TANG [HUMANITAS MEDICINE]

Review

Biological effects of zinc oxide nanoparticles on inflammation

Min-Ho Kim

Department of Computer Aided Mechanical Engineering, Sohae College, Gunsan, Jeonbuk, 54116, Republic of Korea

ABSTRACT

With the rapid developments in nanotechnology, an increasing number of nanomaterials have been applied in various aspects of our lives. Recently, pharmaceutical nanotechnology with numerous advantages has growingly attracted the attention of many researchers. Zinc oxide nanoparticles (ZnO-NPs) are nanomaterials that are widely used in many fields including diagnostics, therapeutics, drug-delivery systems, electronics, cosmetics, sunscreens, coatings, ceramic products, paints, and food additives, due to their magnetic, catalytic, semiconducting, anti-cancer, anti-bacterial, anti-inflammatory, ultraviolet-protective, and binding properties. The present review focused on the recent research works concerning role of ZnO-NP on inflammation. Several studies have reported that ZnO-NP induces inflammatory reaction through the generation of reactive oxygen species by oxidative stress and production of inflammatory cytokines by activation of nuclear factor-κB (NF-κB). Meanwhile, other researchers reported that ZnO-NP exhibits an anti-inflammatory effect by inhibiting the up-regulation of inflammatory cytokines and the activation of NF-κB, caspase-1, IκB kinaseβ, receptor interacting protein2, and extracellular signal-regulated kinase. Previous studies reported that size and shape of nanoparticles, surfactants used for nanoparticles protection, medium, and experimental conditions can also affect cellular signal pathway. This review indicated that the anti-inflammatory effectiveness of ZnO-NP was determined by the nanoparticle size as well as various experimental conditions. Therefore, the author suggests that pharmaceutical therapy with the ZnO-NP is one of the possible strategies to overcome the inflammatory reactions. However, further studies should be performed to maximize the anti-inflammatory effect of ZnO-NP to apply as a potential agent in biomedical applications.

Keywords nanotechnology, zinc oxide nanoparticle, inflammation, inflammatory cytokine, nuclear factor-κB, caspase-1

INTRODUCTION

The various products made by the application of nanotechnologies were widely used in everyday life. Pharmaceuticals, cosmetic, powdered food, and sunscreen products contain nanoparticles to enhance the product efficacy and quality (Contado, 2015). The first known use of the word "nanotechnology" dates back to 1974s when prof. Norio Taniguchi coined the term to describe semiconductor processes such as thin film deposition and ion beam milling exhibiting characteristic control on the order of a nanometer (Taniguchi, 1974). Nanotechnology was mainly composed of the processing of deformation, consolidation, and separation of one. Since the 1980s, the term nanotechnology refers to the fabrication, use/manipulation, control and characterization of structures devices or materials with a least one dimension in the size range of nanometer scale (Whatmore, 2006). Nanotechnology has been contributed in the fields of environmental, applied science, biology, engineering, and electronics (Kim et al., 2014). Nanotechnology creates a novel facility with specificity and excellent efficiency through mutual interactions among a group of nanoscale functional components, molecules, or atoms (Nakanishi et al., 2014). Nanoparticles also show peculiar physicochemical characteristic due to their shapes and sizes; these include enhanced reactivity, low cost, high surface area, ability to affect various types of biological systems, and ability to easily enter cells (Wahab et al., 2014).

Zinc (Zn) is an abundant trace metal for regulation of various physiological processes in eukaryotes (Jansen et al., 2009; Maremanda et al., 2014). Zinc oxide (ZnO) is source of Zn. Zinc oxide nanoparticles (ZnO-NP) are one of the most used nanoparticles, and have a broad spectrum of applications ranging from diagnostics, therapeutics, pigments, drug-delivery systems, hair care products, coatings, electronics, cosmetics, sunscreens, ceramic products, paints, and food additives because of their low cost, effectiveness, and vast applications (Kim et al., 2014; Roy et al., 2013; Roy et al., 2014; Sharma et al., 2012; Wahab et al., 2010). ZnO-NPs were internalized into cell by endocytosis and produced Zn^{2+} by dissociation (Jeong et al., 2013). In the protein and enzyme solutions, Zn^{2+} creates ionic signals among various organelles by intra- or intercellular interaction and can also cause cytoxicity (Frederickson et al., 1988; Frederickson et al., 2005). Recently, regulatory effects of ZnO-NP have reported the various experimental models including cancer, bacterial infection, and inflammatory reactions (Dizaj et al., 2014; Kim et al., 2014; Kim and Jeong, 2015; Liu et al., 2016). The presents review focused on the recent research works concerning the roles of ZnO-NP in the

