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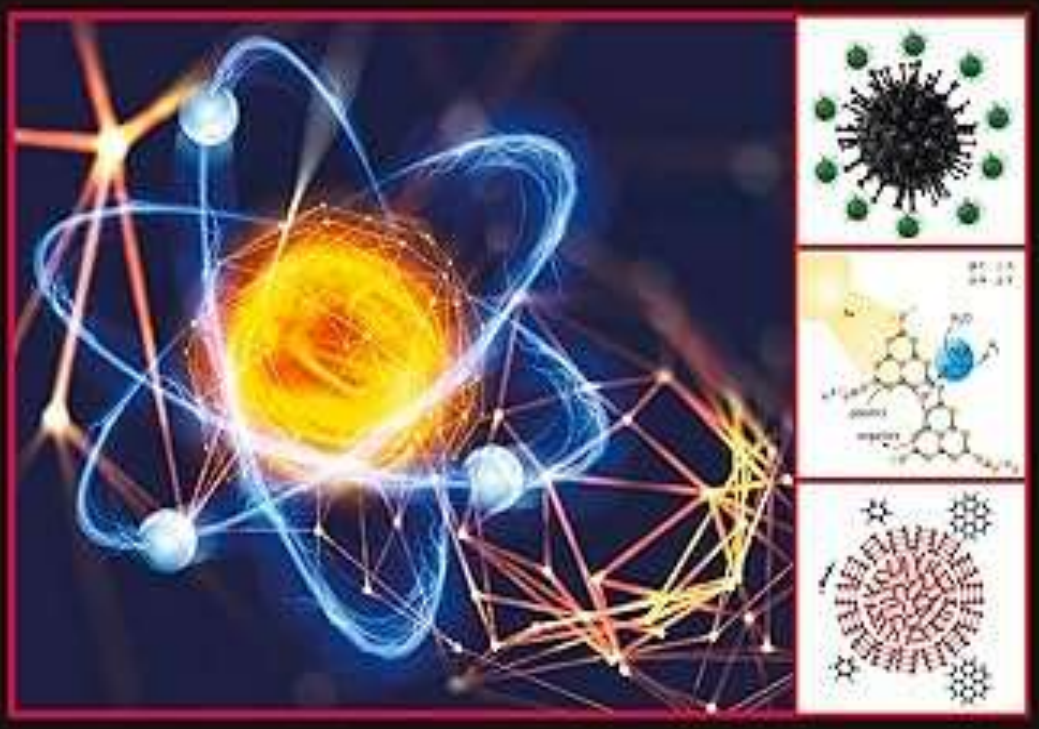
ADVANCES IN NANO AND BIOCHEMISTRY

Environmental and Biomedical Applications



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CHAPTER 13

Toxicological aspects of nanomaterials in biomedical research

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13.1 Introduction

Modern advances in nanoscience and nanotechnology have augmented the increase and production of many new nanomaterials with unique properties for industrial and biomedical uses in recent years. The extremely small size of these materials allows them to be used in a number of applications such as in drug delivery, cancer therapy, prosthetics, dentistry, pharmaceuticals, etc. With advancements in the field of medicine, a number of nanomaterials are synthesized with potential medical applications. For instance, quantum dots are used as fluorescent labels in drug delivery systems and in disease detection [1–3]. Carbon nanotubes can also be used in drug delivery systems due to their capacity to adsorb pharmaceutical formulations as well as in tissue engineering [4–6]. Liposomes, composed of lipid bilayers, are also used as excellent drug delivery carriers with the drug being adsorbed on the surface or sequestered within the core [7,8]. Magnetic nanoparticles also have a number of applications such as hyperthermia treatment, magnetic resonance imaging, and drug delivery [9–11].

However, some of these nanomaterials may exert toxic side effects on nontarget cells and tissues. They may also accumulate in various nontarget organs and exert toxic effects (Fig. 13.1). The size of these nanoparticles with high surface area and uncommon surface chemistry and reactivity can lead to unique problems for biological animals or cells and the environment. Such undesirable effects can be minimized by synthesizing biocompatible nanomaterials or surface coating or surface modifying the nanomaterial before being administered. Various strategies exist to make the nanoparticles biocompatible such as coating them with polymers like polyethylene glycol (PEG) or other biological substances such as aptamers. Nanoparticles may also be synthesized to be biodegradable such that they can be rapidly cleared from the body after therapy. However, even these formulations need to be tested prior to administration to understand possible toxicity and interaction with biomolecules in vivo and in vitro.

