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Review Article

BIOLOGICAL REACTIONS OF MACROPHAGES TO METAL OXIDE NANOPARTICLES

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ABSTRACT

In our daily lives, nanomaterials are utilized extensively in paints, textiles, food goods, cosmetics, and medicine. Several investigations aim to deter investigations of the physiological effects in various cell types. The innate immune system's macrophages regulate a wide range of biological functions. Depending on the stimulus, macrophages can be activated toward pro-or anti-inflammatory (M1) phenotypes; however, polarization may change in conditions including cancer, autoimmune illnesses, and bacterial and viral infections. Metal oxide nanoparticles have recently gained significant interest due to their diverse range of unique features with applications in research and industry. The production and usage of nanomaterials will rise significantly as the nanotechnology business grows. As a result, testing the consequences of nanomaterial exposure in biological systems is critical. A comparative analysis is conducted on the toxicities of several metal oxide nanoparticles. The significance of biogenically generated metal oxide nanoparticles has been growing in recent years. However, more research is needed to thoroughly characterize the potential toxicity of these nanoparticles to ensure nanosafety and consider environmental views. To that end, nanotoxicology seeks to assess the toxicity of nanomaterials to physicochemical factors such as size and form. In this review, we focus on the biological reactions of macrophages to metal oxide nanoparticles. Because macrophages are the first cells to engage with nanoparticles when they enter the body, they can absorb them through various processes.

Keywords: Nanotoxicology, Macrophages, Toxicity, Oxide metallic nanoparticles

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INTRODUCTION

In recent years, nanotechnology has caused a revolution in the industrial and scientific sphere by enabling the study and manipulation of interactions and phenomena at the atomic and molecular levels, giving rise to a new generation of nanometric materials with unique properties and applications [1]. Nanomaterials are all materials synthesized naturally, incidentally or manufactured with at least one dimension equal to or less than 100 nm. They are classified according to their origin, dimensionality, chemical composition and potential toxicity [2]. In the case of nanomaterials, the physicochemical characteristics such as small size and large surface area give them optical, electrical, mechanical, chemical, thermal, and magnetic properties, among others, that differ from bulk material (micro or micrometric) and that are of interest to the industrial area [3]; however, these characteristics also impact on their interaction with biological systems and their toxicity. Due to the broad spectrum of applications of nanomaterials in multiple areas, it is estimated that by 2022, the market value of nanotechnology will be approximately $55 billion [4-8].

One of the most promising fields derived from nanotechnology is bio-nanotechnology, whose study objective is the interactions of nanomaterials with biological systems to develop new diagnostic strategies and therapies against diseases that currently have no cure or successful treatment. These strategies include drug nano-carriers, biosensors, antimicrobials, and immunomodulatory [9]. Now, it is possible to find various products on the market containing metal oxide nanoparticles in everyday products, food additives, or even medicines [10]. In this context, it is a fact that nanomaterials are and will be part of our daily lives, and, therefore, the synthesis, application and exposure to nanomaterial will be seen to increase considerably in the coming years; therefore, it is of vital importance to assess their safety and regulate their marketing and final disposal [11-13].

The present review sourced its article choices from specialised databases (covering the years 2016–2023), including Elsevier, Pubmed, Cambridge, online sources, and online publications. The search used the following keywords: nanotoxicology, toxicity, macrophages, and oxide metallic nanoparticles.

Nanotoxicology: how safe is a nanomaterial?

Nanotoxicology is born of the need to evaluate the toxicity of nanomaterials. One of its challenges is to design and adapt conventional toxicology methods of analysis to study nanomaterials. The toxicity of nanomaterials depends on a large number of factors, such as their size, shape, and surface chemical properties. It can induce toxicities through direct contact, ingesting contaminated water or food, or incorporating it into everyday products [14-16].

