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Nanomaterial Induced Immune Responses and Cytotoxicity

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Nanomaterials are utilized in a wide array of end user products such as pharmaceuticals, electronics, clothes and cosmetic products. Due to its size (<100 nm), nanoparticles have the propensity to enter through the airway and skin, making its path perilous with the potential to cause damages of varying severity. Once within the body, these particles have unconstrained access to different tissues and organs including the brain, liver, and kidney. As a result, nanomaterials may cause the perturbation of the immune system eliciting an inflammatory response and cytotoxicity. This potential role is dependent on many factors such as the characteristics of the nanomaterials, presence or absence of diseases, and genetic predisposition. Cobalt and nickel nanoparticles, for example, were shown to have inflammogenic properties, while silver nanoparticles were shown to reduce allergic inflammation. Just as asbestos fibers, carbon nanotubes were shown to cause lungs damage. Some nanomaterials were shown, based on animal studies, to result in cell damage, leading to the formation of pre-cancerous lesions. This review highlights the impact of nanomaterials on immune system and its effect on human health with toxicity consideration. It recommends the development of suitable animal models to study the toxicity and bio-clearance of nanomaterials and propose safety guidelines.

Keywords: Nanomaterials, Nanoparticles, Nanotoxicology, Cellular Uptake, Inflammation, Macrophages, Cytochrome P450, Apoptosis, Necrosis, Autophagy, Pyroptosis.

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1. INTRODUCTION

The recent development in nanotechnology has provided scientists with new momentum to target diseases that could not be treated traditionally. However, the drive to employ nanomaterials has raised health concerns and risks. Currently, nanotechnology is being implemented in various fields of medicine, where nanomaterials are used in clinical and imaging diagnostics, and as drug delivery vehicles (see Table I-Nanomaterials and their Application).^{1–9}

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Ashraf Ali is working as a Lecturer in KFMRC, KAU, Jeddah (KSA). He has done post-graduation in Biochemistry from Jamia Hamdard, New Delhi (INDIA), in 2008. After finishing his Post Graduation in 2008 he worked in several research projects which helped him in learning several techniques in the area of biochemistry, molecular biology and microbiology. Earlier to that he worked as a Junior Research Fellow in an International project entitled “Development of conformationally preferred peptide immunogens as vaccine candidates against HIV-infection” funded by IAVI at ICGEB, New Delhi, India. He is part of Medical Biotechnology and Translational Research group at KFMRC. He has also delivered a couple of seminars and attended an international conference held in Pune (India). He is particularly interested in interdisciplinary research and wants to contribute significantly in this area.



Mohd Suhail is an expert in isolation of protein from *Mycobacterium tuberculosis* by Ni-NTA Affinity Chromatography, Resin regeneration and basic Techniques of Yeast genetics. He has done his Masters in Biotechnology from Jamia Hamdard University, New Delhi, India and Presented his Dissertation work entitled “Development of RAPD markers to find out the genetic variations between different samples of “*Aconitum balfourii*” at the Centre of Biotechnology, Hamdard University, New Delhi. During his Master’s, he participated in Regional Seminar on Intellectual Property Protection and Management organized by the National Research Development Corporation in collaboration with Central Council for Research in Unani Medicine in 2009 at Hamdard University, New Delhi. He worked as Project Assistant from October 2010 to March 2012 at the Institute of Microbial Technology (IMTECH), Chandigarh, India. Mr. Mohd Suhail joined King Fahd Medical Research Center, King Abdulaziz University (KSA) as a Lecturer in March 2012.



Shilu Mathew graduated her Bachelors in Industrial Biotechnology with distinction from Dr. MGR University (2004) and therefore she was awarded to study with scholarship from Department of Science and Technology (DST) from New Delhi to complete her Master in Engineering and Technology in Medical Nanotechnology at SASTRA University (2008) as well as Master’s in Bioinformatics from Loyola College. She accomplished both her degree projects, by combination of both wet lab and *insilico* study, which had encouraged boosting her skills in Bioinformatics too. She is currently working at the Centre of Excellence in Genomic Medicine Research (CEGMR) as Research Assistant for 4 years in various cancer research projects, utilizing genetic and epigenetic up-to-date technologies and approaches. Her current research projects utilize next-generation sequencing technology to perform whole exome sequencing, mRNA sequencing, genome wide methylation analysis, gene expression, and cloning as well as methylation analysis for different types of cancer specific type of genes.



Muhammad Ali A. Shah completed his Ph.D. from Nanjing Agricultural University, China in 2009 with specialization in field of DNA vaccines. He has completed his Post Doctorate with distinction from Biomedical Engineering at School of Biological Sciences and Medical Engineering, Southeast University, China. During the Post Doctorate studies he had an opportunity to work with legend like Professor He Nongye. He worked on different possibilities of application of nanoparticles with drug delivery. There are almost 40 publications at his credit, which have been cited in 3, 00 plus publications by other research groups throughout the world. He has co-authored a couple of books as well and Editor of a couple of journals from the The Science Publishers. He is the recipient of 6 international R&D grants funded from Higher Education Commission, China Science Foundations, and Jiangsu Science Fund etc. He has worked as Assistant professor and

Associate professor in different universities where he has been involved in various teaching, research and administrative activities. He has 16 years of Research and teaching experience. Currently he is working as Chairman, Department of Pathobiology in Arid Agriculture University. His current research interests include immuno-therapeutics especially DNA vaccination and Nano vaccines against Infectious agents and their delivery.



Steve M. Harakeh received his B.Sc. and M.Sc. from the American University of Beirut (AUB). He was awarded his Ph.D. degree in Microbiology from the University of Surrey, UK. He spent two years as a Postdoctoral Research Fellow in the Microbiology and Immunology Department, School of Medicine, at Stanford University, USA, and then he was appointed as a Research Associate (Research Assistant Professor) in the same department. Professor Steve joined the Linus Pauling Institute for Science and Medicine where he worked and published with Professor Pauling who is the only holder of two unshared Noble prizes in the world. After that he was appointed as a professor of Microbiology at the AUB. Then he worked as a research professor at Dr. Rath Research Institute in California, USA. Currently, Professor Steve is a professor at the Special Infectious Agents Unit—Biosafety Level 3 (SIAU). He is the vice chairman of the KFMRC quality control and biosafety committee, member of infectious disease research group.



