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RHEUMATOID ARTHRITIS AND NANOTHERAPEUTICS

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune, symmetrical polyarticular disease that affects primarily the diarthrodial joints, which are characterized by chronic inflammation of the synovial joints. Inflammation is the net result of a cascade of highly regulated events propagated upon stimulation, and is the major process through which the body repairs tissue damage and defends itself against foreign materials. Acute inflammation is typically caused by an external chemical, mechanical, or pathogenic influence; while chronic inflammation requires no external stimulus and can cause a range of painful and debilitating symptoms. Histological changes occur with abnormal cell distribution in targeted tissues and indicate localized population of macrophages and lymphocytes, then fibrosis and necrosis. Nanoparticles sized between 1 and 100 nm are already in use including cosmetics, food industry, medicine, electronics, and others. Exposure to nanomaterials induces cell dysfunctions at various levels, such as cell death by oxidative stress, DNA damage, and protein damage. Cell damage produces free radicals including reactive oxygen species (ROSs) and reactive nitrogen species (RNSs). It was also reported that generation of various inflammatory mediators, depends on type of nanoparticles. Present review highlights on the role of various nanoparticles on inflammation including, silica, iron oxide, cerium oxide, yttrium oxide, zinc oxide, silver, nickel oxide and Synthetic hydroxyapatite nanoparticles.

KEY WORDS: Inflammation, nanoparticles, proinflammatory mediators, cytokines, rheumatoid arthritis, silica nanoparticles.

INTRODUCTION

Inflammation is the net result of a cascade of highly regulated events propagated upon stimulation, and is the major process through which the body repairs tissue damage and defends itself against foreign materials. Acute inflammation is typically caused by an external chemical, mechanical, or pathogenic influence; has a relatively short duration (hours to days); and is a necessary protection tool that removes foreign bodies and damaged tissue, preventing further damage. Chronic inflammation requires no external stimulus and can cause a range of painful and debilitating symptoms[1]. Further, such uncontrolled inflammation is often indicative of a more serious, underlying cause whose analysis may be used as a diagnostic marker for a number of conditions, including autoimmune, infectious, neurological, cardiovascular, and metastatic diseases. Histological changes will have occurred with abnormal cell distribution in targeted tissues and indicates localized populations of macrophages and lymphocytes, then fibrosis and necrosis.[2, 3]

The application of nanotechnology in industry is rapidly growing, with a worldwide market size estimated to be in excess of US$1 trillion by the year 2015.[4] Despite the quick progress and early acceptance of nanotechnology, there are lot of research groups revealing, potential for adverse health effects in humans and the environment. Although several research groups have demonstrated that exposure to nanoparticles may affect cellular viability and growth, through inflammatory pathway, and thus, little is known regarding the potential mechanism(s) of toxicity. It is thought that nanoparticles can disrupt and impair normal cellular function through a number of mechanisms.[5]

Role of immune cells in rheumatoid arthritis and other inflammatory diseases

Rheumatoid arthritis (RA) is an autoimmune, symmetrical polyarticular disease that affects primarily the diarthrodial joints, which is characterized by chronic inflammation of the synovial joints.[6] There is great heterogeneity in the cells of immune system, most of which originate from hematopoietic stem cells in the fetal liver and the postnatal bone marrow. Immune responses are mediated by a variety of cells and the soluble molecules that these cells secrete. Monocytes belong to class of reticuloendothelial system also named as mononuclear phagocyte system (MPS). Monocytes upon circulation in blood matured and become macrophages. Macrophages are key members of the MPS and play vital roles in inflammation, including

phagocytosis, antigen presentation, and the production of various cytokines and immune regulators.[7] Resident macrophages are found in all organs and mainly in connective tissues, involve in the primary immune response of tissues. Upon activation of macrophages, release chemokines that adhere to circulating monocytes, trafficking MPS cells to the inflammation site and generating an immune response. The ability to visualize the migration of MPS cells would contribute to many common disorders, including atherosclerosis, autoimmunity, and major infections.[8] The cytokines produced by macrophages not only sequester other immune cells to the tissue, they can also propagate an autoimmune response and inflammation. Cytokines maintain part of a complex regulatory network, and disruption of the balance between pro- and anti-inflammatory cytokines has been implicated in the pathogenesis of a number of inflammatory disorders.[9] This can be illustrated with tumor necrosis factor-α (TNF-α), a cytokine implicated to play a key role in RA. Targeting TNF-α as a central product of macrophages has been demonstrated as a powerful approach to treat RA, with many drug treatments utilizing antibodies or receptor fusion proteins to TNF- α.