The interactions of nanomaterials with biological systems leading to toxic biological responses consist of four main phases: 1) introduction of nanomaterials into the biological system, which can be produced through six pathways: intravenous, dermal, subcutaneous, inhalation, intraperitoneal and oral, the most significant exposure is through the inhalator pathway followed by the gastrointestinal; 2) adsorption: occurs when the Nanomaterial interacts with biological components such as proteins and cells, resulting in the formation of a protein crown that covers the Nanomaterial and gives it a biological identity, or the Nanomaterial can be opsonized, i.e. it can be covered by molecules known as opsonin's that have the function of facilitating phagocytosis; 3) biodistribution: consists in the distribution of the Nanomaterial through the bloodstream to several organs of the body where they can be modified, metabolized or accumulated, and, 4) excretion and waste of the Nanomaterial, in which organs such as the kidney, liver or bile canal can participate (fig. 1). Their long-term behaviour is unknown if nanomaterials are not excreted [17-20].

Once absorbed by the body, nanomaterials can interact with cells passively and actively by regulating cellular functions through

molecular mechanisms, in which their physicochemical properties determine their biocompatibility and safety. Thus, the cellular response varies considerably between different cell lines and in the study of nanomaterials, even if these are similar [21]. This complicates predicting the toxicity of a nanomaterial according to its characteristics in a specific biological system. Some of the cytotoxic responses triggered by exposure to nanomaterials include the generation of highly reactive oxygen species (ROS), which can lead to oxidative stress, mitochondrial disturbance, endoplasmic reticular stress, protein degradation and denaturalization, cell cycle alteration, DNA damage, lipid peroxidation, among others [22]. The cytotoxicity triggered by nanoparticles consists of 4 fundamental mechanisms: 1) adhesion to the membrane surface, 2) penetration inside the cell and nucleus, 3) ROS generation and cell toxicity, and 4) cell signalling modulation [23].

Macrophages: role and importance

One of the most studied ways of introducing nanomaterials is inhalation, where, depending on the size, it is likely to occur. Reservoir of nanomaterials in the respiratory system [24]. Due to constant exposure to pathogenic microorganisms and exogenous agents in the respiratory system, in these tissues, there is a high concentration of innate immune system cells with phagocytic capabilities to eradicate and prevent possible damage to the host. The physiological function of the immune system is to defend the host against infectious microorganisms and foreign substances. The immune response to an exogenous microorganism or agent is orchestrated primarily by innate immunity, consisting of a rapid response that lacks specificity, followed by adaptive immunity, a late response with high specificity. Inborn and adaptive immunity are closely linked and essentially dependent on each other [25-30].

One of the primary cells of the innate immune system in the lung system are macrophages and, due to their natural ability to phagocyte nanomaterials, some authors suggest that they are the first to interact with nanoparticles, therefore also to mediate the immune response. Therefore, studying the effect on the function of macrophages and the mechanisms of recognition of nanoparticles is extremely important [31]. Macrophages are distributed in various tissues and play a key role in innate and adaptive immune responses. Some of its functions include phagocytosis, antigen presentation and induction of inflammation, as well as in the maintenance of cellular homeostasis through the removal of apoptotic cells and repair of damaged tissue, among others; so that, generally, macrophages, depending on their phenotype, may have pro-inflammatory or anti-inflammatory functions [32-37].

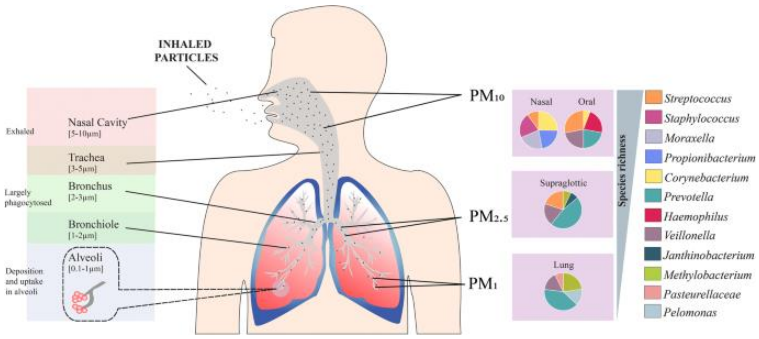

Fig. 1: Introduction of nanomaterials to the human body through inhalation [38]

