanocrystalline silver particles.	CD163, CD206, and TGF-β	NO and CCR7	No answer	In vivo and in vitro	M2
6	Ag-PVP NPs [58]	Nanoparticles of silver-polyvinyl pyrrolidone are available in sizes of 10, 20, and 80 nm.	No answer	CD86, TNF-α, CD80, IL-12p70, IL-6, GM-CSF, IL-1α, GCSF, CXCL10, and CCL5	NOD2 (↓) TLR2 (↓) IRAK3(↓) CD40 (↓)	In vitro	M2
7	SNP-ApAGP [65]	Arabinogalactan protein from ApAGP is bioconjugated with silver nanoparticles (SNP).	TNF-α, IL6, IL-12, ROS, and NO	Arg-1,IL-10, IL-4	No answer	In vitro	M1
8	FA-AgNPs [52]	AgNPs are modified through PEGylation and adorned with folic acid (FA).	IL-10 and Arg-1	IL-6, TNF-α, and IL-1β	No answer	In vivo and in vitro	M2
9	IONP@D-SiO_2 [40]	In the core of a large-pore dendritic silica shell (D-SiO_2), Fe_3O_4 (magnetite) iron oxide nanoparticles (IONP) are available.	CD80, CD86, CD64, and IL- 23	CD206 and Arg-1	IRF5-IL23 signaling (↑)	In vivo and in vitro	M1
10	IO-LPMONs [44]	Large-pore mesoporous organosilica contains embedded Fe_3O_4 nanoclusters.	CD80, MHC II, CD86, iNOS, and TNFα	CD206, Arg-1, and IL-10	No answer	In vivo and in vitro	M1

No.	Nanoparticles [Ref.]	Explanation	Increased/ Upregulated	Decreased/ Downregulated	Process/Operation	Study Type (In Vivo/ In Vitro)	M1/M2 Polarization
11	PHNPs@DPA-S-S-BSA-MA@3-MA [43]	The formulation involves porous hollow iron oxide nanoparticles (PHNPs) carrying the small molecule inhibitor of PI3K γ (3-methyladenine, 3-MA). These nanoparticles are blocked with bovine serum albumin (BSA) and additionally modified with mannose.	iNOS, CD86, and TNF-α	CD206, Arg-1, and IL-10	NF-κB p65 protein(↑) PI3K γ protein (↓)	In vivo and in vitro	M1
12	AuNPs [31]	Spherical AuNPs with a diameter of 21 nm are present.	CD206, Arg-1, IL-10, and PPARγ	CD86, iNOS, TNF-α, IL-6, and IL-1β	No answer	In vivo and in vitro	M2
13	Peptide-coated gold NPs [32]	AuNPs coated with hexapeptides (Cys-Leu-Pro-PhePhe-Asp) have an average diameter of 13.0±0.4 nm.	CD206 and IL-10	CD80, IFN-γ, and IL-2p40	TRIF-dependent pathway (↓)	In vivo and in vitro	M2
14	Ligand-coated GNRs [33]	GNRs of different nanoscale anisotropies (aspect ratios: 1, 2, 4, and 7) are conjugated to a substrate with similar surface areas. Subsequently, they are coated with RGD.	Arg-1 and Ym2	CD80 and iNOS	ROCK pathway (↑)	In vivo and in vitro	M2
15	MFC-MSNs [74]	Mesoporous silica nanoparticles (MSNs) anchored with 6 nm-sized manganese ferrite and 3 nm-sized ceria nanoparticles are referred to as MFC-MSNs.	CD206, IL-10, and Arg-1	iNOS, TNF-α, IL-6, IL-1β, and Cox-2	HIF-1α and ROS production (↓)	In vivo and in vitro	M2
16	Porous Se@SiO_2 [82]	Monodispersed and uniform spherical porous Se@SiO_2 nanospheres, with an average diameter of approximately 55 nm, feature small Se particles distributed from the center to the surface, resembling quantum dots with diameters less than 5 nm.	CD206, CD163, IL-10, Arg-1, IL-10, and TGF-β	TNF-α, iNOS, IL-1β, IL-6, and IL-12	ROS-NF-κB pathway (↓)	In vivo and in vitro	M2
17	NCDot-2 and NCDot-1 [78]	On the surface of 316LSS, microarrays are constructed with mesoporous silica nanospheres (MSNs), forming NCDot. Two variations are specified: NCDot-1 with a diameter of 50.6±6.3 nm and NCDot-2 with a diameter of 65.4±5.5 nm.	CD206 and IL-10	IL-6, CD86, IL-1β, and TNF-α	No answer	In vitro	M2
18	P4 A [83]	AuNPs conjugated with IL-4, denoted as PA4, are characterized by monodisperse sizes of 30, 60, and 100 nm. After partial PEGylation, a slight right shift in size distribution is observed, and a second right shift follows IL-4 conjugation.	CD206	CD86 and CD80	No answer	In vivo and in vitro	M2

