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OXIDATIVE STRESS: A POSSIBLE MECHANISM BEHIND NANOPARTICLE TOXICITY

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ABSRTUCT
Nanoparticle is nanometer sized materials or device or system. Nanoparticle were used for developmental new biomaterials and analytical tool kits .As well as for understanding life science because of their size dependent physical and chemical properties. Some of elastration for nanoparticle mediated toxicity and include oxidative stress inflammation genetic damage and the inhibition of cell division and cell death. Most work to death has suggested that reactive oxygen species (ROS) generation (which can be either protective or harmful) during biological interaction) and consequent oxidative stress are observed with nanoparticle toxicity. Few nanoparticles have been shown to active inflammatory cells such as macrophages neutrophils which can result in the increase production of ROS. And some nanoparticle likes gold nanoparticles have been investigated for bio-medical application targeting cancer.

INTRODUCTION

Nanotechnology.[1] is enabling technology that deals with nano-meter sized objects. It is expected that nanotechnology will be developed at several levels: materials, devices and systems. The nanomaterials level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties.[2] The growing field of nanotechnology has transformed many sectors of the industrial field with their breakthrough applications in the areas of biotechnology, electronics, medicinal drug delivery, cosmetics, material science, aerospace engineering, and biosensors. Manufactured nanomaterials (NM) have gained commercial interest in a variety of consumer products. Their novel physicochemical, thermal, and electrical properties facilitate their application in clothing, medicine, and cosmetics thereby increasing the probability for human and environmental contact with these NM.[3] Their widespread use raises concerns of their inadvertent exposure in humans and the consequent deleterious health effects. Some of the paradigms for NP mediated toxicity include oxidative stress, inflammation, genetic damage, and the inhibition of cell division and cell death.[8–11] Most work to date has suggested that ROS generation (which can be either protective or harmful during biological interactions) and consequent oxidative stress are frequently observed with NP toxicity.[3, 9] Some NP have been shown to activate inflammatory cells such as macrophages and neutrophils which can result in the increased production of ROS.

Other NP such as titanium (TiO2),Zinc oxide (ZnO),Cerium Oxide (CeO2) and Silver NP have been shown to deposit on the cellular surface or inside the subcellular organelles and induce oxidative stress. Signaling cascades that eventually resulting oxidative stress to the cell.[16] The mechanism for ROS generation is different for each NP. Many NP such as gold NP have been investigated for biomedical applications targeting cancer.

Fig:-1 List of studies describing the ROS-dependent effects of metal-based N

Nanoparticles	ROS – dependent effect	Reference
Iron Oxide	Necrosis & apoptosis in murine macrophage cells.	[4]
Copper oxide	Genotoxicity in human lung epithelial cells.	[5]
Copper oxide	Mitochondrial dysfunction ,oxidative DNA damage , cell death in A549 cell line	[6]
Cerium Oxide	Lung inflammation and alveolar macrophage apoptosis in vivo	[7]
Zinc Oxide	Cellular oxidant injury ,excitation of inflammation ,and cell death.	[8]
Zinc Oxide	Mitochondrial damage ,genotoxic and apoptotic cell effects in vitro human liver cells.	[9]

Nickel Oxide	Lipid peroxidation ,apoptosis in vivo in human epithelial airway cells	[10]
Ag—NP	JNK—mediated mitochondrial apoptosis in NIH3T3 fibroblasts.	[11]

GENERATION OF ROS

Molecular oxygen can be reduced to water. The intermediate steps of oxygen reduction are the formation of the superoxide anion radical, hydrogen peroxide and the hydroxyl radical, corresponding to the steps of reduction by one two and three electrons, respectively.