The phagocytosis, in addition to having a fundamental role in the nutrition of the cell, has other functions as a product of evolution. It is an active Energy-dependent receptor-mediated process, which allows the internalization in vesicles of particles up to 10 μm, and includes the following stages: 1) recognition of the microorganism or exogenous agent by membrane receptors by the macrophage, which can be pattern recognition receptors, opsonic receptors or receptors of apoptosis bodies; 2) the membrane of the phagocytic cell suffers an alteration that surrounds the particle to phagocytize; 3) the exogenic agent is ingested through its internalization in a cyst that receives the name of a phagosome, and, 4) the phagolysosome is formed through the fusion of the phagosome and lysosome, the latter contains a low pH and digestive enzymes that produce the destruction of the particulate (fig. 2). This process is crucial for the adaptive immune system, as after digestion, the macrophages can present antigens to B and T lymphocytes, respond to the stimulation in a specific way and generate memory against subsequent invasion by the same agent [38, 39]. However, these processes do not occur after the phagocytosis of nanoparticles and the molecular mechanisms and consequences of persistence in macrophages due to the inability to degrade them through enzymes, as well as their impact on the functions of the immune system in general, is unknown [40, 43].

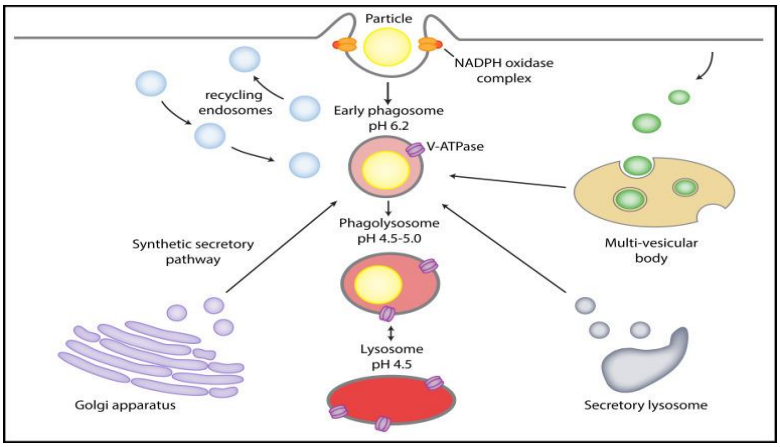

Fig. 2: Stages of phagocytosis of microorganisms or exogenous agents by macrophages [44]

Phagocytosis is activated through four molecular signalling mechanisms: Fcg receptor-mediated phagocytosis, TLR receptor-mediated phagocytosis, C-type lectin-receptor-Mediated phagocytosis, and scavenger-receiver-mediated phagocytosis [45]. Phagocytosis mediated by the Fcg receptor Fcg receptor activation (FcgR) is a replication process as the membrane envelops the particle to the phagocyte. This is possible thanks to the extension of the pseudopods that allows additional encounters between the unoccupied receptors and the ligands available on the particle surface, which at the same time enables the approximation of the immunoreceptor tyrosine-based activation pattern (ITAM), which is a substrate for phosphorylation by Tyrosine kinases of the Src family. Subsequently, incorporating adaptive proteins acts as a downstream platform for recruiting signalling components [46-49].

An example of an adaptive protein is CrkII, which recruits the complex between a nucleation promoter factor (Dock180) and a guanine nucleotide exchange factor. (ELMO1). The nucleation-promoting factors activate the Arp2/3 actin nucleation complex through Rac1, which in turn causes the polymerization of actin, a protein in the cellular cytoskeleton, which promotes the extension of the pseudopods, allowing phagocytosis [50]. The main activated transcription factors are NFk-β and AP-1.