However, the observed biotoxicity associated with AlNPs may pose an obstacle to their advancement in areas, such as intracellular delivery of therapeutic nucleic acids and proteins [68, 69]. It has been suggested that AlNPs result in the polarization of macrophages to M1 phenotype by altering factors, such as the production of ROS, the pH inside the endosome, the phagosomal membrane stability, the production of damage-associated molecular patterns (DAMPs), and metabolic reprogramming (Figure 6a) [70]. In another study by Vrieling et al. [71], the polarization of human macrophages to M1 phenotype by hexagonal- and rod-shaped AlNPs was compared to classical aluminum oxyhydroxide. It was indicated that the secretion of IL-1ß and IL-6 was notably increased with rod-shaped and classical aluminum oxyhydroxide nanoparticles, the former associated with a much milder stress response. Hexagonal-shaped nanoparticles, on the other hand, barely activated the M1 phenotype [72, 73].

Silicon (Si)

Researchers have been exploring the use of Si nanoparticles (SiNPs) in a growing number of medical fields, such as drug delivery, photothermal therapy, and molecular imaging, like PET and lymph node mapping. SiNPs are attractive for these applications due to their high thermal stability, antimicrobial properties, low permeability, ability to hold a large amount of drugs, and cost-effectiveness. There are two types of silica, amorphous and crystalline, with the former being considered a promising option for biomedical use. Studies have suggested that SiNPs have the ability to shift macrophage polarization toward M2 through various mechanisms. Kim et al. [74] found that the impact of SiNPs on HIF-1α and ROS was a crucial factor in macrophage polarization. While HIF-1α and ROS have usually been linked to M1 polarization, mesoporous silica NPs were observed to decrease HIF-1α expression, increase oxygen generation, and promote oxidative resistance through ROS scavenging. These effects were believed to be responsible for the shift toward M2 phenotypes observed following in vitro and in vivo administration of mesoporous SiNPs, resulting in increased levels of IL-10, Arg-1, and CD206, and decreased levels of TNF-α, iNOS, IL-6, and IL-1β. Another study found that SiNPs promoted M2 polarization by reducing the IKK inhibitor of nuclear factor-κB and preventing p65 phosphorylation, thereby blocking the downstream NF-kB pathway. In addition, one study has highlighted the role played by STAT and IRF signaling pathways in regulating macrophage polarization through silicon (Figure 6b) [75-77].

The impact of SiNPs on polarizing cells and their cellular uptake can be influenced by various factors, like size, dosage, surface area, length of treatment, structural composition, etc. Ni et al. [78] studied the impact of the size and shape of SiO_2-based NPs in the form of nano-convex dots (NCDots) and nano-concave pits (NCPits) of two different nanoscale sizes. Both forms reduced the levels of IL-1-β, IL-6, and CD86, but the decrease was more pronounced in NCDots after 24 hours of exposure, and NCDots were found to significantly increase the level of CD206. The size of SiNPs was also found to affect MP polarization, as smaller SiNPs were shown to increase the M2/M1 activation ratio, as indicated by a greater reduction in TNF-α and IL-1β levels and a significant increase in IL-10 production [79, 80] (Table 1.).

Conclusion and future trends

In recent times, much focus has been placed on the use of MP-altering treatments to address a diverse range of diseases and influence various bodily processes. Our understanding of the innate immune system, which includes MPs, has been continuously advancing. Previously, it was believed that MPs' function was confined to only a phagocytic and antigen-presenting role in the innate immune system; however, current research has expanded upon this and revealed various functions of MPs in both normal and abnormal conditions. Although the significance of MPs in infectious diseases is noteworthy, their role is not limited to just these diseases. Through MP-elimination techniques, researchers have uncovered the specific role of MPs in numerous non-communicable bodily disorders, such as cancer, autoimmune diseases, inflammatory diseases, atherosclerosis, bone and nerve deficiencies, fibrotic diseases, etc.

The classification of M0 MPs into various subpopulations with different functions and properties has been made possible due to advances in molecular biology. M1 and M2 MPs are two of the most prominent subpopulations. M1 MPs produce inflammatory cytokines, making them targets for the treatment of inflammatory diseases and inducing tissue repair and regeneration. However, strengthening their polarization and function is useful in combating cancer, infections, and fibrotic diseases. M2 MPs, on the other hand, secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, which make them beneficial for regenerative processes, including wound healing and bone and nerve regeneration.

