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Effects of Nanomaterials on Oxidative Stress and Protein Oxidation in Biological System: Biochemical and Biological Aspects

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Abstract

Oxidation and reduction is a ubiquitous phenomenon reflecting the structural, functional aspects of cell, tissue, organ and organism. Primarily oxidative process in a biological system is the imprint of structural and functional integrity because of its role to maintain a state of healthy equilibrium. This homeostatic state is the result of combined and coordinated interactions between pro oxidants, antioxidants, inactivated free radicals and oxidants present in the cell. Proteins alone and in conjugated from are amongst those biomolecules which are basically devoted to cellular structural, functional, inter and intracellular communication. Electrochemical aspects of oxidation reduction are applicable to the oxidation of proteins. High energy radiations are capable to form free radicals of oxygen, when proteins are exposed to such free radicals gross modifications in amino acids and/or fragmentation of proteins occurs. Redox metabolism reflects on the functional aspects of proteome; there is every probability that any temporal and spatial fluctuations can direct the functional aspect of cell. Conditions like resistance to insulin, dysfunction of immune system and inflammatory responses are concerned with oxidative stress. Diseased conditions and senescence are parameters directly related to the declined efficiency of antioxidant system indicating oxidative stress. This in turn is capable to causes modifications in DNA, carbohydrates, proteins and lipids. In the recent past nanotechnology has attained significant importance due to its multidimensional potentials in almost all fields of life. The nanomaterials, natural as well as engineered, are sought after to solve most of the problems related to man-kind and industries. The physicochemical properties of nanomaterials are the basis of their applications in all spheres of life. In this presentation an effort is made to over view the developments in the field of nanomaterials that have taken place in the recent past and more over their impact on redox process and protein oxidation encompassing biological, biochemical, physiological, and pathological aspects in a biological system.

Keywords: Oxidative stress; Free radicals; Protein oxidation; Nanomaterials; Pathological impact; Feedback system reactive species

List of Abbreviations: AKT: Protein Kinase B; ATP: Adenosine Tri Phosphate; C60: Fullerene; Ca^{++}: Calcium Ions; CaO: Calcium Oxide; CdSe/ZnS: Cadmium Selenium and Zinc Sulphide; Cd-Te: Cadmium-Tellurium; QDs: Quantum Dots; Cd/hso: Cadmium-Human Sulfide Oxidase; DNA- Deoxyribose Nucleic Acid; Fe_3O_4 and Fe_2O_3 : Iron II, III Oxide Nanoparticles; GO: Graphene Oxide; G_0, G_1 to G_5: Generations of Dendrimers; GQD: Graphene Quantum Dot; H_2O_2: Hydrogen Peroxide; H1F-I: Histone H1protein; IL-1β: Interlukin 1β; LC3-I and LC3-II: Microtubule Associated Protein Light Chain3, Indicative of Autophagic Activity; MA: Mercaptopropionic Acid; MWCNT: Multi Walled Carbon Nanotubes; NAD- Nicotinamide Dinucleotide; NAD^+: Oxidized Nicotinamide Dinucleotide; NADH: Reduced Nicotinamide Adenine Dinucleotide; $NADP^+$: Oxidized Nicotinamide Adenine Dinucleotide Phosphate; NADPH: Reduced Nicotinamide Adenine Dinucleotide Phosphate; NO*: Reactive Nitric Oxide; NO: Nitric Oxide; NF-E_2: Transcription Factor Encoded by NFE_2 Gene; NF-KkB: Nuclear Transcription Factor-B; 2Nrf2- Nuclear factor Erythroid-Derived 2; ONOO: Peroxinitrite; ONOO*: Activated Peroxinitrite; O_2*: Reactive Oxygen; OH-1: Heme Oxygenase; p62: Nucleoporin (Protein Recognizes Toxic Cellular Waste); P13K: Phosphatidylinositol 3 kinase; P13K/ATK: Signaling Transduction Pathway; PAMAM: Polyamidoamine; QD: Quantum Dots; RNA: Ribose Nucleic Acid; RNS: Reactive Nitrogen Species; ROS: Reactive Species of Oxygen; Si: Silicon; SiO_2: Silicon Dioxide; SiO_2*: Reactive Silicon Dioxide; SiO*: Reactive silicon monoxide; SWCNT/SWNT: Single Walled Carbon Nanotubes; TiO_2: Titanium Oxide; TNF-α : Tumor Necrotic Factor α; V-Vanadium; ZnO-Zinc Oxide