TLR-mediated phagocytosis

Toll-type receptors (TLRs) are type 1 transmembrane receptors. Currently, ten different TLRs have been described in humans with a wide range of ligands ranging from structural motifs characteristic of microorganisms such as bacteria, fungi and parasites to components derived from the host [51]. Following the bonding of the ligand with its TLR receiver, a dimerization occurs, which causes the necessary conformational changes for signalling downstream due to the presence of adapting molecules with MyD88, TIRAP/MAL, TRIF, TRAM, IL-2 receptor-associated kinases (IRAK), kinases activated by the transformer factor beta/TGF-β (TAK1), among others. The intracellular signalling route promotes the transcription of genes of pro-inflammatory cytokines, chemokines and co-stimulators in a way that depends on the adapting molecule upstream [52-55].

C-type lectin receptor-mediated phagocytosis

Lecithin C receptors are a group of non-opsonic receptors that recognize carbohydrates, and one of the most studied is the receptor for the MRC1 mannose that recognizes carbs present in microorganisms such as mannose, fucose, N-acetyl glucosamine and other ligands for their elimination, and its adapting molecules include CDC42 and Rho [56].

Scavenger-mediated phagocytosis

This group of receptors includes scavenger A (SRA-1), collagen-structured macrophage receptor (MARCO) and CD36. These promiscuous receptors bind to polyanionic ligands, have poorly defined signalling capacity, vary in the structural domain and have distinct, though overlapping, recognition of apoptotic and microbial ligands. In most cases, CD36 involvement causes activation of the kinase tyrosines of the SRC family [57]. After low-density oxidized lipoprotein binding (ox-LDL), prolonged activation of focal adhesion kinase 1 (FAK1), together with VAV1-mediated activation and inhibition of non-muscular myosin II, result in actin polymerization, increased cell proliferation and loss of cellular polarity. Other CD36-orchestrated signalling cascades induce actin reorganization and stimulate the production of pro-inflammatory cytokines and pro-apoptotic signals [58].

These receptors differ from each other because they have different degrees of affinity to a group of ligands, their expression in macrophages varies between the different phenotypes, and their activation directs different immune responses that are specific against the pathogen to be eradicated, which directly impacts on its toxicity [59, 60]. While many of the molecular processes mentioned earlier could be involved in the internalization of nanoparticles due to the adsorption of proteins, it has been observed that mannose and Fcg receptors internalize nanoparticles faster and more efficiently than scavenger receptor-mediated phagocytosis. Even it is suggested that more than one group of receptors could cause internalization as a whole [61, 62]. However, due to the promiscuity of scavenger receptors and their ability to bind polyanionic ligands, this particular mechanism is of particular interest because it allows the host to recognize foreign materials such as nanoparticles and surgical implants, and their internalization by macrophages contributes to chronic inflammation and progressive tissue damage. For example, a study by [63, 64] determined that TiO2 particles were recognized and internalized by macrophages through the MARCO scavenger receptor, which in turn caused changes in gene expression. On the other hand, [65, 66] demonstrated that inhibition of MARCO scavenger receptors prevents the internalization of iron oxide nanoparticles coated with dextran.

Finally, the physicochemical characteristics of nanoparticles determine the molecular process that entails their internalization and, thus, the orchestrated immune response. Among these features are its size, shape and surface load [67, 68]. Therefore, several authors suggest that modifying the physicochemical properties of nanoparticles could decrease their internalization in immune system cells and, thus, their toxicity or direct internalization by a specific pathway for therapeutic purposes. Strategies for evading certain pathogenic microorganisms from the immune system have also been studied so that nanoparticles can mimic them [69, 70]. However, more studies are needed on the relationship between these characteristics and internalization to improve our knowledge and design nanoparticles, specifically to reduce toxicity and increase specificity [71, 72].