Sultan Ahmad He is a Lecturer in the Metabolomics and Enzymology Unit of the KFMRC. Mr. Ahmad received his Master's degree in Zoology from Patna University, India. He also attained a Degree in Education from the same university. He has over ten years of experience in teaching Biology. He studied the effects of Endosulphan on mouse Leydig cells and the possible effects of Curcuma longa and Emblica officinalis in controlling pollutant toxicity in mice. His current research interest is to study and investigate the metabolic events underlying the pathology of neurological disorders. In particular his research at KFMRC will focus on the role of various risk factors in the pathogenesis of Alzheimer's and Parkinson's disease in Saudi Arabia. Additionally his research is aimed at identifying the role of modifiable factors and to investigate their efficacy in halting or slowing down the progression of Alzheimer's and Parkinson's disease.



Zulqarnain Kazmi was born in 1990. She completed her B.Sc. (HONS) degree at the Atta-ur Rehman School of Applied Biosciences, NUST University in 2012. She joined King Fahd Medical Research Centre (KFMRC) as a trainee research assistant in 2013. Her research interests focus on hippocampal development, immune responses induced by neurological disorders and neurodegeneration. This is her first publication.



Mohammed Abdul Rahman Alhamdan is Teaching Assistant in Department of King Abdulaziz University and is now demonstrator at orthopedic surgery department, King AbdulAziz University. He had an MBBS in medicine and surgery in 2013, with excellent with second honor degree. He is interested in translational clinical research.



Adeel Chaudhary after being awarded Ph.D. in 1998 from University of Sheffield, UK, Dr. Adeel was appointed as assistant professor at the department of Medical Laboratory Technology, FAMS, KAU (King Abdul Aziz University). He was involved in establishing state-of-the art core diagnostic facility for Cytogenetic and Molecular Genetics in 2003. Since then he has focused on establishing training programs in molecular genetics for Saudi graduates from various health faculties at KAU.



Ghazi Abdullah Damanhoury Dr. Ghazi A. Damanhoury obtained his degree of M.B. Ch.B. from Medical College, Al Azhar University in 1976 and DCP (RPGMS) from London University in 1984. His major research interest is in the area of Hematology. Apart from this he is continuing as the Director of Post-Graduate Studies in Hematology, Hematology Department, King Abdulaziz University, Jeddah and working as a Regional Advisor for Royal College of Pathologists, London, UK as well.



Ishtiaq Qadri Dr. Ishtiaq Qadri is a Professor at the King Fahd Medical Research Center King Abdul Aziz University, Jeddah Saudi Arabia where he is enthusiastically involved in the study of liver adaptive responses, nanosensor development, specific gene expression and regulation during insulin resistance and hepatic steatosis. He completed his Ph.D. in 1989 from Imperial College of Science and Technology, London UK (1984–1988) and later carried out postdoctoral research at the University of California San Francisco, CA, US (1988–1993), and University of Colorado Health Sciences Center, Denver CO USA (1994–1998). He has published over 100 peer-reviewed research papers in international journals. He is the recipient of over 28 international R&D grants funded from NIH USA, American Liver Foundation, Colorado League of Cancer, US-State Dept, Bio-Safety Engagement Program of US, Pasteur Institute of France, Higher Education Commission, Ministry of Science and Technology Science Foundation.

In addition, nanomaterials are commonly used in commercial products such as hygiene and cosmetics products, and paints.^{3, 10–19} Nanomaterials are defined as crystalline, tiny particles with large surface area, proton exchangeability and high degree of surface charge with the size limit of 1–100 nm. Due to its smaller size; its physiochemical properties are quite different from other substances.^{20–38} Humans have exposure to these nanomaterials by different sources and after entering inside the body with different routes they show various immune responses and cytotoxicity (see Table II-The adverse effects of some of the commonly used metals used in nanotechnology). Inflammation is one of the major immune response generated by these nanomaterials.

Inflammation is cascade of events propagated by different stimulus and it is the major process by which body repairs damaged tissue and protects it from foreign materials and pathogens. Acute inflammation is generally caused

by various external factors and lasts for short duration of time. It is effective protection tool of the immune system that removes foreign particles and repair damaged tissue. Compared to acute inflammation, chronic inflammation causes a range of painful and unwanted symptoms. Macrophages with mononuclear phagocyte system (MPS) plays central roles in inflammation of the cells, including antigen presentation, phagocytosis and the production of immune regulators and various cytokines.^{39–43} Due to higher surface reactivity and cell permeability, the influx of nanomaterials produces several biological activities on cellular level. These particles are immersed in the body by several routes and induce biological toxicity.^{44–47} Besides mitochondrial perturbation and apoptosis these materials produces oxygen radicals,^{48–50} which is followed by inflammation and cytotoxicity. Nanomaterials are strong inducers of oxidative stress in macrophages along with epithelial cell linings across the lungs. These particles also

Table I. Nanomaterials and their application.

S.N	Type of nanomaterial	Application	References
1	Ceramics, catalysts, films and coatings, composites, metals	Structural applications	[209, 210, 211–220]
2	Metal oxides (e.g., TiO ₂ , ZnO)	Skincare products	[210, 213, 221, 222]
3	SWNT, nanoelectronic and optoelectronic materials (excluding CMP slurries), organic light emitters and electronics, nanophosphorous	Information and communication technologies	[223–226]
4	Nanocomposites and encapsulates, targeted drug delivery, diagnostic markers, biosensor	Biotechnology	[209, 223, 227–229, 17, 226, 230–249, 303, 304, 307–310]
5	Nanofiltration, membranes	Environmental	[210, 157, 242, 250–254]

Table II. The adverse effects of some of the commonly used metals in nanotechnology.

Metal	Product/uses	Health risk	Reference
Beryllium	Electrical, electronic parts, plastics	Pneumonia-like symptoms, lung damage, granulomas, anorexia, weight loss, cyanosis of the extremities, and heart enlargement	[255]
Lead	Batteries, paints, insecticides sanding of surfaces	Impairment of mental functions, fatigue, lack of appetite, abdominal pain, kidney disease, decreased visual motor performance and attention span, and anemia	[256, 257]
Cobalt	Batteries	Asthma, acute illnesses (fever, anorexia, malaise), difficulty in breathing, and interstitial pneumonitis	[258]
Cadmium	Batteries, pigments, metal coating, plastics	Severe lung irritation, nausea, vomiting, lung emphysema, impairment of the immune system, central nervous system and liver damage, and cancer	[259, 260]
Aluminum	Antacids antiperspirants	Breast cancer, anemia, bone disease, and dementia	[261–263]
Nickel and chromium	Stainless steel and other nickel alloys	DNA damage, oxidative stress, lung and sinus cancer	[264]
Manganese	Essential nutrient	Neurotoxic effects, neurological impairment, and Parkinson's disease	[265–267]
Iron	Oxygen transport and gas exchange	Increased risk of tumors and cancer, and pneumoconiosis	[268–270, 305]

induce the activity of several molecules like MAPK, NF- κ B and AP-1 as well as the oxygen free radicals which lead to chronic inflammatory reaction across respiratory tract.^{51–56}