Hence, it is evident that selective polarization of MPs could lead to various positive outcomes. The differentiation of MPs is brought about by cytokines secreted by T helper lymphocytes, and this process can be facilitated by administering these natural substances. However, the challenges of unwanted immunological reactions, complicated synthesis, and administration have limited their use. To overcome these issues, different types of biomaterials have shown promise in inducing MP polarization. Recent advancements in biomaterial synthesis, surface modification, and improvement of drug loading and safety have made them promising candidates for disease diagnosis and treatment. As reviewed in the article, biomaterials can have the potential to shift M0 MPs toward an M1 or M2 phenotype, repolarize M1 to M2, or vice versa. The efficacy of these effects depends on various factors, such as the nature, size, anisotropy, and architecture of the biomaterial. Additionally, these nanostructures can be loaded with biological molecules, like peptides, siRNA, or miRNA, which can directly impact the strength of their polarization effect.

In the upcoming years, there will be a growing recognition of the significance of understanding the properties and modes of action of nanomaterials in relation to regulating the immune system and MPs. AI can assist scientists in precisely defining, anticipating, and enhancing the physical and chemical characteristics of nanostructures to achieve effective MP programming. It is also crucial to conduct controlled clinical trials, after conducting experimental studies, to assess the safety and effectiveness of these nanoparticles.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Xu Y, Li Y, Liu X, Pan Y, Sun Z, Xue Y, et al. SPIONs enhances IL-10-producing macrophages to relieve sepsis via Cav1-Notch1/HES1-mediated autophagy. International Journal of Nanomedicine. 2019; 14:6779-97. [DOI:10.2147/IJN.S215055] [PMID]

[2] Chen S, Chen Y, Chen Y, Yao Z. InP/ZnS quantum dots cause inflammatory response in macrophages through endoplasmic reticulum stress and oxidative stress. International Journal of Nanomedicine. 2019; 14:9577-86. [DOI:10.2147/IJN.S218748] [PMID]

[3] Cicuéndez M, Fernandes M, Ayán-Varela M, Oliveira H, Feito MJ, Diez-Orejas R, et al. Macrophage inflammatory and metabolic responses to graphene-based nanomaterials differing in size and functionalization. Colloids and Surfaces. B, Biointerfaces. 2020; 186:110709. [DOI:10.1016/j.colsurfb.2019.110709] [PMID]

[4] Wei M, Le WD. The role of nanomaterials in autophagy. Advances in Experimental Medicine and Biology. 2019; 1206:273-86. [DOI:10.1007/978-981-15-0602-4_14] [PMID]

[5] Liang WL, Xiao L, Gu HW, Li XJ, Li YS, Zhang WK, et al. Solid lipid nanoparticle induced apoptosis of macrophages via a mitochondrial-dependent pathway in vitro and in vivo. International Journal of Nanomedicine. 2019; 14:3283-95. [DOI:10.2147/IJN.S200395] [PMID]

[6] Hu G, Guo M, Xu J, Wu F, Fan J, Huang Q, et al. Nanoparticles targeting macrophages as potential clinical therapeutic agents against cancer and inflammation. Frontiers in Immunology. 2019; 10:1998. [DOI:10.3389/fimmu.2019.01998] [PMID]

[7] de Brito Sousa K, Rodrigues MFSD, de Souza Santos D, Mesquita-Ferrari RA, Nunes FD, de Fátima Teixeira da Silva D, et al. Differential expression of inflammatory and anti-inflammatory mediators by M1 and M2 macrophages after photobiomodulation with red or infrared lasers. Lasers in Medical Science. 2020; 35(2):337-43. [DOI:10.1007/s10103-019-02817-1] [PMID]

[8] Jin R, Liu L, Zhu W, Li D, Yang L, Duan J, et al. Iron oxide nanoparticles promote macrophage autophagy and inflammatory response through activation of toll-like Receptor-4 signaling. Biomaterials. 2019; 203:23-30. [DOI:10.1016/j.biomaterials.2019.02.026] [PMID]

[9] Reichel D, Tripathi M, Perez JM. Biological effects of nanoparticles on macrophage polarization in the tumor microenvironment. Nanotheranostics. 2019; 3(1):66. [DOI:10.7150/ntno.30052] [PMID]

[10] Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. European Journal of Pharmacology. 2020; 877:173090. [DOI:10.1016/j.ejphar.2020.173090] [PMID]

[11] Verma N, Kumar N. Synthesis and biomedical applications of copper oxide nanoparticles: An expanding horizon. ACS Biomaterials Science & Engineering. 2019; 5(3):1170-88. [DOI:10.1021/acsbiomaterials.8b01092] [PMID]

[12] Díez-Tercero L, Delgado LM, Perez RA. Modulation of macrophage response by copper and magnesium ions in combination with low concentrations of dexamethasone. Biomedicines. 2022; 10(4):764. [DOI:10.3390/biomedicines10040764] [PMID]