Polymorphonuclear (PMN) neutrophils are short lived phagocytes and constitute majority of blood leucocytes and develop from the same early precursors as monocytes and macrophages. Mast cells are important effector cells in IgE-mediated reactions by secreting histamine, chymase, tryptase, leukotrienes (LTs), prostaglandin D2 (PGD2) and several multifunctional cytokines; they include interleukin-6 (IL-6), IL-8, IL-13, TNF- α, stem cell factor (SCF) and many chemotactic factors.[10,11] These cytokines contribute to the late-phase allergic reactions and to allergic inflammation through the recruitment of immune cells into the site of inflammation.[12, 13]

Frontline of nanotherapeutics

Nanotechnology is one of the exponentially developing technologies of the 21st century. Nanoparticles are submicron moieties (diameters ranging from 1 to 100 nm according to the used term, although there are examples of nanoparticles several hundreds of nanometers in size) made of inorganic or organic materials, which have many novel properties compared with the bulk materials. Nanoparticles used for the most part including cosmetics, food industry, medicine, electronics, and others.[14] However, because nanoparticles have large surface areas, high chemical reactivity, internal pore volumes, and enhanced cell penetrability, it may induce much more toxic effects.[15, 16]

Dark side of nanotherapeutics

Exposure to nanomaterials induces cell dysfunctions at various levels, such as cell death by oxidative stress, DNA damage, and protein damage. DNA damage is associated with malignant tumors and is closely related to inflammation. For instance, inhalation or intratracheal exposure can cause acute and chronic inflammation to the respiratory tract and pulmonary alveolar space[17, 18], in particular, inflammation causes fibrosis of the lung and pleura and progresses to lung cancer or malignant mesothelioma[19] Cell damage produces free radicals including reactive oxygen species (ROSs) and reactive nitrogen species (RNSs). In the ROSs, there are superoxide ions (O_2^-), hydroxyl radicals (·OH), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$). The ·OH is the most reactive of these ROSs. On the other hand, in the RNSs, there are nitric oxide (NO), nitrosonium ion (NO^+), nitrite ion (NO_2^-), and peroxynitrite ($ONOO^-$). The $ONOO^-$ is the most reactive of these RNSs[20] Free radicals are produced spontaneously in the energy metabolism of the cell. It was reported that generation of ROSs are depends on type of nanoparticles.

Nanomaterials and asbestos are taken into the body, and free radicals are produced on their surface by inflammatory cells or epithelial cells phagocytising them. The phagocyte cells such as neutrophils and macrophages play a role essential to the host defence to produce superoxides by the active oxygen production enzyme system, such as NADPH oxidase[21] Mutations of 8-hydroxydeoxyguanosine (8-OHdG) and 8-nitroguanine (8-NG) are known as DNA damages caused by ROSs and RNSs respectively[22] Further accumulation of mutants may induce apoptosis or tumours[23, 24] The possible relationship between nanoparticles and inflammation is depicted in figure 1.

PHARMACOLOGICAL EVIDENCES FOR INFLAMMATION INDUCED BY NANOPARTICLES

Silica nanoparticles (SiNPs)

Inhalation of higher doses of SiNPs can particularly occur in occupations such as ceramic, mine or foundry workers, dental laboratory technicians, agricultural workers or stone cutters. Amorphous SiNPs are being applied increasingly in industrial manufacturing, high-molecule composite materials, tyre compounds, thermal insulation materials, cosmetics, and food stuffs[25] To date SiNPs play an important role in modern technology and nanomedicine. Silicon dioxide exists in either crystalline or amorphous forms[26] It is well established that occupational inhalation exposure to crystalline silica causes silicosis. Silica has been considered an ideal nanoparticle for biomedical applications such as gene therapy, drug delivery, biomedical imaging, biosensors, and enzyme immobilization.[26, 27, 28]