Introduction

Back ground: oxidative stress and protein oxidation

Primarily oxidative process in a biological system is concerned with the retention of structural and functional integrity of cell and its organelles, it also maintains a state of equilibrium during which a combined and coordinated interactions between prooxidants, antioxidants, inactivated free radicals and oxidants are established in a cell [1]. Any form of disturbance or distortion to the redox homeostatic state results in oxidative stress in the tissue or biological system. Proteins are among the biomolecules which are subjected to redox reactions. Protein oxidation may be referred as a modification in the covalent features of a given protein, these covalent features are caused directly and/or indirectly by the reactions that are occurring due to oxidative stress [2]. The research group of Pojlak-Blazi has elaborated the risk caused due to different nanoparticles in the form of cellular oxidative stress in a biological system [3]. When proteins are exposed to free radicals of oxygen produced by high energy radiations it results in gross modifications in amino acids along with the fragmentation of proteins. When proteins are subjected to metal catalyzed oxidation very less amino acids residues undergo modifications and comparatively less number of peptide bonds exhibit cleavages [4]. The process of protein oxidation is related to aging of an individual; reactive oxygen species are the oxidants and have potential to damage most of the biomolecules like proteins, lipids, nucleic acids and carbohydrates [5].

Protein oxidation initiates collection of toxic proteins or induce apoptosis in the affected cells. Hence, it is preferable to remove them from the biological system. Such dysfunctioning proteins are eliminated by enzymatic degradation (proteolysis). When these types of remedial actions become deficient it results in accumulation of dysfunctioning proteins. Proteins are the prime target during biological oxidation and suffer more either intra and/or inter cellular damage because these are present relatively more in amount and varieties, [6]. It is opinioned that better understanding on the role of oxidative stress is likely to provide insight of the therapeutic possibilities related to different molecules along with the concerned mechanisms in the behavior of antioxidants; such molecular agents may reduce the extent of formation of reactive species and may alter the signaling path ways [7]. Glycation of proteins and activation of polyol mechanism are also having potential to enhance the oxidative stress leading to the production of reactive species. The ratio of NADH/NAD acts as a basis for catabolic activities and production of ATP while the ratio between NADPH and NAD acts as central axis for anabolic activity and regulation of redox potential [8]. The polyol path way is accomplished in two steps, in first step the glucose (excess) is reduced to sorbitol with the help of enzyme aldose reductase and $NADP^+$ while in the second step the sorbitol is converted in to glucose involving enzyme sorbitol dehydrogenase and NAD^+ [9]. There is a direct involvement of nanomaterials in electrochemistry where redox proteins, immobilized enzymes like glucose oxidase, horseradish peroxide, cytochrome P450, hemoglobin, glutamate dehydrogenase and lactate dehydrogenase, can be used and such nanomaterials act as electrochemical enzyme biosensor [10].