The reduction of molecular oxygen (O2) produces superoxide (O2) and is the precursor of most other reactive oxygen species

O2+e ----- O2

Dismutation of superoxide produce hydrogen peroxide (H2O2)

2H+ + O2 + O2 ---- H2O2 + O2

Hydrogen peroxide in turn may be partially reduced to hydroxyl radical (OH) or fully reduced to water:

H2O2------OH+OH

H2O2+ H2O2------ H2O+ H2O+ O2

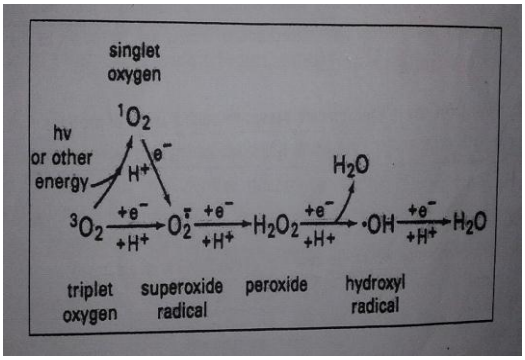

Fig:-2 ROS production pathway

Inflammatory phagocytes such as neutrophils and macrophages induce Oxidative outburst as a defense mechanism towards environmental pollutants, tumor cells, and microbes. A variety of NP including metal oxide particles induce ROS as one of the principal mechanisms of cytotoxicity.[22] NP have been reported to influence intracellular calcium concentrations, activate transcription factors, and modulate cytokine production via generation of free radicals.[12]

STRESS INDUCED BY ROS: OXIDATIVE STRESS

Oxidative stress is defined as an imbalance between oxidation and antioxidants in favor of the former leading to potential damage. Oxidants are formed as a normal product of aerobic metabolism but can be produced at elevated rates under pathophysiological conditions. Protection against their formation of ROS regarding protection against radical formation, some of the enzymes prone to generate free radical species are ingeniously designed.

a) Cytochrome oxidase, which carries out most of the cellular oxygen reduction does not release superoxide or other radicals, even though it contains iron and copper iron.

b) The three-dimensional structure of the enzyme ribonucleotide reductase keeps the radical generating character of the subunit B from spreading to the environment by forming an appropriate 'cage'.

c) The prevention of initiation of chain reactions includes the binding of metal ions, in particular iron and copper ions. Thus the metal binding proteins ferritin, transferrin, coeruloplasmin and others, e.g. metallothionein, are of central importance in the control of potential radical generating reactions.

To overcome the excess ROS response, cells can activate enzymatic and nonenzymatic antioxidant systems. During conditions of mild oxidative stress, transcriptional activation of phase II antioxidant enzymes occurs via nuclear factor (erythroid-derived 2)-like 2 (Nrf2) induction. At an intermediate level, redoxsensitive mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain enhancer of activated Bcells (NF-κB) cascades mount a proinflammatory response. However, extremely toxic levels of oxidative stress result in mitochondrial membrane damage and electron chain dysfunction leading to cell death. Some of the key factors favoring the prooxidant effects of engineered NM include either the depletion of antioxidants or the increased production of ROS.

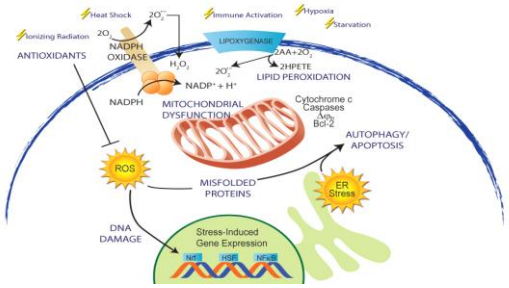

Fig:-3 oxidative stress induce by ROS

NANOPARTICLE- INDUCED OXIDATIVE STRESS

The key factors involved in NP-induced ROS include (i) prooxidant functional groups on the reactive surface of NP; (ii) active redox cycling on the surface of NP due to transition metal-based NP; and (iii) particle-cell interactions.[12, 13] From a mechanistic point of view, we discuss the sources of ROS based on the physicochemical parameters and particle-cell interactions.

