Preface

Nanotechnology advancement has developed a plethora of novel and intriguing nanoparticle (NP) applications in many sectors, including research and medicine. Components of living cells have already been constructed at the nanoscale level. Production of engineered NPs for commercial use has been increasing exponentially. The complexity and combination of advanced chemistry and cell biology make it important that future research on NPs is performed in close collaboration between scientists with different backgrounds. Cell death and phagocytosis regulatory networks offer a multitude of targets for toxic chemicals. Understanding the mechanism of NP-induced toxicity is the first defense for hazard prevention. Reaching this ultimate goal will enable us to avoid synthesizing toxic nanomaterials for commercial use. This is important to prevent misleading/wrong interpretations and thus aid in bringing NPs into clinical use faster. Ecotoxicology, nanotoxicology, and nanopathology of the interactions between heavy metals, free radicals, and NPs on biological systems are of significant interest. Therefore the safety and toxicity of NPs have become issues of interest to the public.

Exposure to heavy metal ions, free radicals, particulate matter, and NPs is a common phenomenon due to their environmental pervasiveness. The wide application of NPs in industry, consumer products, and medicine has raised concerns regarding the potential toxicity of NPs in humans by generating reactive radicals. Several metal ions in trace amounts are required for metabolism, growth, and development. Toxic xenobiotic metals (Hg, Pb, Cd, As, Sn) have no known biological function. Reactive oxygen species (ROS) and oxidative stress are considered to be the cause of aging and pathological cell death; however, very little is known about their functions in the natural processes that support the formation of an organism. In cell organisms, NPs represent foreign elements with their own physicochemical properties due to their small size. Metal ions interfere with a number of body functions, including damage to lipids, proteins, enzymes, and DNA via the production of free radicals. Metal intoxication, particularly neurotoxicity, genotoxicity, or carcinogenicity, is widely known. Ecotoxicology, nanotoxicology, and nanopathology effects of free radicals, NPs, reactive oxygen and nitrogen species (RONS), and endoplasmic reticulum (ER) stress on biological systems are of significant interest. Studying the toxicity of NPs is complicated by a host of factors such as the variety of substances, variation in size and surface area, chemical charge, and chemical coating. Lack of information and methods of characterizing nanomaterials make existing technology extremely difficult to detect NPs in air for environmental protection. Due to the complication of free-radical formation and reaction, the elucidation of a detailed biochemical mechanism of nanomaterial-induced RONS formation leading to toxicity is challenging. Mechanistically, RONS drive sustained cell proliferation, cell death, including both apoptosis and necrosis, formation of nuclear and mitochondrial DNA mutations, and in some cases stimulation of a proangiogenic environment.

The roles of RONS ($^1O_2$, $O_2^{\bullet-}$, H_2O_2, $^{\bullet}OH$, OH^- $HO_2^{\bullet}$, $NO^{\bullet}$, $ONOO^-$) with associated ER stress, which is a complex protein-folding and trafficking organelle, are considered important regulators of physiological and pathophysiological processes and not simply detrimental due to their chemical nature or that they cause oxidative stress. This is further supported by findings indicating that redox active compounds are essential components of living organisms. Thereby, recent advances in genomics and proteomics have led to the identification of a "redoxome" consisting of hundreds of proteins involved in redox systems. It comprises enzymes generating RONS such as NADPH oxidases and nitric oxide synthases, redox relays such as peroxiredoxins, thioredoxins, and glutaredoxins, enzymes degrading ROS such as superoxide dismutase or catalase, as well as numerous proteins dependent on redox modifications, which are involved in the defense against oxidant, inflammatory, and/or proteotoxic stress. Although a number of substances, factors, products of metabolism, and nutrients are important for normal cell biology and redox signaling of all species, toxins are rather important for causing deleterious effects. Since toxins act universally on almost all species, it is conceivable that their action may, at least in part, involve ROS or oxidative stress and that antioxidant defense mechanisms could help to avoid the deleterious effects of toxins. The potential influence of metabolic activity and the resulting ROS production on development cannot be dismissed. A function of ROS in development is likely, due to the large amount of evidence showing that ROS can regulate fundamental cellular processes. Furthermore, it is possible that oxidation of specific molecules changes their activity, and in such a way defines the fate of a developing cell.