Formation and biochemical impacts of reactive species

Reactive species are formed as a result of redox reactions and under normal conditions maintain redox homeostasis and energy balance within the ambient cellular environment of a biological system. These endogenous and exogenous small molecules play very effective role in various cellular functions and specifically during inter and intracellular signaling and chemotaxis. Biomolecules can be modified by oxidation-reduction reactions in time based (temporal) and sequence-specific manner to adjust their three dimensional structural aspect to ensure their specific normal function; this fact can be illustrated by the structure of enzyme crystal revealing the formation of lysozyme (muramidase – glycoside hydrolases) from hen egg white. It involved 4-disulfide bonds when 8 cysteine side-chains undergoes oxidation and forms a stable structure – lysozyme, [11,12]. Lysozyme is one of the components of innate immune system, it attacks peptidoglycans (murein) specifically present in gram positive bacteria, [12].

ROS are produced in a given biological system under hypertension and injury trauma; traumatic injury to spinal cord triggered many effects such as oxidative stress, compromised energy metabolism influencing biochemical and pathological changes, generation of free radicals and lipid peroxidation in spinal cord; these effects depend on the stages or degree of injury [13]. If reactive species are handled in a sophisticated manner then these can be utilized to motivate essential cellular physiological processes. Reactive species are liable to act as signaling molecules under initial stages of redox reaction; these seemingly absurd biological small molecules play an essential role in sustaining integrity and fitness of biological system [14,15]. The reactive species should be used as markers for oxidative process and ROS signaling pathways under normal and other conditions which prevail either within or outside the biological system [16]. H_2O_2 functions as second messenger and it mediates intracellular signal transduction via chemo-selective oxidation of cysteine residues in signaling proteins; thus, there is a very good possibility of H_2O_2, a signal mediating product may be exploited to seek understanding the mechanistic insight to illustrate the mechanism of functioning of those proteins in which H_2O_2 plays a regulatory role [16]. ROS are the group of small molecules; these are formed perpetually, transformed and consumed in a biological system as a result of aerobic mode of life [17].

Current findings indicate that ROS can cause favorable conditions that enhance physiological and fitness levels in a biological system. Under such conditions ROS molecules have ability to act as signals to contribute towards the fitness level in a given biological system. Chemical aspects of ROS are dependent on their identity, concentration, ambient environment and these parameters decide their biological responses at molecular level and organismal strata [17]. Since, stem cells proliferation, chemotaxis, neurogenesis, circadian rhythm etc, these functions are based on the signals released by reactive species and specific redox modifications of protein molecules that are directly involved in cytoskeletal rearrangement of the cell. Perturbation of normal redox state contributes to the production of peroxide and free radicals that affects the cell components like DNA, proteins and lipids; ZnO nanoparticles possess the ability to induce the nitric oxide synthase activity and initiate phagocytes to produce large amount of genotoxic RNA including nitric oxide (NO*) and highly reactive peroxinitrite ($ONOO^{*-}$); peroxinitrite is formed by the interaction between NO* and O_2 resulting in fragmentation of DNA, protein oxidation and/or oxidation consequently contributing to particle induced lung injury [18]. Nitric oxide exhibits affinity for heme iron of hemoglobin under influence of CaO nanoparticles, this feature can be exploited to reveal the electrochemical role of hemoglobin. Nitric oxide penetrates the pocket of hemoglobin and disturbs the coordinated bond between heme and oxygen forming met-hemoglobin and gets immobilized at carbon-electron, the surface of carbon-electron induces reduction of oxygen [19].

Iron oxide nanoparticles caused mediate cytotoxicity via P13K/AKT path way; in response to the exposure of iron oxide resulted in enhanced level of malondialdehyde protein carboxyl contents in the experimental sets of mice [20]. When cysteine thiol side chains were oxidized by H_2O_2 it resulted in protein sulfenylation, the product formed was found to be important in the transduction of signal. Cysteine is present in protein in very low percentage; cysteine is considered to be an amino acid that has many biological applications [21]. Cysteine undergoes many post-translational changes due to the presence of thiol side chain; this thiol side chain plays an effective role in regulating structure and functions of proteins. When ROS oxidizes to cysteine sulfenic acid in a biological system either H_2O_2 or RNS (reactive nitrogen species) like peroxinitrite ($ONOO^-$) are formed [21]. This step is reversible and intrinsic in nature. Sulfenic acid has an ability to accomplish varied transformations; one of them is the formation of 'Disulfide Bridge'. This modification is

responsible for regulation of protein folding, oligomerization and S-glutathionylation. Polypeptide, a back bone of protein, may react with sulfenic acid and sulfenamide is formed. Briefly, all these modifications are likely to result in the structural and functional variations in proteins [21].