Free radicals are generated from the surface of NP when both the oxidants and free radicals bound to the particle surface. Surface bound radicals such as SiO' and SiO2' present on quartz particles are responsible for the formation of ROS such as OH' and O2'.[14, 13] Ozone and

nitrogen dioxide (NO2) adsorbed on the particle surface is capable of inducing oxidative damage. Reduced particle size results in structural defects and altered electronic properties on the particle surface creating reactive groups on the NP surface.[15, 16] The electron donor or acceptor active sites interact with molecular O2 to form O2' which in turn can generate additional ROS via Fenton-type reactions. Si and Zn with identical particle size and shape lead to diverse cytotoxicity responses due to their surface properties. ZnO being more chemically active than SiO2, led to increased formation resulting in oxidative stress. Free radicals are either directly bound to the NP surface or may be generated as free entities in an aqueous suspension. Aqueous suspensions of quartz particles generate H2O2, OH, and O. Transition metals including iron (Fe), copper (Cu), chromium (Cr), vanadium (V), and silica (Si) are involved in ROS generation via mechanisms. Fenton reactions usually involve a transition metal ion that reacts with H2O2 to yield OH and an oxidized metal ion. For example, the reduction of H2O2 with ferrous iron (Fe2+) results in the formation of OH that is extremely reactive and toxic to biological molecules.[21] Cu and Fe metal NP have been reported to induce oxidative stress (and OH). In addition, some metal NP (Ar, Be, Co, and Ni) promote the activation of intercellular radical inducing system such as the MAPK and NF-κB pathways.

MECHANISM OF ROS PRODUCTION AND APOPTOSIS WITHIN METAL NANOPARTICLES

Apoptosis has been implicated as a major mechanisms of cell death caused by NP induced oxidative stress. The intrinsic pathway plays a major role in metal oxide NP induced cell death since mitochondria are one of the major terget organelles for NP induced oxidative sstress. High levels of ROS in mitochondria can result in damasge to membrane phospholipids inducing mitochondrial membrane depolarization.small proportion of electrons escapec the mitochondrial chain intracts with molecularoxygen to form O2- which than gives rise to H2O2 or reduces to the damaging OH .NP can catalyze the O2- either by blocking the ETS or accelerating electrton transfer to molecular O2.

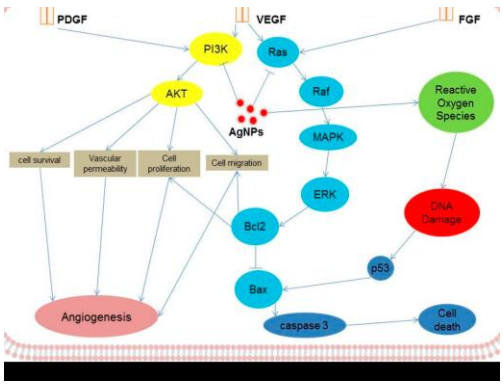

Fig-4 Possible signaling pathways of inhibition by silver nanoparticles on various angiogenic processes induced by growth factors in endothelial cells. PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; RAS, Ras is a membrane-associated guanine nucleotide-binding protein; RAF, RAF kinases are a family of three serine/threonine-specific protein kinases; MAPK, mitogen-activated protein kinases; ERK, extracellular-signal-regulated kinases; PI3K, phosphatidylinositide 3-kinases; AKT, also known as protein kinase B (PKB); Bcl-2, B-cell lymphoma 2; Bax, BCL2 associated X; p53, tumor suppressor p53.

CELLULAR SIGNALLING EFFECTED BY METAL NANOPARTICALS

1. NF -kB

The NF -kB group of protein activates genes which resposcible for defense mechanism againest cellular stress and regulates many funtions such as imflammation, immune resposce ,apoptosis cell proliferetion.Prooxidant H2O2 mediated NF-kB activation through the IkKdependent pathway .ROS such as OH ,HOCL,O2,and RNS such as ONOO- activated NF-kB via the release of IkBs resulting inthe nuclear translocation of NF-kB .ROS activates NF-kB to modulate the production of proinflammatory TNF-a, IL-8,IL-2 IL-6 from macrophages and lung epithelial cells.