[13] Waris A, Din M, Ali A, Ali M, Afridi S, Baset A, et al. A comprehensive review of green synthesis of copper oxide nanoparticles and their diverse biomedical applications. Inorganic Chemistry Communications. 2021; 123:108369. [DOI:10.1016/j.inoche.2020.108369]

[14] Sandoval C, Ríos G, Sepúlveda N, Salvo J, Souza-Mello V, Farías J. Effectiveness of copper nanoparticles in wound healing process using in vivo and in vitro studies: A systematic review. Pharmaceutics. 2022; 14(9):1838. [DOI:10.3390/pharmaceutics14091838] [PMID]

[15] Xu D, Qian J, Guan X, Ren L, Yang K, Huang X, et al. Copper-containing alloy as immunoregulatory material in bone regeneration via mitochondrial oxidative stress. Frontiers in Bioengineering and Biotechnology. 2021; 8:620629. [DOI:10.3389/fbioe.2020.620629] [PMID]

[16] Mohammad-Hasani A, Mohammadi S, Saeidi M, Fallah A, Khosravi A. The modulation of SHED-induced macrophage polarization and plasticity through paracrine mediators. Tissue Cell. 2025; 96:103038. [DOI: 10.1016/j.tice.2025.103038]

[17] Díez-Tercero L, Delgado LM, Bosch-Rué E, Perez RA. Evaluation of the immunomodulatory effects of cobalt, copper and magnesium ions in a pro inflammatory environment. Scientific Reports. 2021; 11(1):11707. [DOI:10.1038/s41598-021-91070-0]

[18] Shen Q, Beucler MJ, Ray SC, Rappleye CA. Macrophage activation by IFN-γ triggers restriction of phagosomal copper from intracellular pathogens. PLoS Pathogens. 2018; 14(11):e1007444. [DOI:10.1371/journal.ppat.1007444] [PMID]

[19] Arancibia S, Barrientos A, Torrejón J, Escobar A, Beltrán CJ. Copper oxide nanoparticles recruit macrophages and modulate nitric oxide, proinflammatory cytokines and PGE2 production through arginase activation. Nanomedicine. 2016; 11(10):1237-51. [DOI:10.2217/nnm.16.39] [PMID]

[20] Yang C, Wang W, Zhu K, Liu W, Luo Y, Yuan X, et al. Lithium chloride with immunomodulatory function for regulating titanium nanoparticle-stimulated inflammatory response and accelerating osteogenesis through suppression of MAPK signaling pathway. International Journal of Nanomedicine. 2019; 14:7475-88. [DOI:10.2147/IJN.S210834]

[21] Schoenenberger AD, Schipanski A, Malheiro V, Kucki M, Snedeker JG, Wick P, et al. Macrophage polarization by titanium dioxide (TiO2) particles: size matters. ACS Biomaterials Science & Engineering. 2016; 2(6):908-19. [DOI:10.1021/acsbiomaterials.6b00006] [PMID]

[22] Zhang Y, Cheng X, Jansen JA, Yang F, van den Beucken JJJP. Titanium surfaces characteristics modulate macrophage polarization. Materials Science & Engineering. C, Materials for Biological Applications. 2019; 95:143-51. [DOI:10.1016/j.msec.2018.10.065] [PMID]

[23] Kartikasari N, Yamada M, Watanabe J, Tiskratok W, He X, Kamano Y, et al. Titanium surface with nanospikes tunes macrophage polarization to produce inhibitory factors for osteoclastogenesis through nanotopographic cues. Acta Biomaterialia. 2022; 137:316-30. [DOI:10.1016/j.actbio.2021.10.019]

[24] Ariganello MB, Guadarrama Bello D, Rodriguez-Contreras A, Sadeghi S, Isola G, Variola F, et al. Surface nanocavitation of titanium modulates macrophage activity. International Journal of Nanomedicine. 2018; 13:8297-308. [DOI:10.2147/IJN.S185436] [PMID]

[25] Moura CCG, Zanetta-Barbosa D, Dechichi P, Carvalho VF, Soares PBF. Effects of titanium surfaces on the developmental profile of monocytes/macrophages. Brazilian Dental Journal. 2014; 25(2):96-103. [DOI:10.1590/0103-6440201302260] [PMID]

[26] Xu WC, Dong X, Ding JL, Liu JC, Xu JJ, Tang YH, et al. Nanotubular TiO2 regulates macrophage M2 polarization and increases macrophage secretion of VEGF to accelerate endothelialization via the ERK1/2 and PI3K/AKT pathways. International Journal of Nanomedicine. 2019; 14:441-55. [DOI:10.2147/IJN.S188439] [PMID]