Overall impact of nanomaterials on oxidative stress: biochemical and biologial aspects

In the recent past profound overall multidimensional impact of nanomaterials and nanotechnology in almost all spheres of life, is very evident. It has been witnessed that when any aspect of scientific achievement has influenced majority of the human life it leaves some of its negative or derogative impact too, these are the points to be investigated in order to maintain a balance between the beneficial and harmful aspects of any technology. In this presentation an evaluation on overall influence of nanomaterials specifically carbon nanomaterials, quantum dots and dendrimers, in relation to some biochemical, biological effects have been envisaged. When proteins are subjected to metal catalyzed oxidation very less amino acid residues undergo modifications and comparatively less number of peptide bonds exhibit cleavage; the products of this interaction react with metal-binding sites located on the protein resulting in the formation of reactive oxygen species [22]. Electrochemical aspect of oxidation reduction is also applicable to the oxidation of proteins these features are

(i) location of peroxidant functional group on the reactive surface of nanomaterials,

(ii) occurrence of reactive redox-cycle on the surface of nanoparticles made from transitional metals,

(iii) inter reactive ability of nanoparticles with cell and cell organelles,

(iv) physicochemical parameters of nanomaterials and their reactive affinity towards the cell [23,24].

There are some specific features present on the surface of nanoparticles which readily induce oxidation while some nanoparticles enhance the oxidative system of cell to generate reactive species of oxygen and nitrogen involving mitochondria, NADPH-oxidase enzymes and primary inflammation by the particles and generation of ROS and RNS because of inflammation [25]. Once nanoparticles access mitochondria could stimulate generation of ROS by impairing electron transport chain; these cause damage to structure by activating NADPH like enzyme and depolarizing the membrane of mitochondria [26]. Transition metals such as iron, copper, V (vanadium) and silicon undergo Haber-Weiss and Fenton type of reactions resulting in the production of ROS. SiO* and Si_2O* were found to be present on the surface of quantum dots. These reactive species have the capacity to form OH* and O* and ROS, in the presence of ozone and/or NO_2^- then these could induce oxidative damage in the cell [24]. Nano-sized nanoparticles exhibit alteration in their electronic properties related to their surface these resulted in the conditions that create reactive groups on the surface of nanoparticles; these nanoparticles ably undergo 'Fenton–type' of reaction [27]. This fact is supported by the similar sized nanoparticles of Zn and Si when interacting with cells result in varied degree of cytotoxicity; zinc nanoparticles being more active chemically in comparison to SiO_2 caused relatively more formation of O_2^{*-}, thus created higher degree of oxidative stress in comparison to SiO_2. Further, free radicals bounded to the surface of nanoparticles either directly or could produce free entities in aqueous suspension [27]. Some of the nanomaterials like quantum dots and others release metal ions and this feature was capable to increase ROS response; quantum dots in aqueous suspension form exhibit an ability to generate H_2O_2, OH*and $^1O_2^-$. Silver nanoparticles result in the formation of protein carbonyl contents in about 3h post treatment while cytoprotective enzymes like 'Heme oxygenase-1' (OH-1); (this enzyme is found to be antioxidant in nature and protect cell during pathological conditions) [28]. This enzyme regulated those reactions which limit the degradation of heme) were detected at 8 h post administration in response to specific range of silver nanoparticles (5-20µg/ml) [28].