Immunomodulation of macrophages by exposure to metal oxide nanoparticles

The role and importance of the immune system for the proper functioning of the body have been discussed earlier; however, an adequate immune response depends on a delicate balance. In pathological conditions, as in some autoimmune diseases, there is an exacerbation of the immune response and a lack of tolerance to the same that causes damage to the host, so the treatment consists of trying to decrease this response; this process is known as immunosuppression [73, 74]. On the other hand, the development of vaccines and recent advances in immunotherapy against cancer are aimed at stimulating the immune response, which is why they are defined as immunostimulants. In general, immunosuppression and immunostimulant are types of immunomodulation, which consists of optimizing the immune response [75, 76]. The immunomodulatory capabilities of some metal oxide nanoparticles have been studied for use in immunology [77, 78]. Some bionanotechnological strategies for the use of nanoparticles in immunotherapy are described below.

Macrophage modulation for cancer immunotherapy

Immunotherapy consists of harnessing and enhancing the natural ability of the immune system to combat diseases of a different nature. Promising results have been obtained in the research of immunotherapy as a treatment for certain types of cancer to overcome the obstacles imposed by the tumour in evading and controlling immune cells [79, 80]. In this sense, the immune system can inhibit or promote tumour growth. Therefore, immunomodulators are proposed to enhance the immune response and selectively cleanse immune cells. Due to the high phenotypic plasticity that macrophages possess, these can take on different functions in response to the microenvironment signals, known as macrophage polarization [81, 82]. Tumor-associated macrophages (TAMs) have been extensively studied as therapeutic whites in cancer immunotherapy by being localized in the natural microenvironment of the tumour, and it has been observed that they can play both antitumoral and protumoral roles and that they differ from the functions of macrophages present in healthy tissue. In the early stages of tumour formation, monocytes and macrophages are recruited that are polarized towards a phenotype known as M1, characterized by having anti-tumor effects. As the tumour advances to an advanced stage, the M1 macrophages are transformed into M2, which have protumoral effects and suppress the immune response [83, 84]. Some metal oxide nanoparticles can modulate these phenotypes and the activities of TAMs (fig. 3).

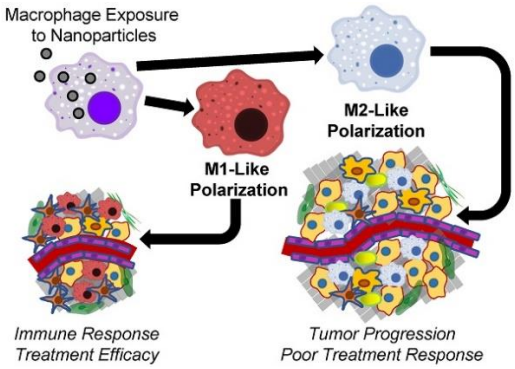

Fig. 3: Polarization of the phenotype of tumor-associated macrophages (TAM) [85]

For example, in 2016, Zanganeh *et al.* observed that the drug Ferumoxytol, consisting of iron oxide nanoparticles approved by the United States Food and Drug Administration (FDA) for the treatment of iron deficiency, has an intrinsic therapeutic effect on tumours as tumour cells co-injected with Ferumoksytol showed a significant delay in tumour growth rate compared to injection of cells without Ferum oxytol [86, 87]. In addition, an increased presence of M1 phenotype pro-inflammatory macrophages was observed in the tumour. Subsequent studies showed that treatment with Ferumoxytol caused increased gene expression involved in pro-inflammatory responses [88-91]. The authors suggest that this type of compound modules the TAM phenotype through the Fenton reaction, where the hydrogen peroxide secreted by the M1 macrophages could react with the iron to produce toxic hydroxyl radicals. In another study, it was also that the targeted delivery of manganese dioxide nanoparticles conjugated with manne and coated with hyaluronic acid to tumor-associated macrophages increased tumour oxygenation and caused the polarisation of M2 to M1 phenotype macrophages [92-96].

Cellular responses of macrophages to exposure to metal oxide nanoparticles: modulation or immunotoxicity?