An association of crystalline silica exposure and silicosis, as well as lung cancer, chronic obstructive pulmonary disease, and pulmonary tuberculosis, have been recently reported.[29] The development of nanotechnology has raised new interest in the use of amorphous SiNPs in biomedical, pharmaceutical, and many other industrial applications.[26, 28] Ultrafine silica induced oxidative stress and pro-inflammatory responses in macrophages, mice and rats.[30, 31] Also, pulmonary

inflammation, emphysema, alveolar hyperinflation, and apoptosis of alveolar and granulomatous cells have been found in animals exposed to silica.[32, 33] Lot of works has been done on the toxicity of SiNPs to produce inflammatory mediators. Some are mentioned here.

The study hypothesized that direct exposure of human aortic endothelial cells (HAECs) to various nanoparticles induces an inflammatory response. The mechanisms governing the correlation between exposure to nanoparticles and the increased incidence of cardiovascular disease is of particular concern in nanotoxicology related fields. Nanoparticles appear to cross the pulmonary epithelial barrier into the bloodstream, raising the possibility of direct contact with the vascular endothelium.[34] And nanoparticle- triggered endothelial dysfunction is hypothesized to be a dominant mechanism in the development of the diseases.[35] Acute and chronic inflammation of the endothelium plays a central role in the development of atherosclerosis and other cardiovascular diseases.[36]

There is a growing body of evidence that amorphous SiNPs can cause toxic and inflammatory effects due to their unique physicochemical profile. A concentration-dependent cytotoxicity of SiNPs on endothelial cell line EA.hy926, epithelial cell line A549, and monocyte-macrophages J774 has been reported.[37, 38] SiNPs have been reported to induce cytotoxicity and inflammatory responses *in vitro* in a co-culture model of the alveolar–capillary barrier.[39] There is evidence that SiNPs can induce impairment of proliferative activity and proinflammatory stimulation of endothelial cells *in vitro.*[40]

The measurement of proinflammatory cytokine showed a significant increase of TNFα after the administration of 50 nm SiNPs and IL-1β following the exposure to both 50 nm and 500 nm SiNPs. This finding also confirmed by another study by Nemmar et al. (2013), and they suggested that occurrence of systemic inflammation, which can explain the thrombotic effects of SiNPs.[41] The i*n vitro* release of IL-1β and TNFα has been reported following exposure to amorphous SiNPs.[42]

The study finds, SiNPs shows the placental inflammation and pregnancy complications. SiNPs upregulated the inflammasome component nucleotide-binding oligomerization domain-like receptor (NLR) family pyrin domain-containing 3 (NLRP3) and induced placental inflammation and also ROS's generation, resulting in pregnancy complications. Furthermore, NS-induced pregnancy complications were markedly improved in $Nlrp3^{-/-}$ mice but not in component apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-deficient ($Asc^{-/-}$) mice, indicating the independence of NLRP3 inflammasomes. Pregnancy complications in $Nlrp3^{-/-}$ and $Asc^{-/-}$ mice phenotypes were dependent on the balance between IL-1α and IL-10. SiNPs-induced pregnancy complications were completely prevented by either inhibition of ROS generation or forced expression of IL-10. These findings provide important information about SiNPs-induced placental inflammation and pregnancy complications and the novel pathophysiological roles of NLRP3 and ASC in pregnancy.[43]

Kyeongah K and Jong-Seok L (2012), studied SiNPs induces inflammation and also a cytotoxic effect in mouse dendritic cells (DCs). SiNPs decreased the viability of DCs and increased the amount of cell deaths. In addition to the effect on DC differentiation, it induced TNF-α production in DCs and led to inflammatory responses *in vitro* and *in vivo.*[44]