Recently, there have been reports concerning the effects of nanomaterials and cell signaling. Metals like iron, copper, chromium, vanadium etc exhibit redox cycling; metals like cadmium, mercury, lead and nickel deplete glutathione sulfhydryl groups attached to proteins cause the production of reactive oxygen species and hydroxyl radical. During these interactions signaling system of the cell was also involved, [27]. Signaling pathways such as H1F-1, NF-KkB, P13k, and mitogen activated protein kinase were affected when the redox homeostasis was altered; cellular functions like cell division, inflammation, growth, apoptosis, survival, metastasis etc. have been reported to be adversely influenced with varying degree of functionality. The above mentioned cellular signaling pathways were found to be

responsible for such cellular functions. Further, the specific balance between normal status of equilibrium and proinflammatory status was established to restore redox homeostasis [27].

Whenever fibrotic pathogenic conditions arose proinflammatory process got activated with the help of TNF-α, IL-1β as signaling mediators. The affected cells exhibit the tendency to counteract disturbed oxidative stress/redox equilibrium; this was accomplished by enhancing the activity of kinase of cytokines like interleukins and TNF-α and reducing the activity of phosphorylation, this counter action is involved during the cellular functioning and responses such as mitogenesis, cell adhesion, planned cellular death and cancerous changes [27,29]. The protein phosphorylation primarily acts as regulatory factor. Such factors are closely related to ROS responses. Nanoparticles which have same size and magnitude similar to protein molecules have the ability to interfere with signaling process of cell. Further, the interaction between protein and nanoparticles is through chaperones like activity or through changing the conformation of protein. Wagner and his associates proposed that although α-helical coiled coil folding motif decides the design of the peptide but parameters like pH can influence the changes in such cases and β-sheet formation takes place depending on the pH [30]. CuO, Fe_3O_4, Fe_2O_3, TiO_2, Ag nanoparticles caused oxidative stress and also affect adversely the functions of mitochondria [31].

The interactions related to free radicals have been regulated by inducible antioxidant system at cellular level; when these radicals are found in low concentration, these were not hazardous and participated in the signaling and homeostasis at physiological level but when these are in higher concentration induced oxidative stress, this in turn enhances the damage of biomolecules and their accumulation in cell, tissue/biosystem [31]. During aging process and pathogenesis an increased extracellular and intracellular status of oxidative stress was observed. This disturbed balance could act as a parameter to affect the responses of cells in normal condition, oxidative stressed condition and repair mechanism. This status overall either arrests the growth (transient), leads to premature senescence or death. Some of the responses were likely to be tumor suppressing like apoptosis while others have potential to cause damage, accumulation but these derogative responses retained the ability to proliferate, arresting transient growth, cause inflammation, senescence, necrosis, in short, these have potential to initiate, promote and sustain tumorogenic tissue [32].

Carbon nanomaterials

There are varied forms of carbon nanomaterials and these elicit their impact of protein oxidation and or biological system. The physical (structural aspects) and physicochemical features are one of the parameters which play role in their interaction in biosystem and affect protein oxidation. Single walled carbon nanotubes (SWCNTs) induce oxidative stress and activate nuclear transcription factor (NFkB) in a biological system. Kamat and his associates observed that fullerene (C_{60}) caused damage to membrane by inducing oxidative stress. They used rat liver microsomes as an experimental model and exposed it to UV and visible wave lengths [33]. Oxidative damage caused by the nanomaterials under study was expressed as lipid peroxidation, damage to protein and membrane bound enzymes. This interaction was found to be time and concentration dependant. The research group of Manna observed dose dependant elevation in fluorescence reflecting formation of ROS in human keratinocytes when exposed to SWCNT, the oxidative stress on cells lead to the decline in cell proliferation and/or death of cell by inducing apoptosis or necrosis [34].