Despite promising results in immunotherapy with the use of different metal oxide nanoparticles, several authors have that macrophage exposure to metal Oxide Nanoparticles induces immunotoxicity responses, including induction of inflammation, nanoparticle internalization, disruption of phagocyte functions, increased production of ROS and nitric oxide, among others (fig. 4) [97-99]. Immunotoxicity is defined as any adverse effect on the immune system's or other systems' structure or function due to immune dysfunction. Thus, a negative or immunotoxin effect affects the humoral or cellular immunity necessary for the host to trigger an adequate response for its defence (immunosuppression) or cause unnecessary tissue damage (auto-immunity, hypersensitivity or chronic inflammation) [100-104]. In this context, it must be borne in mind that while a nanomaterial may have exciting properties and therapeutic potential, it is essential not to lose sight of its toxicity since the latter limits its application [105-108].

Over the past few years, various research groups have focused on clarifying the toxicological mechanisms of nanomaterials; however, the results are sometimes contradictory due in part to differences in the physicochemical characteristics of the nanomaterial evaluated. Several authors have toxicity *in vitro* in macrophages exposed to different concentrations of zinc oxide nanoparticles (ZnO-NPs) of different sizes and agree that smaller nanoparticle sizes and positive charge have higher toxicity, which depends on concentration and time. In addition, there has been an increase in the production of pro-inflammatory cytokines IL-1b, TNF-α and IL-8, which suggests immune activation [109, 110]. On the other hand, in 2014, Wang *et al.* demonstrated that the solubility of Zn2+ions is dependent on the pH of the medium, so that, at lower pH, higher Zn2+ion concentration. This suggests that the toxic potential of ZnO-NPs could be seen increased in macrophages since, as mentioned above, the phagolysosome formed after phagocytosis of exogenous agents has a low pH; therefore, it has been speculated that the toxicity of ZnOs is mainly due to the release of Zn2+ions resulting from their dissociation [111-113].

On the other hand, omic tools have been used to study cellular responses caused by macrophage exposure to ZnO-NPs in a more general way. An example of this is a transcriptomic profile study of human macrophages exposed to ZnO-NPs of 15 and 12 nm diameter conducted in 2013 by Tuomela *et al.*, where it was established that the primary biological processes affected were growth regulation, cell death, development and control of the immune system. On the other hand, the proteomic analysis revealed alterations in routes involved in oxidative stress that could lead to genotoxicity and a strong response in protein degradation routes [114-119, 139]. However, clarifying a molecular mechanism that explains the toxic and inflammatory effects of metal oxide nanoparticles in macrophages requires even more research.

In this context, in 2014, Roy *et al.* demonstrated that the increase in ROS is caused by the decrease and inhibition of the activity of antioxidant enzymes due to the suppression of transcription factor Nrf2, leading to lipid peroxidation and protein. Other studies conducted by the same research group indicate that ZnO-NPs of approximately 50 nm have adjuvant properties to the oval albumin allergen in Balb/c mice. Furthermore, they described that this effect involves Toll and Src-type receptor-mediated signalling pathways due to increased expression of TLR2, 4 and 6, as well as myeloid differentiation primary response protein 88 (MyD88), IL-1 receptor-associated kinase 1 (IRAK-1) and TNFR-associated factor 6 (TRAF-6). All this is attributed to inflammatory responses by the recruitment and activation of adhesion molecules and inflammation cells [120-123]. While the authors suggest that this mechanism could be used to develop strategies for its therapeutic use, it is necessary to consider the adverse effects that could be triggered by exposure to 50 nm ZnO-NPs in healthy patients due to the immunomodulating potential of this type of NPs.

As with ZnO-NPs, multiple studies suggest that the rapid dissolution and release of Cu2+ions, size and shape are the main factors influencing the toxicity of copper oxide nanoparticles [124-127]. Due to their obvious toxicity potential, the authors suggest that CuO-NPs could be good candidates as positive controls in nanotoxicology trials. *In vivo* tests also show the toxicity potential of CuO-NPs. For example, Gosens *et al.* 2016 conducted a study in rats who were given CuO-NPs of an average size of 14 nm. After five days of exposure to CuO-NPs, the rats presented lung inflammation, and histopathological ana-lysis indicated alveolitis, bronchiolitis and vacuolation of the respiratory epithelium and pulmonary emphysema. Adverse effects due to toxicity were disappearing within three weeks of post-exposure [128-131].