2. ENTRY AND ROUTE OF NANOMATERIALS INSIDE THE BODY

Though the human body is well adapted to protect itself from the adverse effects of nanoparticles, it remains susceptible to damage caused by them. Studies have shown that inhaled and ingested nanoparticles are less efficiently removed by macrophages in comparison to larger particles, and these nanoparticles can cause various body damages.⁴¹ The extent of the body damage caused by the intake of nanoparticles depends on the nature and duration of the exposure, and the dose of the nanoparticles. For example, the metal fume fever, which has similar effects to influenza-like infections, results from inhaling fumes of metals such as zinc and cobalt. In addition, asthma and pulmonary fibrosis can be associated with the inhalation of metallic dust such platinum, nickel, chromium and cobalt. Entry of nanomaterial into body takes place by inhalation, ingestion or through skin.^{57–63} Skin is the first source which gets exposed to nanomaterials and can induce toxicity which is shown in cell culture models as well as animal models.^{64–67} These nanoparticles enter into cells by transcytosis across different cells and into lymph circulation to reach sensitive parts of the body such as bone marrow, brain, lymph nodes, spleen and heart.^{58–60} As these nanomaterials are not naturally found, immune system behaves differently towards them. When they interact with human and animal cells or organs they can kill those cells or damage the organs, can block blood flow

which leads to several diseases.^{59, 61} Disease associated with these nanoparticle include bronchitis, asthma, lung and liver cancer, Parkinson's disease, Alzheimer's disease, Crohn's disease, heart disease and colon cancer.^{57, 58, 68} The respiratory tract is considered an important route for the entry of nanomaterials into the body (see Fig. 1-Entry of nanomaterials into the body by different routes and their effects). Thus, the lungs are most susceptible to exposure to nanomaterials. The health risks associated with the exposure of the lungs to nanomaterials are exacerbations in the airway and cardiovascular diseases.^{69, 70} The most known mechanism for the damage caused by the nanomaterials to the lungs is oxidative stress. The damage to the lungs leads to the activation of different transcriptional factors with an up regulation of the pro-inflammatory protein synthesis.⁷¹ The inhaled nanomaterials lead to the activation of mitogen-activated protein kinase and nuclear factor-kappa B signaling pathways and production of pro-inflammatory transcripts such as IL-8, IL-6 and TNF- α .^{72–74} Moreover, different sizes of nanomaterials can induce different inflammatory reactions and consequently different rates of lung damage.^{75–78} Studies have shown a significant correlation between the surface area of nanomaterials and rate of inflammatory induction through oxidative stress.⁷⁶

3. EFFECTS OF EXPOSURE TO NANOMATERIALS

Due to higher surface reactivity and membrane permeability the influx of nanomaterial induces stress on cellular level. By various route they get accumulated in the body thereby inducing various biological toxicity.^{58, 59} Besides apoptosis and mitochondrial perturbation they produce

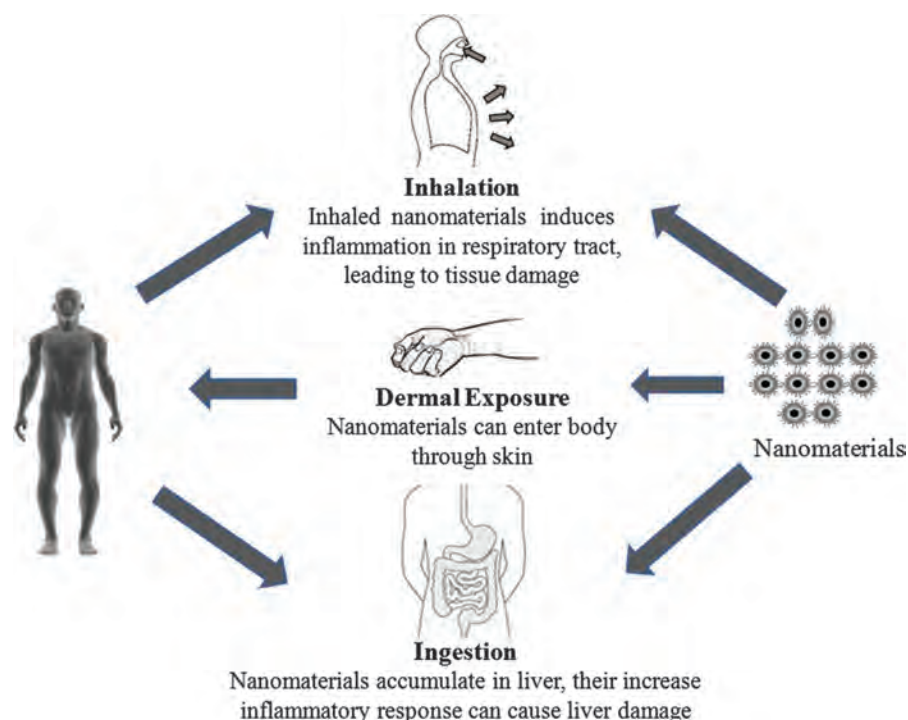


Figure 1. Entry of nanomaterials into the body by different routes and their effects.

oxygen free radicals.^{60,61} Based on several studies it is assumed that oxidative stress and inflammatory responses provoke the occurrence of immunotoxicity directly or indirectly (see Table III-Immunotoxicity of different types of nanomaterials based on metal, carbon and silica). Nanomaterials induce cytotoxicity which leads to several diseases. Some of the diseases in which nanomaterials play their role are asthma, emphysema lung cancer, bronchitis

and liver cancer, colon cancer and heart problems.^{58,59} The use of nanomaterials has become controversial due to the health risks associated with its applications.^{79–84} Though the exposure of humans to nanomaterials is generally low, its removal is slow. Thus, chronic accumulation of nanomaterials takes place, leading to health-related problems.⁸⁵ The structural and chemical properties of nanomaterials play an important role in determining its adversity, where

Table III. Immunotoxicity of different types of nanomaterials based on metal, carbon and silica.