Tantra and Cumpos have observed that nanotubes can behave like asbestos particles that cause diseases and toxicity [35]. The research group of Pacuarari noted the generation of ROS, death of cells, increased DNA damage, in normal and malignant human mesothelial cells and this interaction was observed to be dose dependence [36]. Buckminster fullerenes (C60) in the form of water suspension (nC60) have potential to form ROS [37]. (C_{60}) induces ROS independent oxidative stress in microbes reflecting on the protein oxidation. They further proposed that this form of carbon nanomaterials establish direct contact between nanomaterial and the bacterial cell thereafter reduce the membrane potential on the bacterial cell membrane and also interrupts the respiration in the affected cell. This mechanism is different from those nanomaterials that exhibit antimicrobial activity. SWCNTs penetrate easily in the skin because of their physical features and exhibit dose dependant activation of NFkB when murine epidermal cells and SKH-1 mice (hairless mouse) were exposed topically to 40μg/mouse, 80μg/mouse and 160μg/mouse of SWCNT [38]; this exposure also resulted in oxidative stress, depletion of glutathione, oxidation of proteins (thiols and carbonyls), increased myelo-

peroxidase activity, an increase in dermal cells, thickening of skin due to aggregation of mast cells and polymorphonuclear leukocytes. The SWCNT resulted in the induction of free radicals, oxidative stress and inflammation. Graphene and nanomaterials based on it are suitable for the biological applications; these act as efficient modes for delivering drugs, related to anti-inflammation, water soluble anticancer drugs and exhibit higher capacity for loading of drugs [39].

Graphene materials are produced in charcoal roasted meat and plant charcoal; it is in this form of graphene oxide and nitrogen is doped due to pyrolysis of protein in air. Graphene is not-toxic to human and even to infants [40]. Graphene oxide (GO) and oxidized carbon nanotubes were found to be adhering to cell membrane of *Chlorella vulgaris* but the rate of uptake of SWCNT was twice than the graphene oxide [41]. SWCNT reduced the membrane potential of mitochondrial membrane and viability of cells. Exposure of cell to SWCNT elevated the starch grains, formation of lysosomes. Both, graphene oxide and SWCNT increased reactive species formation but SWCNT exhibited relatively more intensity. Both of these nanomaterials were also found to inhibit the metabolism of fatty acids and amino acids. Metabolism of alkanes, lysine, octadecadienoic acid and valine appeared to be related to the reactive species formation hence, can be used as biomarkers for ROS; graphene is very suitable to be used for biomedical applications like diagnostics, cancer therapy and drug delivery agents [42]. But the group of Jaroze reported on the cytotoxic effects such as cellular viability, morphology and membrane integrity are affected, even damage of DNA, gene expression and induction of ROS generation have been observed. These researchers have applied these features to the human cancer cells and elaborated the role of ROS, fragmentation and condensation of DNA and damage of cell membrane, reduction of mitochondrial cell membrane potential, increased Ca^{++} and cell death in cancer cells on exposure to graphene.

Quantum dots

Quantum dots are being exploited in various fields specifically in nanomedicine but the risk of their being toxic lingers and it needs due consideration. Quantum dots are identical in their interaction in biosystem particularly the engineered quantum dots [43]; quantum dots do possess some inherent physicochemical features which regulate the absorption, distribution, metabolism, clearance and their toxic impacts in and on any biological system, the environmental conditions have their role in such interactions. The physicochemical properties such as size, charge, concentration, biological activity of the respective outer coating, play a prominent role that govern the oxidative, photolytic and mechanical stability outside and inside the biosystem. Classical CdSe/ZnS quantum dots and novel carbon dots produce free radicals of oxygen and singlet of oxygen in vitro.

The observations revealed that when Carbon dots or quantum dots generated ROS and acted as prooxidants when subjected to external radiation, these nanomaterials were found to scavenge free radicals generated chemically during their interaction with azo-compounds. Carbon dots and quantum dots exhibit dual features may be exploited for photodynamic, photocatalytic and as antioxidant agents [44].