*Correspondence: Min-Ho Kim
E-mail: minho@sohae.ac.kr
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Table 1. The functions of inflammatory mediators

Category	Mediators	Functions
Vasoactive amines	Histamine, Serotonin	Produced when mast cell and platelets degranulate. Increased vascular permeability and vasodilation, or vasoconstriction. Resulted in vascular and respiratory collapse during anaphylactic shock (Medzhitov, 2008)
Vasoactive peptides	Substance P	Released from sensory neurons. Induced mast cell degranulation (Andoh et al., 1998).
Complement fragments	C3a, C4a, C5a (anaphylatoxins)	Promote granulocyte and monocyte recruitment. Induce mast cell degranulation (Stone et al., 2013)
Lipid mediators	Eicosanoids, Platelet-activating factors	Derived from phospholipids such as phophatidylcholine. After activation by intracellular Ca^{2+} ions, cytosolic phospholipase A2 generates arachidonic acid and lysophosphatidic acid, the precursors of the two classes of lipid mediator listed above, from phosphatidylcholine. Arachidonic acid is metabolized to form eicosanoids either by cyclooxygenases (COX1 and COX2), which generate prostaglandins and thromboxanes, or by lipoxygenases, which generate leukotrienes and lipoxins (Higgs et al., 1984; Kumar et al., 2003).
Proteolytic enzymes	Elastin, Cathepsins, matrix-metalloproteinases	Host defence, tissue remodeling, leukocyte migration (Shapiro et al., 1991; Skjøt-Arkil et al., 2010)
Chemokines	macrophage inflammatory protein-2, and intercellular adhesion molecule-1	Control leukocyte extravasation and chemotaxis towards the affected tissues (Spencer et al., 2009)
Inflammatory cytokines	TNF-α, IL-4, IL-5, IL-13, IL-6, IL-1β	Produced from macrophages and mast cells. Activation of endothelium and leukocytes. Induction of acute-phase responses (Jeong et al., 2002; Kim and Jeong, 2015)

inflammatory reactions.

Inflammation is an adaptive immune response that is induced by pathogen, irritants, and damaged cells, and tissue injury (Majno and Joris, 2004; Kumar and Cotran, 2003). The aims of inflammation are to delete the initial cause of cell injury, tissues damaged from the original insult, and clear out death cells (Kumar and Cotran, 2003). Low levels of inflammation caused to progressive tissue destruction by harmful pathogens, while chronic inflammation induced the periodontitis, atherosclerosis, hay fever, cancer, rheumatoid arthritis, and allergic inflammation. Therefore, inflammation was normally regulated by the body (Kumar et al., 2004). At a basic level, the primary inflammatory response induced by tissue injury or infection involves the infiltration of neutrophils, eosinophils, basophils, mast cells, macrophages, T-cells and B-cells to the site of infection or injury (Majno and Joris, 2004; Kumar et al., 2003). This response is triggered by receptors of the innate immune system, such as nucleotide-binding oligomerization-domain protein-like receptors and Toll-like receptors (Barton, 2008). The initial responses by infection is mediated by tissue resident cells such as mast cells and macrophages, leading to the secretion of various inflammatory mediators such as inflammatory cytokines, eicosanoids, vasoactive amines, chemokines, and products of proteolytic cascades (Majno and Joris, 2004; Kumar et al., 2003). The cellular mediators were mainly produced by tissue resident mast cells and macrophages or by cells present in local tissues. The most of mediator are preformed and circulate as inactive precursors in the plasma. The bio-amines (histamine and serotonin) are preformed and stored in the granules of basophils, mast cells, and platelets. The plasma levels of these inflammatory mediators can increase noticeable as a result of increased production of the precursors by hepatocytes during the acute-phase response. Other mediators are released directly by stimulators of inflammation. Inflammatory mediators can be split into seven groups according to their biological functions (Majno and Joris, 2004; Kumar et al., 2003): vasoactive amines, vasoactive peptides, lipid mediators, chemokines, fragments of complement components, proteolytic enzymes, and cytokines. The roles of these mediators were summarized in Table 1.