The inflammatory and also cytotoxic responses of mono-disperse amorphous SiNPs of 30 nm in size on an *in vitro* coculture model mimicking the alveolar-capillary barrier and compared these to conventional monocultures by using epithelial cell line (lung adenocarcinoma cell line NCI H441, H441) and the endothelial cell line (clone of the angiosarcoma cell line ISO-HAS, ISO-HAS-1) were used in monoculture and in coculture on opposite sides of a filter membrane. The study evaluated, release of proinflammatory mediators like, soluble intracellular cell adhesion molecule-1 (sICCAM-1), IL-6, and IL-8. Additionally cytotoxicity and apoptosis markers were investigated. This experimental work suggested that much more sensitive fashion than the conventional monoculture for the release of inflammatory markers. At concentrations that were 10-100 fold less than the toxic concentrations the apically exposed coculture showed a release of IL-6 and IL-8 to the basolateral side. This may mimic the early inflammatory events that take place in the pulmonary alveoli after SiNPs inhalation.[39] Marzaioli et al (2014), expressed, SiNPs showed a strong proinflammatory effect from broncho-alveolar lavage fluid (BALF) of BALB/c mice, leading to neutrophil and lymphocyte recruitment after intratracheal instillation, showing neutrophils recruitment in the early inflammation stages (up to 1 week after instillation) following intratracheal instillation of SiNPs.[45]

Iron oxide nanoparticles

Iron oxide nanoparticles (Fe_2O_3 and Fe_3O_4) or magnetic nanoparticles are used in important bio applications, including magnetic bioseparation and detection of biological entities (cell, protein, nucleic acids, enzyme, bacterials, virus, etc.), clinic diagnosis and therapy such as magnetic resonance image (MRI) and magnetic fluid hyperthermia (MFH), targeted drug delivery and biological labels.[46]

Zhu et al. (2011), studied the proinflammatory action of iron oxide nanoparticles (Fe_2O_3 and Fe_3O_4) on HAECs and monocyte, phagocytosis and activation; and also investigated ICAM-1, IL-8, expression, as well as NO and nitric oxide synthase (NOS) activity. In the study, HAECs and U937 cells were exposed to 2, 20, 100 μg/mL of 22nm-Fe_2O_3 and 43nm-Fe_3O_4 particles. This

work shown that intravascular iron oxide nanoparticles may induce endothelial system inflammation and dysfunction by three ways: first, nanoparticles may escape from phagocytosis that interact directly with the endothelial monolayer; second, nanoparticles are phagocytized by monocytes and then dissolved, thus impact the endothelial cells as free iron ions; and third, nanoparticles are phagocytized by monocytes to provoke oxidative stress responses.[47]

Andrea et al. (2007), hypothesized that direct exposure of HAECs to ultrafine particles induces an inflammatory response and that this response depends on particle composition; by incubating HAECs for 1–8 hr with different concentrations (0.001–50 μg/mL) of Fe_2O_3, Y_2O_3, and ZnO nanoparticles and subsequently measured messenger RNA (mRNA) and protein levels of the three inflammatory markers, namely ICCAM-1, IL-8, and monocyte chemotactic protein-1 (MCP-1). Overall study recommended that, Fe_2O_3 nanoparticles fail to provoke an inflammatory response in HAECs at any of the concentrations tested; however, Y_2O_3 and ZnO nanoparticles elicit a pronounced inflammatory response above a threshold concentration of 10μg/mL. This study also suggested that animal studies of the impact of nanoparticles on vascular inflammation should help to find the action of on Fe_2O_3 inflammation.[48]

Kennedy IM et al (2009), studied that, incubation of HAECs with Fe_2O_3 (0.001-50 ug/mL) for 1 to 8 hrs. Measured mRNA levels of three markers of inflammation namely, ICCAM-1, IL-8, and MCP-1 using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Also studied interactions of nanoparticles with HAECs, by using inductively coupled plasma-mass spectrometry (ICP-MS) to measure the concentration of internalized particles. However, overall the study revealed that Fe_2O_3 nanoparticles did not provoke an inflammatory response in HAECs at any of the concentrations tested. These results demonstrate that inflammation in HAECs after acute exposure to metal oxide nanoparticles depends on the concentration and composition of the particles.[34]