[27] Huang Q, Ouyang Z, Tan Y, Wu H, Liu Y. Activating macrophages for enhanced osteogenic and bactericidal performance by Cu ion release from micro/nano-topographical coating on a titanium substrate. Acta Biomaterialia. 2019; 100:415-26. [DOI:10.1016/j.actbio.2019.09.030] [PMID]

[28] Jämsen E, Pajarinen J, Lin Th, Lo CW, Nabeshima A, Lu L, et al. Effect of aging on the macrophage response to titanium particles. Journal of Orthopaedic Research. 2020; 38(2):405-16. [DOI:10.1002/jor.24461] [PMID]

[29] Lee RS, Hamlet SM, Moon HJ, Ivanovski S. Re-establishment of macrophage homeostasis by titanium surface modification in type II diabetes promotes osseous healing. Biomaterials. 2021; 267:120464. [DOI:10.1016/j.biomaterials.2020.120464] [PMID]

[30] Di Bella D, Ferreira JP, Silva RdNO, Echem C, Milan A, Akamine EH, et al. Gold nanoparticles reduce inflammation in cerebral microvessels of mice with sepsis. Journal of Nanobiotechnology. 2021; 19(1):52. [DOI:10.1186/s12951-021-00796-6] [PMID]

[31] Taratummarat S, Sangphech N, Vu CTB, Palaga T, Ondee T, Surawut S, et al. Gold nanoparticles attenuates bacterial sepsis in cecal ligation and puncture mouse model through the induction of M2 macrophage polarization. BMC Microbiology. 2018; 18(1):1-10. [DOI:10.1186/s12866-018-1227-3]

[32] Wang L, Zhang H, Sun L, Gao W, Xiong Y, Ma A, et al. Manipulation of macrophage polarization by peptide-coated gold nanoparticles and its protective effects on acute lung injury. Journal of Nanobiotechnology. 2020; 18:1-16. [DOI:10.1186/s12951-020-00593-7] [PMID]

[33] Kang H, Wong SHD, Pan Q, Li G, Bian L. Anisotropic ligand nanogeometry modulates the adhesion and polarization state of macrophages. Nano Letters. 2019; 19(3):1963-75. [DOI:10.1021/acs.nanolett.8b05150]

[34] Cheng J, Zhang Q, Fan S, Zhang A, Liu B, Hong Y, et al. The vacuolization of macrophages induced by large amounts of inorganic nanoparticle uptake to enhance the immune response. Nanoscale. 2019; 11(47):22849-59. [DOI:10.1039/C9NR08261A] [PMID]

[35] Codullo V, Cova E, Pandolfi L, Breda S, Morosini M, Frangipane V, et al. Imatinib-loaded gold nanoparticles inhibit proliferation of fibroblasts and macrophages from systemic sclerosis patients and ameliorate experimental bleomycin-induced lung fibrosis. Journal of Controlled Release. 2019; 310:198-208. [DOI:10.1016/j.jconrel.2019.08.015] [PMID]

[36] Mulens-Arias V, Rojas JM, Barber DF. The use of iron oxide nanoparticles to reprogram macrophage responses and the immunological tumor microenvironment. Frontiers in Immunology. 2021; 12:693709. [DOI:10.3389/fimmu.2021.693709]

[37] Mertens C, Marques O, Horvat NK, Simonetti M, Muckenthaler MU, Jung M. The macrophage iron signature in health and disease. International Journal of Molecular Sciences. 2021; 22(16):8457. [DOI:10.3390/ijms22168457]

[38] Xia Y, Li Y, Wu X, Zhang Q, Chen S, Ma X, et al. Ironing out the details: How iron orchestrates macrophage polarization. Frontiers in Immunology. 2021; 12:669566. [DOI:10.3389/fimmu.2021.669566] [PMID]

[39] Behmoaras J. The versatile biochemistry of iron in macrophage effector functions. The FEBS Journal. 2021; 288(24):6972-89. [DOI:10.1111/febs.15682] [PMID]

[40] Gu Z, Liu T, Tang J, Yang Y, Song H, Tuong ZK, et al. Mechanism of iron oxide-induced macrophage activation: the impact of composition and the underlying signaling pathway. Journal of the American Chemical Society. 2019; 141(15):6122-6. [DOI:10.1021/jacs.8b10904] [PMID]

[41] Gan ZS, Wang QQ, Li JH, Wang XL, Wang YZ, Du HH. Iron reduces M1 macrophage polarization in RAW264.7 macrophages associated with inhibition of STAT1. Mediators of Inflammation. 2017; 2017:8570818. [DOI:10.1155/2017/8570818] [PMID]

[42] Recalcati S, Cairo G. Macrophages and iron: A special relationship. Biomedicines. 2021; 9(11):1585. [DOI:10.3390/biomedicines9111585] [PMID]