S.N	Nanomaterial	Possible immunotoxicity and immune response	Reference
1	Carbon black	Induction of CCL2, IL-6, C-reactive protein in animals induced expression of CD86 and CD80 in endothelial cells	[198, 271–273]
2	Single walled carbon nanotubes	Induction of ROS, inflammatory cytokines, inhibition of production of IL-8, 6, TNF- α in A549 cells	[274–278, 195]
3	Multi-walled carbon nanotubes	Induction of fibrosis in asthma animal model, Induction of ROS, inflammatory cytokines in A549 or BEAS-2B cells	[279, 280]
4	TiO ₂	Induction of ROS, monocytes, lung inflammation, cardiac edema, systemic inflammation, induction of apoptosis and necrosis in macrophage cells	[281–285]
5	Gold	Induction of apoptosis and acute inflammation in liver, up-regulation of TLR-2, IL-1 α , GM-CSF and NO in microglia	[286–290, 306, 310]
6	Fe ₂ O ₃	Induction of pro-inflammatory cytokines, TGF- α and IgE, decrease in cell viability	[22, 34, 192, 291–294]
7	Zinc oxide	Induction of ROS, apoptosis and inflammation	[295–297]
8	Silica particles	Increased blood level of IL-1 β and TNF- α , NO and mRNA expression of different cytokines	[298, 299]
9	Silica	Induction of liver damage and inflammatory cytokines	[238, 300–302]
10	Polystyrene	Toxic to BEAS-2B cells, human micro vascular endothelial cells and macrophages	[92]
11	Latex nanomaterial	Induction of fibrinogen, MCP-1 etc	[124]
12	Cerium oxide	Inhibition of ROS	[295]

the main properties to be considered are size, agglomeration state, and chirality. The exposure to nanomaterials affects the cytoskeleton, DNA repair machinery, cell signaling, and production of cytokines and chemokines, and increases the risk of inflammation. Due to the slow progressing effect of airborne and engineered nanomaterials, its immunotoxicity on hyper susceptible subjects especially those with immune-mediated pulmonary inflammation has not been fully studied. In addition, some studies showed that nanomaterials aggravate the effects of pre-existing pathological conditions.

4. NANOMATERIAL MEDIATED OXIDATIVE STRESS, INFLAMMATION AND GENOTOXICITY

The applications of nanomaterials in the field of medicine is rapidly increasing, making the study of inflammatory responses associated with nanomaterials a must. It is important to determine and characterize the nanomaterials mediated inflammatory reactions to further develop and implement nanotechnology. To date, the mechanism in which the nanomaterials induce pro-inflammatory reactions is still not clear. The accumulation of nanomaterials in the body leads to the generation of free radical oxygen species which cause inflammation and consequently cytotoxicity.¹⁰ The proposed mechanism is that nanomaterials generate reactive oxygen species that regulate the intracellular concentration of calcium, activate transcription factors, and induce the transcription of cytokines.⁸⁶ The cellular mechanisms associated with nanomaterials mediated inflammatory responses are presented in brief and simplified manner as below.

4.1. Oxidative Stress

Nanomaterials, along with fullerenes, are able to generate reactive oxygen species.⁷⁶ These oxygen species affect the signaling pathways of the cell, peroxidize the cellular lipids, alter proteins, disrupts DNA, and moderate the gene transcription (See Fig. 2-Demonstrating the nanomaterial induced alteration of autophagy signaling Pathways).⁸⁷⁻⁸⁹ In the presence of free radicals and oxidants, reactive oxygen species are generated on the surface of nanomaterial and cause oxidative damage.^{86,90} Nanoparticles of transitional metals are best example for this. They are oxidized to generate reactive hydrogen peroxides which form hydroxyl radicals. These hydroxyl radicals are extremely reactive and can attack key cellular pathways.^{91,92} Ultrafine nanoparticles can enter the mitochondria and cause oxidative stress.⁹³⁻⁹⁵ The phagocytosis of nanomaterials activates neutrophils and macrophages, which leads to the generation of reactive oxygen and nitrogen species.⁹¹ According to the research, the amount of reactive species generated is directly correlated with the size of the surface area of the nanomaterials.⁹⁵

4.2. Inflammatory Mediators of Stress

The accumulation of nanomaterials has shown to trigger pro-inflammatory responses leading to oxidative stress. The extent and severity of these inflammatory responses is dependent on the characteristic properties of the nanomaterials such as its type and size.⁹¹ The oxidative stress caused by the nanomaterials is mediated through intracellular chemical messengers such as cytokines in order to alert the immune system.⁹⁶ It is important to note, however, that some types of nanomaterials are capable of causing mitochondrial damage and consequently death without triggering inflammatory responses.^{94,97}

4.3. Antioxidants

Antioxidants are released by the cells as a defense mechanism in response to low levels of oxidative stress.^{68,91,98} The antioxidants inhibit the production of the reactive oxygen species by preventing the oxidants from binding to the free radicals. For example, ferritin is induced upon oxidative stress by hemeoxygenase, an antioxidant enzyme, to inhibit the oxidation of iron and consequently prevent the generation of reactive hydrogen peroxide and hydroxyl radicals.⁹¹ In addition, the antioxidants modify the surface properties of nanomaterials, rendering it less toxic. For example, *N*-acetylcysteine (NAC) is a thiol antioxidant which neutralizes the redox organic chemicals present on the surface of ultrafine nanoparticles and as a result inhibits the production of hydrogen peroxide.⁹⁴ When the antioxidants fail to eliminate the oxidative stress, proinflammatory and cytotoxic responses are activated.⁹⁴

4.4. DNA Damage

The generated reactive oxygen species are capable of overcoming the antioxidants released by the cells in response to the oxidative stress. Thus, these reactive species can persist and damage key cellular components such as the DNA.^{91,99,100} For example, the reactive oxygen species can oxidize the histones and cause the nucleosomes to disintegrate, making the DNA more prone to alterations and damage.⁹⁸ Therefore, nanomaterials (nanoparticles and fullerenes) can be considered genotoxic to humans.^{101,102}

5. INDUCTION OF DIFFERENT INFLAMMATORY REACTIONS

Studies have shown that different category of nanomaterials can induce different inflammatory reactions.¹⁰³⁻¹⁰⁶ For example, single wall nanomaterials based on carbon have the potential of inducing a dose-dependent epithelioid granuloma and interstitial inflammation in the lungs.^{98,99} In addition, as stated above, nanomaterials have the potential to induce pro-inflammatory reactions.^{76-78,86} Moreover, the route of entry of nanomaterials plays a role in the induced inflammatory reaction. Therefore, studies using animal models should deliver the nanoparticles to its test subjects through inhalation to achieve an accurate