Cerium oxide (CeO_2) nanoparticles

CeO_2 nanoparticles (15-45 nm; 5-40 μg/mL) induced oxidative stress and cell death in cultured human lung epithelial cells. CeO_2 nanoparticles have been tested for their ability to serve as free radical scavengers to render protection against chemical, biological and radiological insults that promote the production of free radicals.[49]

Kennedy IM et al (2009), studied that, incubation of HAECs with CeO_2 (0.001-50 ug/mL) for 1 to 8 hrs. Measured mRNA levels of three markers of inflammation namely, ICCAM-1, IL-8, and MCP-1 using RT-PCR. Also studied interactions of nanoparticles with HAECs, by using ICP-MS to measure the concentration of internalized particles. Overall CeO_2 particles elicited no response at low concentrations and a weak response above 10ug/mL. These results demonstrate that inflammation in HAECs after acute exposure to metal oxide nanoparticles depends on the concentration and composition of the particles.[34]

Yttrium oxide (Y_2O_3) nanoparticles

The Y_2O_3 nanoparticles are used in a number of different applications, including biological imaging, the material sciences, chemical synthesis of inorganic compounds, manufacturing of plasma televisions, cathode ray display panels, microwave filters, in high-temperature/infrared-shielding applications and as additives in paint, plastic, steel, iron, and optics.[50, 51]

Kennedy IM et al (2009), studied that, incubation of HAECs with Y_2O_3 (0.001-50 ug/mL) for 1 to 8 hrs. Measured mRNA levels of three markers of inflammation include, ICCAM-1, IL-8, and MCP-1 using RT-PCR. The study also suggested that, interactions of nanoparticles with HAECs, by using ICP-MS to measure the concentration of internalized particles. Overall Y_2O_3 elicited a pronounced inflammatory response above a threshold concentration of 10ug/mL. These results demonstrate that inflammation in HAECs after acute exposure to metal oxide nanoparticles depends on the concentration and composition of the particles.[34]

Zinc oxide (ZnO) nanoparticles

The biomedical applications of ZnO nanoparticles are biomedical imaging (which includes fluorescence, magnetic resonance, positron emission tomography, as well as dual-modality imaging), drug delivery, gene delivery, and biosensing of a wide array of molecules of interest.[52] Kennedy IM et al (2009), studied that, incubation of HAECs with ZnO (0.001-50 ug/mL) for 1 to 8 hrs. Measured mRNA levels of three markers of inflammation namely, ICCAM-1, IL-8, and MCP-1 using RT-PCR. Also studied interactions of nanoparticles with HAECs, by using ICP-MS to measure the concentration of internalized particles. Overall ZnO elicited a pronounced inflammatory response above a threshold concentration of 10ug/mL. These results demonstrate that inflammation in HAECs after acute exposure to metal oxide nanoparticles depends on the concentration and composition of the particles.[34]

Silver nanoparticles (AgNPs)

Currently, silver nanoparticles (AgNPs) are the most common nanoparticles in nanomedicine. According to the Nanotechnology Consumer Products Inventory, AgNPs are currently claimed to be used in more than 400 consumer products.[53] AgNPs have antimicrobial activity (along with released ions, binding to sulphur- and phosphorous containing biomolecules such as proteins and DNA) and are used in food packaging material, food supplements, odour-preventing textiles, cosmetics, kitchen utensils, toys, electronics, wound dressings, and room sprays.[53, 54]

The study hypothesize that small AgNPs will induce more prominent pulmonary inflammation compared to larger, because of the larger deposited dose in the alveoli and the higher dissolution rate. AgNPs of 15 nm and 410 nm were exposed after short-term nose inhalation. All endpoints were determined at 24 hours and 7 days after the last exposure. The inflammatory markers mainly cytokines were estimated in the BALF and also total blood cell counts and cell damage markers. 12 different proinflammatory cytokines were selected: IL-1β, IL-6, TNF-α, IFN-γ (interferon-gama), IL-13, GM-CSF, MCP-1, IL-12p70, IL-18, macrophage inflammatory protein-1α (MIP-1α), MIP-2 and RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted). Of these cytokines, only IL-1β, MCP-1 and MIP-2 could be measured; all the other cytokines were and stayed below or around the detection level. Both IL-1β and MCP-1 were significantly increased 24 hours after exposure. The study suggested that inflammation in pulmonary was size-related, that is exposure to 15 nm AgNPs induced moderate pulmonary inflammation at 24 hours after exposure, whereas 410 nm AgNPs did not.[55]