The expression of the above-mentioned inflammatory cytokines and chemokines was induced by the activation of nuclear factor-κB (NF-κB), which NF-κB when activated is translocated to the nucleus where it binds to specific DNA sequences and triggers the syntheses of inflammatory mediators such as cyclooxygenase-2, inducible nitric oxide synthase, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 (Kwon et al., 2013; Tornatore et al., 2012). Therefore, normal homeostasis requires the strict regulation of NF-κB activation and this is facilitated by inhibitors of NF-κB, such as, IκB and ubiquitin-editing protein A20 (a zinc finger protein), which has been recently demonstrated to play a critical role in the regulation of the NF-κB signaling cascade (Harhaj and Dixit, 2011; Shembade et al., 2010). Receptor interacting protein2 (RIP2) acts a vital role in the modulation of inflammatory processes and immune response, and its signaling tightly connected with IκB kinaseβ (IKKβ), NF-κB, caspase-1, and mitogen-activated protein kinases (MAPKs) signaling (Perkins,

Table 2. The role of ZnO-NP in inflammatory reactions

In vivo/*In vitro* model	Size (nm)	Signaling Pathway	Reference
Lung inflammation mouse model	71 ± 35	inflammatory cell infiltration ↑ TNF-α, IL-6, CXCL1, MCP-1, IL-10, IL-13 MyD88 ↑	Chang et al., 2013
Mouse lung epithelial cell (MLE12)		TNF-α, IL-6, IL-1β, CXCL1, MCP-1↑	
RWA264.7 macrophages		TNF-α, IL-6, IL-1β, CXCL1, MCP-1 ↑	
Human A549 cells, HepG2 cells, Human skin fibroblast cells, Human skin keratinocytes, Rat primary neuronal cells	195 ± 17	ROS production ↑	Chiang et al., 2012
Human neutrophils	< 20	Syk activation ↑	Babin et al., 2015
OVA-induced murine asthma model	< 50	eosinophil counts ↑ IL-4, IL-5, IL-13 cytokines↑	Huang et al., 2015
RAW264.7 macrophages	89 ± 1	IL-1β↑ NF-κB activation ↑	Giovanni et al., 2015
OVA-induced allergic reaction	21	IgE, IgG1, metallothionein 1, nitric oxide synthase 2, arginase 1↑	Horie et al., 2015
Lung inflammation animal model	20 - 50	lactate dehydrogenase, heme oxygenase-1, IL-6, the chemokine cytokine-induced neutrophil chemoattractants, metallothionein-1 ↑	Fukui et al., 2015
Primary macrophages	< 50	ROS, COX-2, iNOS, IL-6, IFN-γ, TNF-α, IL-17, IL-10, MAPKs↑	Roy et al., 2014
Human keratinocyte (HaCaT cell)	20	TNF-α, ROS-ERK-Egr-1 ↑	Jeong et al., 2013
Human umbilical vein endothelial cells (HUVECs)	50	vascular inflammation↑	Li et al., 2012
Human umbilical vein endothelial cells (HUVECs)	100	intercellular adhesion molecule-1↑ NF-κB activation ↑	Tsou et al., 2010
Primary human nasal mucosa cells	40-86	IL-8 production ↑	Hackenberg et al., 2011
THP-1 cells	- 30	TNF-α, IL-1β, ROS↑ MAPK, NF-κB activation ↑	Senapati et al., 2015
Lung epithelial reporter cell	30 - 40 (in H2O)	IL-8 promoter activity ↑	Stoehr et al., 2015