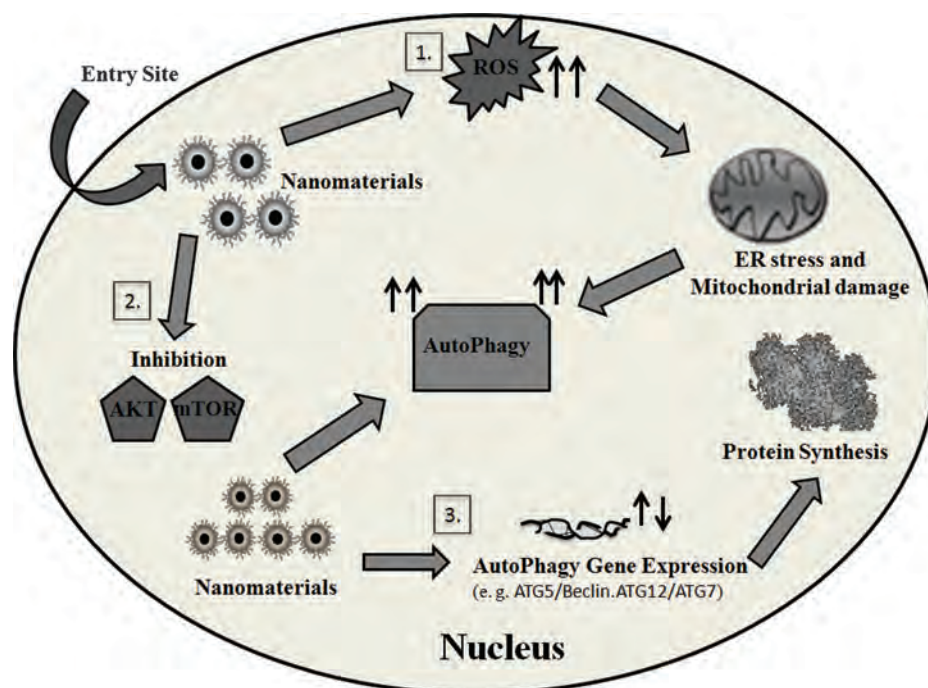


Figure 2. This figure is demonstrating the nanomaterial induced alteration of autophagy signaling pathways which includes the induction of oxidative stress-dependent signaling (1) Suppression of Akt-mTOR signaling (2) Alteration of autophagy related gene expression and further protein synthesis.

assessment of the effects of nanomaterials and that could be able to extrapolate the results to humans. In addition, studies have shown that exposure to nanomaterials increases the threat of lung inflammation. In the lungs, nanomaterials can increase vascular permeability induced by lipopolysaccharide (LPS) and expressions of cytokines such as interleukin (IL)-1 beta, macrophage chemo attractant protein (MCP)-1, and keratinocytes chemo attractant (KC). The presence of nanoparticles (<50 nm) and LPS was shown to result in an increase in the circulatory levels of MCP-1, fibrinogen, IL-1 beta, and KC. In addition, studies indicated that the inflammatory reaction is size dependent, where smaller nanoparticles exacerbated inflammation causing systemic inflammation and coagulatory disturbance.^{76, 109} Moreover, studies on single wall and multi wall nanotubes indicated that these tubes can cause lung inflammation and lead to the expression of cytokines during the pro-inflammatory period. However, there was no evidence to suggest that these nanotubes could work in a synergistic manner to aggravate LPS-induced inflammation.

In contrast, studies on silver-based nanoparticles showed that silver nanoparticles reduces the risk of inflammation and can be used as an inflammatory therapeutic agent. In a recent study, the effects of silver nanoparticles on allergic inflammation were studied by performing an intraperitoneal injection with ovalbumin (OVA) and aluminum hydroxide in BALB/C mice and monitoring the nasal symptoms, levels of serum OVA-specific IgE, interleukin (IL)-4, IL-10, and interferon (INF)- γ secretions.

The results showed that silver nanoparticles reduced the nasal symptoms and repressed the production of OVA-specific IL-4, IL-10 and IgE, without affecting the levels of INF- γ secretions.^{109, 111}

Studies were also conducted to determine the potential effects of silica, titanium, and carbon nanotubes (CNTs) on fibroblasts, macrophages/monocytes, and *T* cells (see Tables II and III). The stimulation by the CNTs caused a boost in the levels of IL-8 and centralization of macrophages/monocytes, while the stimulation by silica caused a raise in the levels of IL-1 α and IL-1 β , and an increase in the gene expression of fibroblasts.¹¹² On the other hand, the stimulation by titanium nanoparticles did not result in any significant changes. These results show that CNTs and silica have a pro-inflammatory and/or a pro-fibrotic effect on macrophages/monocytes, *T* cells and fibroblasts.^{92, 101, 113–115}

6. NANOMATERIALS AND LUNG FUNCTION

There are several lung diseases associated with inhalation of nanomaterials. Example of lung diseases associated with nanomaterials includes bronchitis, emphysema, asthma, chronic obstructive pulmonary diseases, pneumonia, and many other problems.^{58, 59, 116–118} Some lung disease particularly bronchitis and asthma are directly linked with uptake of nanomaterials. After inhalation they can be deposited along the respiratory pathway which has airways that transport air combined with nanomaterials into the body. If there is any damage or broken surface in the respiratory pathway nanomaterials penetrate that part and

causes various lung disease.^{58–62} Nanomaterials are tough inducer of oxidative stress in macrophages and epithelial cells lining the respiratory tract. These particles affect various signaling molecules and pathways such as NF- κ B, MAP kinase and AP-1 besides promoting the production of oxygen free radicals.^{53, 54, 119, 120} This leads to disease such as COPD, which is one of the representatives chronic inflammatory respiratory tract diseases.^{118, 121–123} In one study, murine model of albumin-induced asthma has revealed that the inflammatory responses and the synthesis of immunoglobulins were augmented by nanomaterials in the respiratory tract.^{124, 125} The inhalation of nanomaterials reduces the capacity of the lungs to function properly and increases the risk of death from lung and heart failures. For example, iron nano-particles were shown to induce inflammation and cellular damage upon contact with the skin.^{126, 127} The individuals who are at risk are mainly workers producing or utilizing nano-materials such as single-walled nanotubes (SWNTs) and consumers using end products that contain nanomaterials.¹²⁸ Though nanomaterials can be toxic and damaging, its use is common in many areas of the industry. For example, carbon nanoparticles that use metals as catalysts can accumulate in large quantities and become toxic. The toxicity can be attributed to either the unique carbon structure of the nanoparticles or to the residual levels of the metals. It was reported that these carbon nanoparticles can cause skin irritation and the associated metals can cause oxidative stress by disintegrating into free radicals.