Toxicity of NPs and xenobiotic metals ions (Hg, Pb, Cd, As, Sn) occurs in humans by generating reactive radicals. Metal ions interact with oxygen-containing ligands through the formation of free radicals forming stable bonds with S— and N— in the form of SH or imidazole groups in proteins. Its mechanism of toxicity involves disassembly of iron-sulfur ([Fe-S]) clusters in proteins through the inactivation of iron regulatory protein-1, causing release of iron and alterations of —SH residues. Superoxide anion reacts with the potent vasodilator and cell-signaling molecule nitric acid (NO) to form the toxic peroxynitrite ($ONOO^-$) product. The metal ions deplete glutathione and protein-bound sulfhydryl groups, resulting in the production of ROS as superoxide ion, and the hydroxyl radical may play a primary role in overall toxic manifestations. Toxicities of heavy metals can be increased by deficiencies of certain essential nutrients such as Ca, Fe, Zn, and Se. RONS mainly comprise free radicals like $O_2^{\bullet -}$, $^{\bullet}OH$, and nonradicals like $^1O_2$, OH^-, and H_2O_2. These are lethal and cause extensive damage to protein, DNA, and lipids, and thereby affect normal cellular functioning via the production of free radicals. Following exposure to heavy metals, their metabolism and subsequent excretion from the body depend on the presence of antioxidants (glutathione, α-tocopherol, ascorbate, etc.) associated with the quenching of free radicals by suspending the activity of enzymes (catalase, peroxidase, and superoxide dismutase).

In all the physiologically relevant ROS, the hydroxyl radical possesses the highest one-electron reduction potential and is reactive with almost all types of biomolecules, including lipids, proteins, and nucleic acids. As a result of their reactivity and ability to damage biological targets, hydroxyl radicals can serve as an ideal representative ROS for investigation. Consequently, if a nanomaterial induces ROS, it is important to determine the formation of hydroxyl radicals.

Oxidative attack is a major weapon used by phagocytes and other cell types against invading pathogens, and ROS production can interfere with microbe elimination through myriad mechanisms. Although the current paradigm predicts that ROS production contributes to the elimination of pathogens, it is becoming clear that for viruses, bacteria, and protozoans, ROS production can contribute to increasing pathogen burden. These new findings open an avenue to the use of antioxidants against particular infections.

Enzymatic defenses have evolved to protect against harmful biological oxidants. Superoxide dismutases, peroxidases, and catalases are some of the prominent and extensively studied antioxidant enzymes. Antioxidants also play an important role in preventing/limiting the damage caused by ROS. The hydroxyl radical is the most powerful ROS in causing biological damage. Although there are no antioxidant enzymes that can destroy the hydroxyl radical, some endogenous and dietary antioxidants are effective in scavenging them. Consequently, the development of dietary antioxidants to scavenge hydroxyl radicals formed from nanomaterials may serve as one of the strategies for the prevention of nanomaterial-induced toxicity.

This book presents our current understanding of the roles and mechanisms of RONS-mediated pathways, cellular signaling stress, ER stress, oxidative stress, oxidative damage, nanomaterials, and the mechanism by which metalloids or heavy metals (particularly arsenic, lead, cadmium, and mercury) and NPs induce their toxic effects.

This book is a successful attempt to answer many questions regarding the roles of NP-induced RONS and ER stress in health and disease, for example:

- What level of unfolded protein response (UPR) signaling is ideal to enable cellular adaptation and survival?
- To what extent are the adaptive versus destructive UPR and non-UPR responses to ER stress involved in the pathophysiology of diseases?
- How can we selectively modulate the ER stress responses in sick but not healthy cells?
- How does the ER interconnect with other cellular organelles to modulate cell death?
- What happens to nanoparticles released from cells that have been killed, e.g., by targeted NPs containing drugs.
- How stable are NPs following cellular uptake?
- How can ROS be generated by the various ER pathways?
- What is the role of calcium, manganese, iron, AgNPs, TiO_2NPs, ZnONPs, other NPs, and free radicals in ROS production?
- How can different therapies, by targeting different molecules, produce comparable efficacies?

Thus the book comprises 24 chapters covering in detail recent advances in new nanomedication technologies of the effects of NPs on oxidative stress, RONS, and ER stress. Clinical applications of improvement testing strategies for aligning nanomaterial safety assessments and oxidative stress responses are discussed in detail. Medical imaging of the complexity of NPs and ROS dynamics in vivo for clinical diagnosis applications with effects of interactions between antioxidant defense therapy and ROS are also discussed. Nanobio studies now require further analyses to predict the behavior of NPs in complex biological systems. Finally, the final chapter looks at a Food and Drug Administration breakthrough—drug therapy designations for clinical evidence to date.