There is a greater probability size of quantum dots responsible for their toxicity because quantum dots get localized within cell, nucleus and with possible damage of DNA. The core component and the coating with their specific charge also have their role in toxicity [45]. It has been observed that cadmium tellurium quantum dots having mercaptopropionic acid (MA) coating inhibited the cellular functions of human breast cancer; low concentrations (5μg/ml and 10μg/ml) increased the level of ROS within 30 minutes. This increased ROS level reduced the cell viability, caused blebbing on the membrane of the cell, reduced cytochrome and affected the membrane of mitochondria and its function. Graphene quantum dots electrochemically and irradiating blue light (470nm 1W), they observed that these quantum dots were capable to generate reactive oxygen species and also singlet of oxygen specifically [46].

During the experiments conducted by Markovic et al, human glioma cells U251 were killed because of the oxidative stress caused. When these QDs were excited with light morphological and/or biochemical parameters that are related to apoptosis and autophagy were noticed. They deduced that parameters like externalization of phosphotidyl serine, fragmentation of DNA and activation of caspases indicated the occurring of apoptosis while autophagy was represented by the formation of autophagic vesicles, change in LC3-I – LC3-II and degradation of p62; these features are related to autophagy. Further, it was seen that grapheme-QDs induced the partial abrogation of an essential LC3B protein causing cytotoxicity during photodynamic activity.

Short term exposure of Si/SiO QDs reduced the protein thiol groups while prolonged exposure (7 days) resulted in oxidation of protein thiol group, the protein carbonyl tried to maintain a threshold level [47]. These quantum dots changed the functioning of antioxidant enzymes. Cadmium- tellurium quantum dots induced oxidative stress, destabilized oxidative defiance, and activated protein kinase; all these interactions resulted in apoptosis that involved extrinsic and intrinsic pathways [48]. These Cd-Te-QDs depleted reduced glutathione and the ratio between reduced and oxidized glutathione and enhanced the effectiveness of NF-E2 related factor 2Nrf2 activation. When quantum dots enclosed in polyelectrolyte were applied on to indium tin oxide quantum dots a favorable surface suitable for binding to enzyme was formed that promotes the transfer of electron [49]. Their experimentation exhibited enhanced redox potential of electron transfer domain in presence of CdS/hso modified QDs.

Dendrimers

Dendrimers are branched, synthetic polymers having specific controlled architectural nanomaterials and are suitably applied to the biomedical field. The dendrimers are easily and precisely manipulated with respect to molecular weight and chemical composition hence can be tuned with respect to biocompatibility and pharmacokinetics. Due to their specifically designed architecture these are quite suitable as drug carriers, tissue repair scaffolds, optical oxygen sensors; such multifaceted nanomaterials should be investigated for their toxic and other derogative effects in addition to their beneficial aspects [50]. Dendrimer generations G-4, G-5 and G-6 produced intracellular ROS, genotoxicity and apoptosis in hepatocellular carcinoma cells. This interaction was found to be dose and time dependant in nature; at lower concentrations the generation of ROS was dose dependant and exhibited linear pattern but this linear response was disrupted at higher concentrations [51]; dendrimers are monodispersed, e.g., diazeniumdiolates [52].

Polypropylenimine dendrimers are related to release nitric oxide resulting in the formation of diazeniumdiolates involving different amines, these may induce oxidative stress. Further, the generation-4 poly (amidoamine) dendrimers having nitrosothio exterior had the ability to inhibit thrombin mediated platelet aggregation. El-Sigeny and Abou-Taleb have fabricated different generations of (G-0 to G-5) of polyamidoamine (PAMAM) by using co-precipitation method and changing it with tris (hydroxymethylamino) methane, using as coating of dendrimer on Fe_3O_4 nanoparticles [53]. The polyamidoamine dendrimers (coated Fe_3O_4 nanoparticles) composite exhibited antimicrobial activity probably causing oxidative stress among the affected microbes. Poly-amidoamine dendrimers induce the formation of ROS and autophagic flux in neural cells [26]. When ROS generation and autophagy both were suppressed there was a check on the cytotoxicity among neural cells.