7. NANOMATERIAL INDUCED CYTOTOXICITY

Nanomaterials such as nanoparticles and nanofibers possess higher chemical and physical activities per unit weight. This peculiar property explains their application largely not only in industry but also in the field of medical and scientific research fields. The nano size particles were initially thought to be inert biologically, although many literatures have highlighted the potential toxicity and the risk of their use in various fields. Particulate matter of nanoparticles less than 10 nm is known to cause harmful health effects.^{129–131} Most of the studies, improved production of reactive oxygen species (ROS) leading to activate oxidative stress eliciting the action of proinflammatory response within the body, that is predicted to be in charge for nanomaterials toxicity (see Fig. 3-Features of nanomaterials leading to toxicity). These nano scale particles have a unique character, recognized by the high surface area, correlated with both high interfacial physical and chemical reactivity and therefore resulting in biological reactivity.¹³² Various primary cell cultures study has resulted in cell death with different types of nanomaterials depending on the size of the nanomaterials. Silica nanoparticles of size 40–80 nm can penetrate inside the cell nucleus and concentrate to discrete domains around

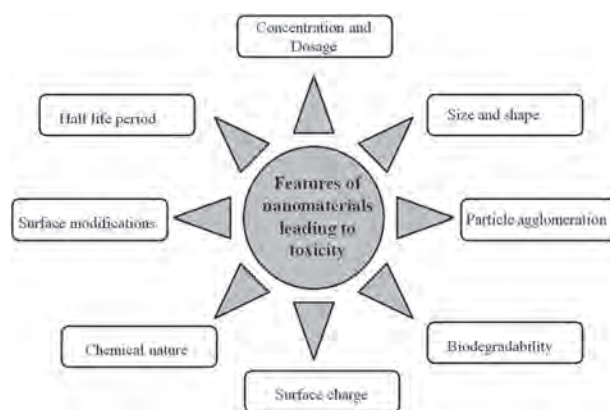


Figure 3. Features of nanomaterials leading to toxicity.

the nucleoplasm, while coarse particles get completely deposited in the cell cytoplasm.^{133, 134} Quantum dots also localize in size dependent manner in different cellular regions.¹³⁵ Gold nanocluster of size 1.4 nm intercalates within the major groove of DNA and acts as a powerful inducer in human cancer cells causing cell death.^{136–141} Recent evidence has suggested that the toxicity of nanoparticles is depended on the size of the aggregated particle and not in the size of the original nanoparticles.^{142, 143} A study done in rats, exposed to inhalation of titanium dioxide (TiO₂) particles of size 20 nm or 250 nm, the half-life time for alveolar clearance for polystyrene test particles were directly proportional to the TiO₂ particles surface area per million of macrophages.^{144–148} CNTs and metal oxide nanoparticles adsorb proteins when dispersed in culture medium, proteins including both serum albumin as well as calcium that introduce change in the biological property of the nanomaterials.^{149–153} Furthermore, the adsorption of these nanomaterials is also dependent on time and particle size.^{154–158} A study by Dutta *et al.* showed CNT adsorbed with albumin was taking part in phagocytosis of the macrophages via scavenger receptor.^{159, 160} It has also been reported that toxicity of human breast cancer cell lines increased as they were correlated with the various internalization.¹⁶¹ The increases in toxicity with cell death have been correlated with the different type of crystal shape of nanomaterials. Degradability of nanoparticles is an important criterium to be taken into study. Nanomaterials which are non-degradable can easily deposit into cells and organs, exerting harm to the nearby tissues.^{132, 162, 163} Therefore the toxicity of nanomaterials are likely to be caused by change in composition, type, shape, surface charge, size as well as surface modifications of nanoparticles, nanomaterials dosage, concentrations and time of exposure (See Fig. 4-Variou mechanism activated due to toxicity induced by nanomaterials).

Apoptosis is one type of cellular suicide that is categorized into intrinsic and extrinsic apoptosis. Intrinsic apoptosis are activated by intracellular stress conditions

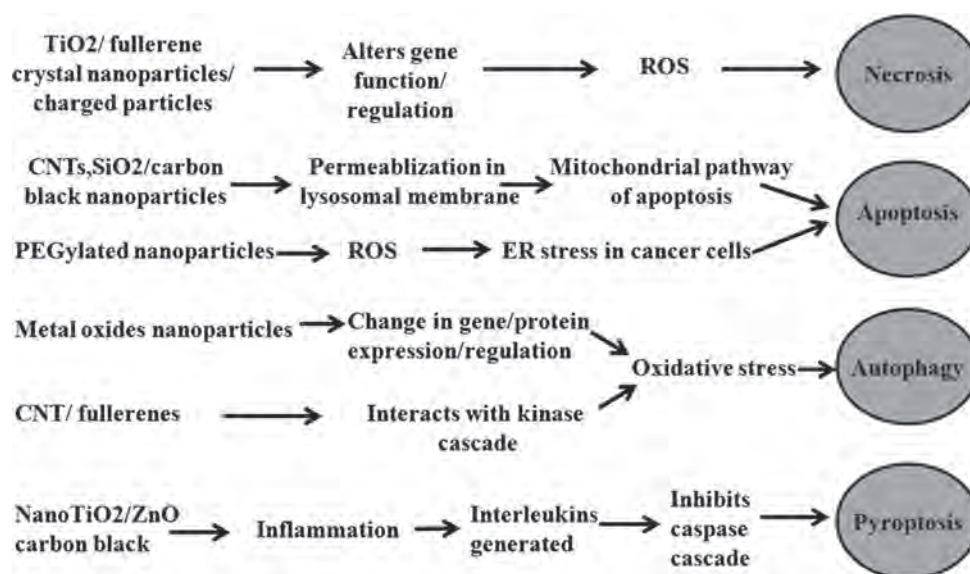


Figure 4. Various mechanism activated due to toxicity induced by nanomaterials.