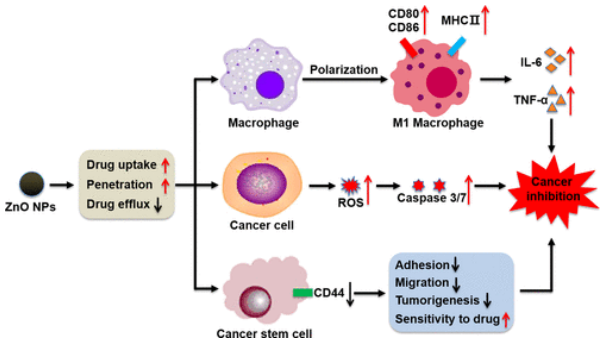

Fig. 4: Cellular responses of macrophages exposed to zinc oxide nanoparticles (ZnO-NPs) [132]

Furthermore, the impact on immune reactivity of the administration or inhalation of this type of nanoparticles has been discussed. The composition of cell populations of innate and adaptive measles immunity present in mice exposed to continuous inhalation of 30 nm CuO-NPs for three months. The results showed that inhalation of CuONPs affected the

cells of innate immunity more severely, as there were changes in the ratio of eosinophils, neutrophils, macrophages and antigen-presenting cells. In contrast, the impact on adaptive immunity cells such as T and B lymphocytes was minimal. This suggests that there is a modulating effect of inhalation time-dependent CuO-NPs on cytokine production by adaptive immune system cells [133-138].

The adverse effects on immune system cells from exposure to CuO-NPs highlight its ability to cause immunotoxicity. This demonstrates the cytotoxic, genotoxic and immunotoxic effects of ZnO-NPs and CuO-NPs in different *in vitro* and *in vivo* models; however, more studies are needed to establish more real scenarios (concentration and exposure time) to understand and clarify the mechanisms involved in these adverse effects; and thus, to design strategies to avoid the toxicity of nanomaterials and to take advantage of their unique properties.

CONCLUSION

Metal oxide nanoparticles present various properties of interest to research and industry, so their potential uses are being explored. Due to its immunomodulatory abilities, it has been suggested to be used for treating immune dysfunctions; however, it is necessary to consider the possible toxic effects. Macrophages are a good model for immunotoxicity study due to their primary functions for maintaining the organism and orchestrating the immune response. Furthermore, it has been suggested that they are the first cells to interact with nanomaterials once they enter the body. While several studies have shown that metal oxide nanoparticles can induce immunotoxicity in macrophages both *in vitro* and *in vivo*, further research is needed to clarify the precise mechanisms of toxicity. This knowledge is indispensable for designing nanomaterials by modifying their physicochemical properties to expand their potential. It thus can be applied in future biomedical applications, specifically in the field of immunomodulation and the fight against chronic diseases such as cancer.

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AUTHORS CONTRIBUTIONS

Mohammed Zorah-He designed the idea of the paper, was the leader of the work, and linked all the paragraphs together after all of the authors found their duties. And did the final editing.

Hassan Lafta Atiyah and Noor Waththab Ali-They were responsible for the biological parts such as Macrophages and cellular responses.

Mustafa Mudhafar-He was the second leader of this paper. I proofread and also made all the comments that you sent previously. Moreover, proceeded with the journal and arranged the style of the paper.

Fatimah H. Zayed and Saif Ahmed Raheem-They were responsible for re-evaluating the biological parts.

Ruaa K. Mohammed Jawad and Alsailawi H. A.-Both of them put the paper's outline and precipitate by writing some paragraphs.

CONFLICT OF INTERESTS

Declared none

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