Conclusion and Prospectus

Under normal conditions oxidative process in a biological system helps to sustain the structural and functional integrity of cell and its organelles in a biological system. Mostly protein oxidation may be understood or investigated by tyrosine nitration, cysteine oxidation and carbonylation processes. ROS or any reactive species acts as intermediates and are potential causes of oxidative stress. During the tyrosine nitration tyrosine undergoes nitration due to reactive species of nitrogen like peroxinitrite and nitrogen-di-oxide resulting in the formation of nitrotyrosine. Cysteine is redox-sensitive towards protein and this interaction may be considered as the regulatory and functional aspects of redox sensitivity of proteins. With references to proteins during carbonylation the amino acids present in the side chain in protein are modified in to carbonyl derivatives. Reactive oxygen species are the oxidants and have potential to damage most of the biomolecules like proteins, lipids, nucleic acids and carbohydrates. Superoxide anion (O^-_2), H_2O_2, hydroxyl radical (OH), NO and peroxinitrite, $ONOO^-$ are some of the most common reactive species and these are generated under various metabolic conditions or due to stressed conditions.

The reactive species can be exploited to screen the oxidants, oxidative process and ROS signaling pathways under normal and other conditions which prevail either within or outside the biological system. H_2O_2 functions as second messenger. The damage caused can be non-specific and wide spread or both. In non-specific oxidation, hydroperoxides are involved that enhance oxidation and chain reaction affecting proteins and related molecules. These proteins can be used as biomarkers to evaluate protein oxidation both *in vivo* and *in vitro* depending on the oxidant used or availability during the process. In most cases the damage caused to proteins is likely to be non-repairable and results are derogative such as loss of enzymatic affectivity, structural and signaling inability (partial or total). Aspects like

proteomics and unbiased screening should be used to elaborate the redox sensing biomolecules coupled with ROS. Magnetic nanoparticles formulated for clinical applications are aimed to be biocompatible, and should be water based colloids for their appropriate utility. It is envisaged that studies on bio-nano-interface may direct the methodology of synthesis of nanomaterials so that size, shape, physicochemical aspects of surface of nanomaterials should match the appropriate intrinsic physicochemical parameters leading to ideal biomedical appliances. Further, biodistribution, duration in the system of nanomaterials and their rate of clearance from biosystem, are quite essential. Classical integrated behavior with integrated nanoimpact index is the parameter that can be used as early warning signals to assess risk boundaries. Multiple Reaction Monitoring technique is probably suitable to analyze sulfonic and sulfonic acid-oxidation, the normal products of chronic oxidation stress and can be a plausible tool in understanding the implication of thiol oxidation as a protein regulator in case of aging and age related diseases.

Electrochemical aspect of oxidation reduction is also applicable to the oxidation of proteins and can be of analytical significance at least as biosensors and clinical estimations. When nanomaterials are taken up by biosystem biomolecules like DNA, proteins, cell membrane and cytoskeleton undergo conformational changes. Modifications in the cell membrane and cytoskeleton reflect changes in cellular elasticity, motility, ability of adherence and invasion. Modifications in the cell membrane and cytoskeleton reflect the changes in cellular elasticity, motility, ability of adherence and invasion, Visualization techniques are likely to provide relatively better understanding of the nanomaterials being investigated; some of the common techniques are fluorescence, transmission electron microscopy, light and electron microscopic autoradiography, fluorescence life time imaging and linear unimixing, supper resolution structured illumination, Raman microspectroscopy and X-ray microscopy. Even though lot of investigation has been done in the recent past but still there does greater need for better understanding of overall mechanism of various aspects of protein oxidation with reference to normal and varied pathogenic situations in biological system.

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