including oxidative stress, DNA damage along with various other factors. This occurs when both bioenergetics and metabolic catastrophe coupled to form multiple active executioner mechanisms. This progression is further activated by caspase dependent or various self-regulating pathway mediated by MOMP linked with irreversible dissipation of mitochondrial transmembrane potential, release of mitochondrial intermembrane space proteins into cytosol as well as respiratory chain inhibition.¹⁶⁴ Extrinsic apoptosis includes cell death, caspase dependent, extracellular stress signals that are sensed and propagated by specific transmembrane receptors. Therefore apoptosis plays an elementary task in growth and maintenance of tissue homeostasis in the adult. Sarkar et al. showed that nano-copper induces intrinsic apoptosis but they also observed activation of FAS, tBID and caspase-8 signifying the association of extrinsic apoptosis.¹⁶⁵ The exposure of Nano-copper particles in dose depended manner caused oxidative stress leading to hepatic dysfunction *in vivo*. Multiwall carbon nanotubes have reported in different *in vitro* methods inducing increase in ROS, cell cycle arrest and decrease in mitochondrial membrane potential.^{166–168} Fubini et al. studies have reported silicon dioxide nanoparticles increased ROS and reactive nitrogen species thereby activating intrinsic machinery pathway.¹⁶⁹ Similarly TiO₂ nanoparticles of size range less than 100 nm resulted in apoptotic cell death through ROS-dependent up regulations of FAS and activation of Bax in normal human lung fibroblast and epithelial cell in breast.¹⁷⁰ Nanomaterials have frequently detected in lysosomes upon internalization and linked with lysosomal dysfunction. Carbon nanotubes have also resulted in inducing lysosomal membrane permeabilization and apoptotic cell death in murine macrophages and human fibroblast.^{171, 172} Comparative study between

nanomaterials and microscale gold nanoparticles verified that nanoparticles have higher potency in the induction of lysosomal membrane destabilization.^{173, 174}

Necrosis is considered as accidental form of cell death but current studies have shown its regulation in various physiological and pathological processes.¹⁷⁵ Recent studies have shown that in Chinese hamster ovary cells, the water soluble germanium nanoparticles conjugated with allylamine (4 nm) induces necrotic cell death by necrostatin-1.¹⁷⁶ Braydich et al. identified that TiO₂ nanoparticles have the mechanism of cell death in mouse keratinized cell line depending on size and crystal shape.¹⁷⁷ Studies have determined that TiO₂ nanoparticles activated necrosis in size dependent behavior. Smaller particles less than 1.4 nm were highly toxic than their larger equivalents. Though nanoparticles less than 1.4 nm causes rapid cell death by necrosis, while particles of size range 1.2 nm in diameter predominantly affect apoptosis.^{178, 179} Surface charge is a major factor for nanomaterials impact on cellular processes. Reports have verified that charged nanoparticles induces cell death through apoptosis, while particles with neutral caused necrosis.¹⁸⁰ Dose of nanoparticles and time of exposure are also other parameters involved in causing apoptosis. Nano-C60 fullerene depending on concentration caused ROS-mediated necrosis with elevated dosage or as ROS dependent autophagy with low dosage in human glioma cell cultures and rat.¹⁸¹ Silver nanoparticles concentrations elicited apoptosis with lower than the concentrations necessary for necrosis in various human fibrosarcoma, skin and testicular embryonal carcinoma cells.^{182, 183} Currently, a multilevel approach including diverse toxicity test and gene expression was used to assess the toxicity of two lanthanide based luminescent nanoparticles, completed with EDTA chelating agent.

The above study exposed that nanomaterials induced necrosis in human lymphoblast's and erythromyeloblastoids leukemia cell lines, whereas no toxicity was observed in human breast cancer cell lines. No *in vivo* effects have been found but separated components showed that the toxicity was chiefly due to EDTA.¹⁵⁵ Therefore, the information regarding character of necrosis and accurate studies are required to confirm the ways necrotic death is causing by nanomaterials.

Autophagy is a homeostasis progression concerned in the recognition and removal of damaged as well as aged proteins and organelles. In the process of autophagy, parts of cytoplasm are sequestered within characteristic autophagic vacuoles and are ultimately delivered to lysosomes for bulk degradation. These processes are in control with autophagy related gene family (ATG) and finally controlled by numerous signaling pathway.¹⁸⁴ Nanomaterials such as europium oxide, iron oxide, manganese, samarium oxide, titanium oxide, yttrium oxide, gold, iron oxide, neodymium oxide gadolinium oxide, palladium, terbium oxide fullerenes and quantum dots. Autophagy is evaluated through electron microscopy methods, immunoblot detection of ATG expression and cellular immune labeling. Nanomaterials induce autophagy through oxidative stress through accumulation of damaged protein¹⁸⁵ as well as altering gene/protein level expression and regulation and interfering with the kinase-mediated regulatory cascades.^{186–192} With response to nanomaterials, there is raise in the production of autophagic vacuoles resulting in adaptive cellular response. Nanoscale level is a major factor in eliciting the autophagic response. Quantum dots that had a propensity to aggregate to microscale particles into cells dint induce autophagy.¹⁹³ Similar reports were also reported for neodymium oxide nanoparticles with larger particles, resulting in less autophagy.¹⁹⁴ Cationic PAMAM dendrimers boosted autophagy more than anionic dendrimers *in vitro*.¹⁹⁴ Similarly carbon nanotubes with carboxylic acid group induced autophagy while those functionalized with poly-aminobenzene sulfonic acid and polyethylene glycol groups dint activate autophagy.¹⁹⁰ Nanomaterials can cause a state of dysfunctions correlated with autophagy flux, which may involve in mechanism of toxicity.^{176, 195}

Pyroptosis is known as peculiar death of macrophages infected especially by *Salmonella typhiphorium*.¹⁹⁶ Pyroptosis cells exhibit both apoptotic as well as necrotic macrophological characters. The early distinctive biochemical feature of pyroptosis is the early caspase-1 activation associated. Recent studies have reported that carbon-black nanoparticles induced cell death was recognized for generation of pyrogenic mediators such as interleukin-1B as pyroptosis caused by inhibition of caspase.¹⁶⁴ It has also been shown that nano TiO₂ and nano SiO₂ but not nano-ZnO as well as carbon nanotubes induced inflammasome activation but not cell death in human macrophages cell

line. Though caspase-1 is cleaved and IL-1B release was induced by inflammation caused by nanoparticles caused by biological effect of IL-1A.¹⁸⁸ Classification of pyroptotic as cellular response to carbon nanoparticles is novel and correlates with health impact of carbon particulates.

However further studies is required to clarify the mechanism underlying the interaction within nanomaterials and other machinery's such as necrosis, autophagy, pyroptosis and apoptosis expand the idea of implications and biological significance of this modulation.