[43] Li K, Lu L, Xue C, Liu J, He Y, Zhou J, et al. Polarization of tumor-associated macrophage phenotype via porous hollow iron nanoparticles for tumor immunotherapy in vivo. Nanoscale. 2020; 12(1):130-44. [DOI:10.1039/C9NR06505A]

[44] Chen L, Ma X, Dang M, Dong H, Hu H, Su X, et al. Simultaneous T cell activation and macrophage polarization to promote potent tumor suppression by iron oxide-embedded large-pore mesoporous organosilica core-shell nanospheres. Advanced Healthcare Materials. 2019; 8(9):1900039. [DOI:10.1002/adhm.201970041]

[45] Yu GT, Rao L, Wu H, Yang LL, Bu LL, Deng WW, et al. Myeloid-derived suppressor cell membrane-coated magnetic nanoparticles for cancer theranostics by inducing macrophage polarization and synergizing immunogenic cell death. Advanced Functional Materials. 2018; 28(37):1801389. [DOI:10.1002/adfm.201801389]

[46] Liu X, Zheng J, Sun W, Zhao X, Li Y, Gong N, et al. Ferrimagnetic vortex nanoring-mediated mild magnetic hyperthermia imparts potent immunological effect for treating cancer metastasis. ACS Nano. 2019; 13(8):8811-25. [DOI:10.1021/acsnano.9b01979]

[47] Liu X, Yan B, Li Y, Ma X, Jiao W, Shi K, et al. Graphene oxide-grafted magnetic nanorings mediated magnetothermodynamic therapy favoring reactive oxygen species-related immune response for enhanced antitumor efficacy. ACS Nano. 2020; 14(2):1936-50. [DOI:10.1021/acsnano.9b08320] [PMID]

[48] Xiao S, Lu Y, Feng M, Dong M, Cao Z, Zhang X, et al. Multifunctional FeS2 theranostic nanoparticles for photothermal-enhanced chemodynamic/photodynamic cancer therapy and photoacoustic imaging. Chemical Engineering Journal. 2020; 396:125294. [DOI:10.1016/j.cej.2020.125294]

[49] Zhou Y, Que KT, Zhang Z, Yi ZJ, Zhao PX, You Y, et al. Iron overloaded polarizes macrophage to proinflammation phenotype through ROS/acetyl-p53 pathway. Cancer Medicine. 2018; 7(8):4012-22. [DOI:10.1002/cam4.1670] [PMID]

[50] Gong T, Dong Z, Fu Y, Gong T, Deng L, Zhang Z. Hyaluronic acid modified doxorubicin loaded Fe 3 O 4 nanoparticles effectively inhibit breast cancer metastasis. Journal of Materials Chemistry B. 2019; 7(38):5861-72. [DOI:10.1039/C9TB01250H]

[51] Costa da Silva M, Breckwoldt MO, Vinchi F, Correia MP, Stojanovic A, Thielmann CM, et al. Iron induces anti-tumor activity in tumor-associated macrophages. Frontiers in Immunology. 2017; 8:1479. [DOI:10.3389/fimmu.2017.01479] [PMID]

[52] Yang Y, Guo L, Wang Z, Liu P, Liu X, Ding J, et al. Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization. Biomaterials. 2021; 264:120390. [DOI:10.1016/j.biomaterials.2020.120390] [PMID]

[53] Chen Y, Guan M, Ren R, Gao C, Cheng H, Li Y, et al. Improved immunoregulation of ultra-low-dose silver nanoparticle-loaded TiO2 nanotubes via M2 macrophage polarization by regulating GLUT1 and autophagy. International Journal of Nanomedicine. 2020; 15:2011-26. [DOI:10.2147/IJN.S242919] [PMID]

[54] Tang C, Wang H, Guo L, Zou C, Hu J, Zhang H, et al. CpG-conjugated silver nanoparticles as a multifunctional nanomedicine to promote macrophage efferocytosis and repolarization for atherosclerosis therapy. ACS Applied Materials & Interfaces. 2023; 15(45):52162-79. [DOI:10.1021/acsami.3c11227] [PMID]

[55] Roszak J, Smok-Pieniążek A, Jeżak K, Domeradzka-Gajda K, Grobelny J, Tomaszewska E, et al. Combined effect of silver nanoparticles and aluminium chloride, butylparaben or diethylphthalate on the malignancy of MDA-MB-231 breast cancer cells and tumor-specific immune responses of human macrophages and monocyte-derived dendritic cells. Toxicology in Vitro. 2020; 65:104774. [DOI:10.1016/j.tiv.2020.104774] [PMID]