Synthetic hydroxyapatite nanoparticles (HANPs)

Synthetic hydroxyapatite (HA) (Ca10[PO4]6[OH]2), a typical bioceramic with good osteoconductive and osteoinductive capabilities, has been used clinically for many years.[56] Due to their better bioactivity, their excellent capacity to penetrate cell membranes, and their increased circulation time, HANPs have gradually garnered significant interest in various medical fields, such as bone tissue engineering, cardiovascular graft coating, contrast agent synthesis, drug delivery, and gene therapy.[57-59] The study measured the stimulation of mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB) in human umbilical vein ECs (HUVECs). Four patterns of cytokine release (TNF-α, IL-1β, IL-6, and IL-8) were also estimated. THP-1 cells exposed to HANPs exhibited significant increases in TNF-α (up to 15-fold) and IL-1β (up to twofold) in both monoculture and co-cultures of monocytes.[60]

Nickel oxide (NiO) nanoparticles

The biomedical applications of NiO nanoparticles includes, in battery cathodes, gas materials, photovoltaic devices and others. The NiO nanoparticles toxicity has been evaluated in the human pulmonary epithelial cell lines: BEAS-2B and A549. The nanoparticles, used at the doses of 20, 40, 60, 80, 100 μg/ml, induced a significant reduction of cell viability and an increase of apoptotic and necrotic cells at 24h. A significant release of interleukin-6 and-8 was assessed after 24h of treatment, even intracellular ROS increased already at 45 min after exposure. The results obtained evidenced that the cytokines release was dependent on MAPK cascade through the induction of NF-kB pathway.[61]

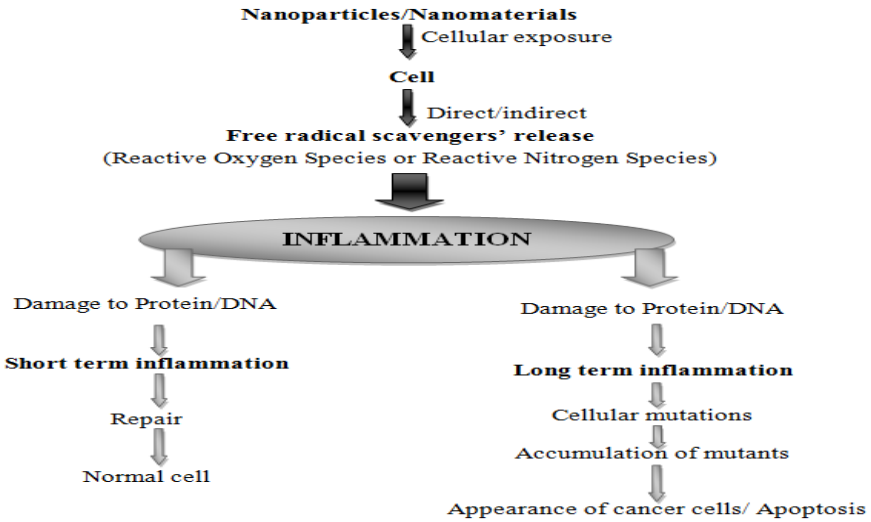

Figure 1: Possible relationship between nanoparticles and inflammation.

CONCLUSION

Reports on the toxicology of nanomaterials have been increasing recently, but the effect of nanomaterials on the human body is inconclusive, for example, in general, inhaled dusts such as particles and fibrous materials in the lung repeatedly induce inflammation and finally lead to pulmonary fibrosis, respiratory cancer and others. Many factors are likely to be involved in the adjuvant activity of nanoparticles, and a consistent mechanism has not been found. In future it is expected to elucidate what factors are involved for the release of inflammatory mediators in inflammation and other inflammatory diseases induced by various nanoparticles.

AUTHORS' STATEMENTS

The authors declare that there is no conflict of interests about the publication of this review paper.

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