2007; Song et al., 2012). And, IKKβ activation induced by RIP2 induce the subsequent ubiquitination and phosphorylation of inhibitory IκBα protein, the isolation of IκBα and NF-κB, and the proteasome-mediated degradation of IκBα (Perkins, 2007). The smaller ZnO-NPs (approximately 20 - 100 nm) triggered the inflammatory reactions by producing inflammatory mediators (Table 2). Meanwhile, larger ZnO-NP (approximately 200 - 500 nm) significantly reduced the inflammatory reaction through the regulation of RIP2, IKKβ1, ERK, caspase-1, or NF-κB (Table 3). The physical and chemical characteristics of ZnO-NP were different from ZnO, bulk materials (Seabra et al., 2013). Kim et al., (2014) reported that ZnO-NP more effectively reduces inflammatory reactions than bulk ZnO.

CONCLUSION

Table 3. The anti-inflammatory effects of ZnO-NP in inflammatory reactions

In vivo/*In vitro* model	Size (nm)	Signaling Pathway	Reference
Human mast cell line (HMC-1 cells)	200	TNF-α, IL-6, IL-1β ↓ RIP2, IKKβ, ERK, caspase-1 ↓	Kim et al., 2014
Atopic dermatitis mouse model	< 50	skin thickness, inflammatory cell infiltration ↓ IL-13, IFN-γ, TNF-α, IL-1β, IL-6, IL-10, IL-33, IL-4 ↓ IgE ↑	Ilves et al., 2014
RAW264.7 macrophages	200	TNF-α, IL-1β, iNOS, COX-2 ↓ NF-κB activation ↓, A20↑	Kim and Jeong, 2015
Human mast cell line (HMC-1 cells)	200	murine double minute 2, signal transducers and activators of transcription 6 (STAT6), IL-13, Bcl2↓ p53, Bax ↑	Kim and Jeong, 2016
Allergic inflammatory reaction animal model	500	skin inflammation ↓	Pati et al., 2014

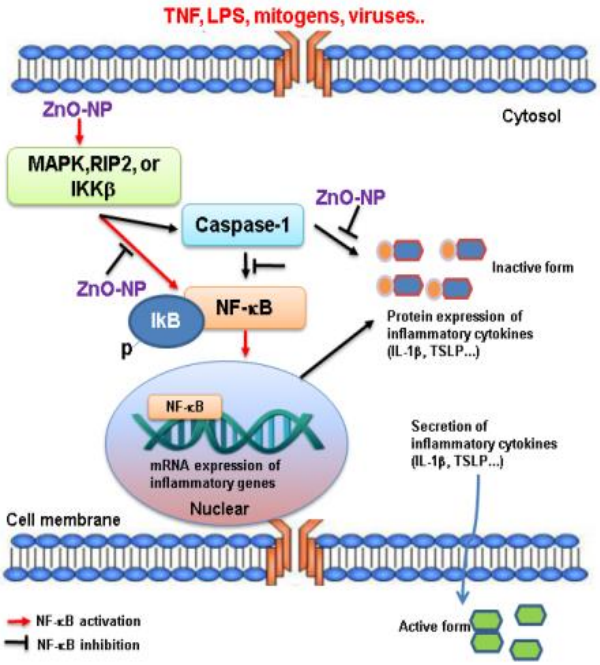

Fig. 1. Schematic diagram of the mechanism responsible for the regulation of inflammatory signaling pathways by ZnO-NP.

ZnO-NP has useful physicochemical advantages, and is used extensively. In the presents review, ZnO-NP exhibits the anti-inflammatory or inflammatory effects (Fig. 1). ZnO-NPs internalized by endocytosis are dissociated to induce Zn^{2+}, which has vital roles in biological activities. Moreover, effects chemistries. However, further studies should be performed to experimental conditions, media, and nanoparticle sizes, shapes and cellular signaling pathways of ZnO-NP were determined by solubilities, chemical compositions, surface areas, and surface maximize the anti-inflammatory effect of ZnO-NP to apply as a potential agent in biomedical applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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