[56] Saleh T, Ahmed E, Yu L, Hussein K, Park KM, Lee YS, et al. Silver nanoparticles improve structural stability and biocompatibility of decellularized porcine liver. Artificial Cells, Nanomedicine, and Biotechnology. 2018; 46(sup2):273-84. [DOI:10.1080/21691401.2018.1457037] [PMID]

[57] Saleh B, Dhaliwal HK, Portillo-Lara R, Shirzaei Sani E, Abdi R, Amiji MM, et al. Local immunomodulation using an adhesive hydrogel loaded with miRNA-laden nanoparticles promotes wound healing. Small. 2019; 15(36):e1902232. [DOI:10.1002/smll.201902232] [PMID]

[58] Yilma AN, Singh SR, Dixit S, Dennis VA. Anti-inflammatory effects of silver-polyvinyl pyrrolidone (Ag-PVP) nanoparticles in mouse macrophages infected with live Chlamydia trachomatis. International Journal of Nanomedicine. 2013; 8:2421-32. [DOI:10.2147/IJN.S44090] [PMID]

[59] Varela P, Marlinghaus L, Sartori S, Viebahn R, Salber J, Ciardelli G. Response of human macrophages to clinically applied wound dressings loaded with silver. Frontiers in Bioengineering and Biotechnology. 2020; 8:124. [DOI:10.3389/fbioe.2020.00124] [PMID]

[60] Glinski A, de Souza TL, da Luz JZ, Junior AGB, de Oliveira CC, de Oliveira Ribeiro CA, et al. Toxicological effects of silver nanoparticles and cadmium chloride in macrophage cell line (RAW 264.7): An in vitro approach. Journal of Trace Elements in Medicine and Biology. 2021; 68:126854. [DOI:10.1016/j.jtemb.2021.126854] [PMID]

[61] Zhang JJ, Kadir TN, Silva RM, Pham AK, Mar TC, Kelty S, et al. Effects of engineered silver nanoparticle size in pulmonary inflammation, cytokine/chemokine release and macrophage phenotype expression over time. American Journal of Respiratory and Critical Care Medicine. 2017; 195:A3854. [Link]

[62] Chen P, Zhang X, Venosa A, Lee IH, Myers D, Holloway JA, et al. A novel bivalent mannosylated targeting ligand displayed on nanoparticles selectively targets anti-inflammatory M2 macrophages. Pharmaceutics. 2020; 12(3):243. [DOI:10.3390/pharmaceutics12030243] [PMID]

[63] Lategan KL, Walters CR, Pool EJ. The effects of silver nanoparticles on RAW 264.7. Macrophages and human whole blood cell cultures. Frontiers in Bioscience-Landmark. 2019; 24(2):347-65. [DOI:10.2741/4722] [PMID]

[64] Veronesi G, Aude-Garcia C, Kieffer I, Gallon T, Delangle P, Herlin-Boime N, et al. Exposure-dependent Ag+ release from silver nanoparticles and its complexation in AgS 2 sites in primary murine macrophages. Nanoscale. 2015; 7(16):7323-30. [DOI:10.1039/C5NR00353A] [PMID]

[65] Raja MRC, Kumar VV, Srinivasan V, Selvaraj S, Radhakrishnan N, Mukundan R, et al. ApAGP-fabricated silver nanoparticles induce amendment of murine macrophage polarization. Journal of Materials Chemistry B. 2017; 5(19):3511-20. [DOI:10.1039/C6TB02095J] [PMID]

[66] Lu H, Zhang Y, Xiong S, Zhou Y, Xiao L, Ma Y, et al. Modulatory role of silver nanoparticles and mesenchymal stem cell-derived exosome-modified barrier membrane on macrophages and osteogenesis. Frontiers in Chemistry. 2021; 9:699802. [DOI:10.3389/fchem.2021.699802] [PMID]

[67] Parthasarathy A, Vijayakumar S, Malaikozhundan B, Thangaraj MP, Ekambaram P, Murugan T, et al. Chitosan-coated silver nanoparticles promoted antibacterial, antibiofilm, wound-healing of murine macrophages and antiproliferation of human breast cancer MCF 7 cells. Polymer Testing. 2020; 90:106675. [DOI:10.1016/j.polymertesting.2020.106675]

[68] Hu X, Xu L, Fu X, Huang J, Ji P, Zhang Z, et al. The TiO2-μ implant residual is more toxic than the Al2O3-n implant residual via blocking LAP and inducing macrophage polarization. Nanoscale. 2021; 13(19):8976-90. [DOI:10.1039/D1NR00696G] [PMID]

[69] Danielsson R, Eriksson H. Aluminium adjuvants in vaccines-A way to modulate the immune response. Seminars in Cell & Developmental Biology. 2021; 115:3-9. [DOI:10.1016/j.semcdb.2020.12.008] [PMID]