8. BIOACCUMULATION AND CLEARANCE

Accumulation of nanomaterials can cause several diseases which we have already mentioned above.^{69, 198} Nanomaterials can cause toxicity by several mechanisms like dissolution in biological medium, catalysis or redox reaction.^{57–59} Till now most studies for toxicity was done on liver its effects on other organs are still needed.⁵⁷ There are several ways by which toxicity of nanomaterials can minimized such as surface treatment, modification and introduction of other functional groups.^{96, 199, 200} The toxicity of nanoparticles after absorption in terms of its levels of dissolved metal ions is currently an important topic for research. Few studies have been done so far to monitor the interactions of dissolved metal nanoparticles in the body. Optimal imaging represents an important tool in these studies. Gold and silver nanoparticles were shown to cause no acute toxicity.²⁰¹ The bioaccumulation of selected nanomaterials was studied. For example, ferric oxide nanoparticles showed a significant accumulation under natural conditions, where the accumulation reached its peak after six hours of exposure. The accumulation of ferric oxide was concentration dependent with a maximum uptake at concentrations of 20 mg/L and higher.²⁰² The study of multi-well carbon nanotubes, using single photon emission computed tomography and quantitative scintigraphy, showed that the degree of functionalization in these carbon nanotubes can improve or worsen its clearance out of the body. An increased degree of functionalization improves renal clearance while a decreased degree of functionalization leads to accumulation at the reticuloendothelial system.²⁰³ In another study, the fate of zinc oxide particles (20 nm and 100 nm) in organic tissues was studied using PET imaging. The zinc oxide nanoparticles were radioactively-labeled, before being orally administered to the body. The PET images revealed the locations and intensities of the labeled zinc oxide particles in the body. The labeled nanoparticles were found at different intensities in the lungs, bones, liver, bladder, gastrointestinal tract, and brain. The PET images also showed that the 100 nm zinc oxide particles were detected at higher intensities in the liver and kidney than that of the 25 nm particles. This study showed the potential of PET imaging in studying the bioaccumulation of nanoparticles in the human body.

9. REGULATION OF NANOMATERIALS DELIVERY

Health and Safety Aspects Against Nanomaterials. The field of nanotechnology is in a state of rapid growth and regulations should be continuously updated to cope with this growth. There is an urgent need to develop safety guidelines for the applications of nanomaterials.^{204–206} The nanomaterials are currently used in a wide range of products, where safety guidelines are lacking. The rapid development of nanotechnology and nanosciences has revealed many exciting features of nanomaterials in nanoscale and the chances of manipulation of these special characters to synthesize a unique machinery or products is becoming a new medical and industrial revolution. On the other hand, there are possible health effects and safety issues introduced by these unidentified physiochemical properties of such materials at nanolevel. Especially nanomaterials such as nanoparticles introduce major concern of their potential quick uptake by the biological system, indefinite distribution pathways and specific interactions with a variety of components within the biological scheme. Nanoparticles are well noticed in the air pollution field such as ultrafine particles which are less than 100 nm in Aerodynamic Equivalent Diameter (AED). These ultrafine nanoparticles are produced by natural processes such as volcanic activities, will fires. Others are derived from anthropogenic sources such as from engines and incinerators. Engineered nanoparticles are particles purposely made for certain functions with at least dimension less than 100 nm. The unique physiochemical properties of nanoparticles are not present in the parent materials. They generally have high reactivity, ultra small size, they can easily penetrate skin as well as cells, and their huge surface area to mass ratio increases the chemical activities and therefore makes them efficient catalyst. The increased chemical and biological properties are resulted especially from the engineered nanoparticles designed specifically purpose such as diagnosis or therapeutic medical uses. Nanomaterials have novel properties with two winged sword. The unique properties that allow to amazing beneficial uses also entail potentially overwhelming adverse side effects. Though many research groups have discovered toxic effects of nanomaterials, the toxicity of nanomaterials are mostly unidentified. Most significantly analytical techniques are required that permit real-time, *in situ* monitoring to optimize synthesize processes, thus reducing waste and energy costs as well providing mechanistic information.²⁰⁷ A structure-activity relationship is required to be developed to predict on biological, ecological and degradation impacts at end of particle life. Ultimately, a comprehensive understanding of nanotechnology precise risks is much crucial if small and large industries are to operate essential information on designing safe nanotechnologies.²⁰⁷ Today, there are increasing initiatives taken by regional institutions to develop guidelines

and regulations for the use of nanomaterials. For example, the European Parliament permitted the modified EU Cosmetics Directive which introduced the term “nanomaterials” into legislation.²⁰⁸ The European Parliament has also requested the development of new safety regulations that introduce an evaluation procedure for the usage of nanomaterials in consumer products. Many countries, however, do not have the resources or the capacity to develop and implement its own safety guidelines. Therefore, it is important to have an international committee that monitors and governs the safety of the usage of nanomaterials. Moreover, consumers should be aware of the health-risks associated with the use of products containing nanomaterials. To date, consumers in most countries do not have a good knowledge of the health risks associated with nanomaterials. In addition, all products containing nanomaterials should be marked as potential agents for triggering inflammation. Furthermore, clinical and epidemiological studies on the toxicity, accumulation, and clearance of nanomaterials should be conducted to determine the mechanism of action of nanomaterials inside the human body and develop proper safety guidelines for the use of nanomaterials. The results of these proposed studies should be compared and verified by different research institutions around the world.

10. CONCLUSION

Nanotechnology is the emerging and most advance technology to the modern world. ‘Nanomaterials’ been the main component of this technology, provides wide range of advantages due to their unique physiochemical properties, high reactivity, smaller size and unique composition. They are key for the revolution of medicinal industry. Despite their tremendous potential, nanomaterials exposure to body poses threat for different diseases and cellular cytotoxicity. Their cytotoxicity has not been studied extensively and most of the studies are limited to liver toxicity. These immune responses and toxicity consideration must be studied in detail in various animal models and diseases. Concluding our review we can say that nanomaterials are found to have both immune stimulatory and immune suppressive effects. To ensure the safety of our administered nanomaterials, we must specify the design of the nanomaterial and they should be tested *in vitro* using cell culture systems and in different mouse models to study their possible immunotoxicity, especially in lungs. At the present, development of new therapeutic applications will help us in identifying possible ways of decreasing negative effects of nanomaterials. Finally, with the extensive investigation on nanomaterials,^{148–325} we believe more promising results will come to us.

ABBREVIATIONS

AP-1(activator protein-1), ATF-activating transcription factor, NFκB-nuclear factor κB, MAPK-mitogen

activated protein kinase, JAK-Janus Kinase (JAK), NAC-N-acetylcysteine, LPS-lipopolysaccharide, IL-interleukin, MCP-macrophage chemo attractant protein, KC-keratinocytes chemo attractant, SWNT-single-walled nanotubes, ROS-reactive oxygen species, AED-aerodynamic equivalent diameter.

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