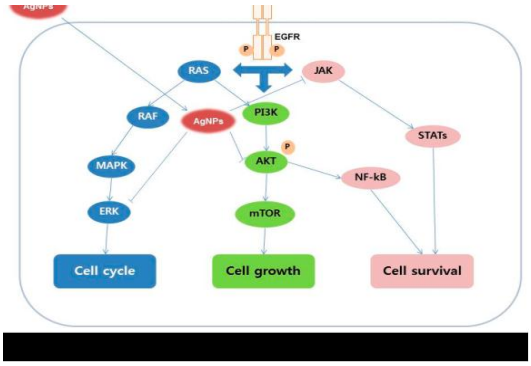

Fig- 5 Proposed possible signaling pathways of cell survival in epithelial cancerous cells. nucleotide-binding protein

RAF, RAF kinases are a family of three serine/threonine-specific protein kinases; MAPK, mitogen-activated protein kinases; ERK, extracellular-signal-regulated kinases; PI3K, phosphatidylinositide 3-kinases; AKT, also known as protein kinase B (PKB); mTOR, mechanistic target of rapamycin; JAK, Janus kinase; STATs, signal transducers and activators of transcription; NF-_B, nuclear factor-kappa B.

2. MAPK

MAP kainase are serine threonine protine kainase the control the prolliferation, gene expression, ifferentiation, mitosis,cell survival ,and apoptosis MAP kainase consist of gbrowth factor regulated extracellular signal related kainase and the stress activated MAPK,c-jun NH2

terminal kainase (JNK) and P38 MAPK .Once ROS production exceeds the capacity of antioxident proteins ,free radicals may induce oxidative modification of MAPK signaling protein (e.g.-RTK & MAP3K) ,leadind to MAPK activation ROS can inhibit and/or degrated of MAPK phosphatases .CeO2 NP trigger P38 MAPK signaling in bronchoal veolar calls.

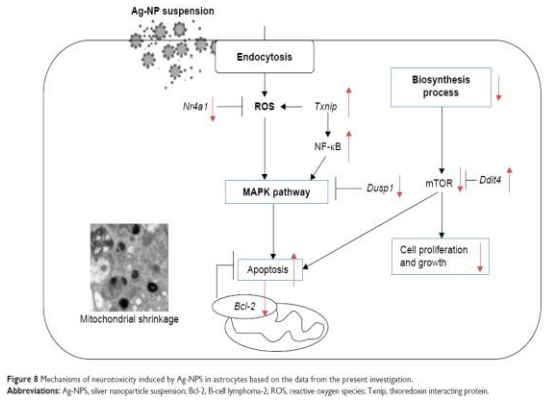

Figure 8 Mechanisms of neurotoxicity induced by Ag-NPS in astrocytes based on the data from the present investigation.
Abbreviations: Ag-NPS, silver nanoparticle suspension; Bcl-2, B-cell lymphoma-2; ROS, reactive oxygen species; Txnip, thioredoxin interacting protein.

Fig:-6 ROS activated MAPK pathway

CONCLUSION

The principal factors for NP-induced oxidative stress involve (a) the oxidative properties of the NP themselves and (b) oxidant generation upon interaction of NP with cellular material. e direct prooxidant effects of NP are attributable to their physicochemical properties including surface reactivity, particle size, surface charge, chemical composition, and the presence of transition metals. Therefore, it is necessary to ensure extensive characterization of the physicochemical properties for safer design and manufacture of NP. Whereas, ROS mediated via NP-cell interaction involve mechanisms including immune cell activation, mitochondrial respiration, and NADPH oxidase system. Given their chemical reactivity, metal-based NP induce oxidative damage to cellular macromolecules such as proteins, lipids, and DNA via Fenton-type and Haber Weiss-type reactions. The key pathophysiological outcomes of oxidative insults during metal NP exposures involve cell membrane damage, lipid peroxidation, protein denaturation, and alteration of calcium homeostasis. Metal-based NP -mediated ROS result in activation of cell signaling pathways, transcription factor activation, cytokine mediator release, and apoptosis. The persistent activation of these signaling cascades has some clinical ramfications. Redox imbalance via engineered NP exerts undesirable pathophysiological outcomes such as genotoxicity, inflammation, fibrosis, and carcinogenesis. It is of utmost importance to understand the molecular and cellular mechanisms of NP-induced oxidative stress which in turn will yield novel strategies to mitigate the toxicity of engineered NP.

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