[70] Pan Y, Han J, Wang G, Zhong T, Liu S, Qi Y, Huang Y. Exploiting aluminum-based metal-organic frameworks as dual-adjuvant delivery platforms for potentiated immune response of subunit vaccines. Chem Eng J. 2025; 507:160128. [DOI: 10.1016/j.cej.2025.160128]

[71] Vrieling H, Kooijman S, de Ridder JW, Thies-Weesie DM, Soema PC, Jiskoot W, et al. Activation of human monocytes by colloidal aluminum salts. Journal of Pharmaceutical Sciences. 2020; 109(1):750-60. [DOI:10.1016/j.xphs.2019.08.014] [PMID]

[72] Ulanova M, Tarkowski A, Hahn-Zoric M, Hanson L. The common vaccine adjuvant aluminum hydroxide up-regulates accessory properties of human monocytes via an interleukin-4-dependent mechanism. Infect Immun. 2001; 69(2):1151-9. [DOI:10.1128/iai.69.2.1151-1159.2001]

[73] Kim H, Lim KY, Kang J, Park JW, Park SH. Macrophagic myofasciitis and subcutaneous pseudolymphoma caused by aluminium adjuvants. Scientific Reports. 2020; 10(1):11834. [DOI:10.1038/s41598-020-68849-8] [PMID]

[74] Kim J, Kim HY, Song SY, Go SH, Sohn HS, Baik S, et al. Synergistic oxygen generation and reactive oxygen species scavenging by manganese ferrite/ceria co-decorated nanoparticles for rheumatoid arthritis treatment. ACS Nano. 2019; 13(3):3206-17. [DOI:10.1021/acsnano.8b08785] [PMID]

[75] Li J, Fan J, Gao Y, Huang S, Huang D, Li J, et al. Porous silicon nanocarriers boost the immunomodulation of mitochondria-targeted bovine serum albumins on macrophage polarization. ACS Nano. 2023; 17(2):1036-53. [DOI:10.1021/acsnano.2c07439] [PMID]

[76] Muñoz-González PU, Flores-Moreno J, Quintero-Ortega IsA, Mantovani D, Mendoza-Novelo B, González-García G. Water-dispersible fluorescent silicon nanoparticles that modulate inflammatory response in macrophages. ACS Applied Nano Materials. 2023; 6(13):11187–97. [DOI:10.1021/acsanm.3c01210]

[77] Li S, Zhao J, Han G, Zhang X, Li N, Zhang Z. Silicon dioxide-induced endoplasmic reticulum stress of alveolar macrophages and its role on the formation of silicosis fibrosis: A review article. Toxicology Research. 2023; 12(6):1024-33. [DOI:10.1093/toxres/tfad099] [PMID]

[78] Ni S, Zhai D, Huan Z, Zhang T, Chang J, Wu C. Nanosized concave pit/convex dot microarray for immunomodulatory osteogenesis and angiogenesis. Nanoscale. 2020; 12(31):16474-88. [DOI:10.1039/D0NR03886E] [PMID]

[79] Yang M, Jing L, Wang J, Yu Y, Cao L, Zhang L, et al. Macrophages participate in local and systemic inflammation induced by amorphous silica nanoparticles through intratracheal instillation. International Journal of Nanomedicine. 2016; 11:6217-28. [DOI:10.2147/IJN.S116492] [PMID]

[80] Yokoi K, Godin B, Oborn CJ, Alexander JF, Liu X, Fidler IJ, et al. Porous silicon nanocarriers for dual targeting tumor associated endothelial cells and macrophages in stroma of orthotopic human pancreatic cancers. Cancer Letters. 2013; 334(2):319-27. [DOI:10.1016/j.canlet.2012.09.001] [PMID]

[81] Li B, Hu Y, Zhao Y, Cheng M, Qin H, Cheng T, et al. Curcumin attenuates titanium particle-induced inflammation by regulating macrophage polarization in vitro and in vivo. Frontiers in Immunology. 2017; 8:55. [DOI:10.3389/fimmu.2017.00055] [PMID]

[82] Yang BY, Deng GY, Zhao RZ, Dai CY, Jiang CY, Wang XJ, et al. Porous Se@SiO2 nanosphere-coated catheter accelerates prostatic urethra wound healing by modulating macrophage polarization through reactive oxygen species-NF-κB pathway inhibition. Acta Biomaterialia. 2019; 88:392-405. [DOI:10.1016/j.actbio.2019.02.006] [PMID]

[83] Raimondo TM, Mooney DJ. Functional muscle recovery with nanoparticle-directed M2 macrophage polarization in mice. Proceedings of the National Academy of Sciences. 2018; 115(42):10648-53. [DOI:10.1073/pnas.1806908115] [PMID]