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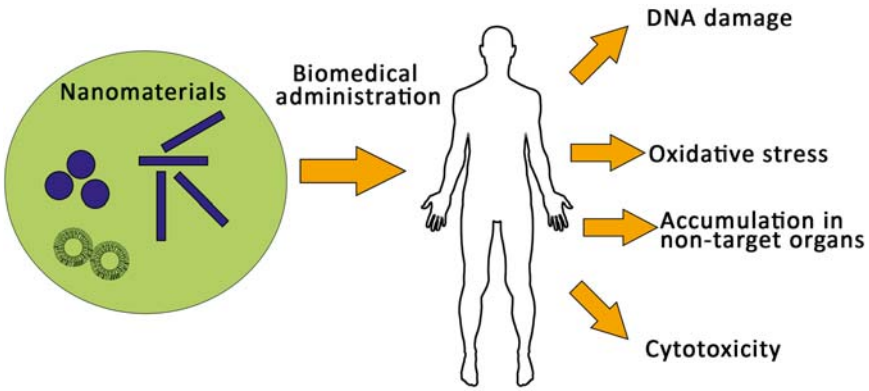

Figure 13.1 Toxic effects of nanoparticles in living organisms.

13.2 Toxicity of nanomaterials in biomedicine

13.2.1 Quantum dots

Quantum dots (QDs) are fluorescence-type semiconductor nano-sized particles used for their unique stability against photobleaching, and excitability for multicolor emission with a single light source [12], made up of either heavy metals or inorganic materials with a size ranging from 2 to 10 nm. QDs contain atom-like discrete electronic energy levels, and are therefore called artificial atoms. They consist of two free functional groups for binding with the molecules of a potential drug. Surface modification of these quantum dots through covalent and/or noncovalent binding of various substances affects and alters the properties of the drug molecules. The outer shell of QDs is made of semiconductor material that provides the surface for bio-conjugation thereby improving its aqueous solubility. This also provides an effective surface area for binding the drugs to the target molecule. Various functionalizations and surface modifications make them suitable for application in the pharmaceutical field such as biomedical imaging, drug delivery, drug release study, and diagnosis [2]. The regulatory status of quantum dots is not yet clear; but is, however, regarded as safe for usage. The first clinical trial of quantum dot technology in humans was approved by USFDA in the year 2011. With upcoming advances in technology, most of the chemotherapeutic and cytotoxic drugs are delivered via quantum dots for improved pharmacological action [2].

Owing to their wide application in the medical field, knowledge of the toxicity of QDs becomes imperative. The toxicity of quantum dots depends upon the size, dose, material used, route of exposure or administration, capping material, and composition. For example, nanosized cadmium QDs are found to be highly toxic because they can easily enter tissues and cells and exert their damaging effects [13,14]. Furthermore, Cd-QDs are extremely toxic compared to non-cadmium QDs [15]. CdTe QDs have also been reported to induce toxicity in the liver and kidney which may be reversible

over a period of time [16]. In distribution and accumulation studies, QDs could be detected in various tissues of mice even after 2 years of exposure [17]. Ref. [18] reported the accumulation of QDs in the immune organs namely, the liver, spleen, lungs, and kidney after intraperitoneal injection of QDs in mice and subsequent inflammation in some of the tissues. Certain studies have revealed that QDs also exert toxic effects on the respiratory system. For instance, Ref. [19] studied the in vivo effects of novel graphene QDs with potential applications in biomedicine. They reported fibrosis evidenced by increase of collagen I and expression of profibrotic genes TGF-β1 and p-Smad3 in the lungs of mice exposed intranasally to QDs. In another study, black phosphorus quantum dots which have been used extensively in biomedicine were found to induce significant cytotoxicity and decreased cell viability in human-derived lung cells in vitro probably brought about by ROS [20]. Lung inflammation and injury are also reported in several QD exposure studies [21–23]. Surface modification thus becomes very important to reduce toxicity and simultaneously impart biocompatibility, stability, and specificity to QDs [15].

13.2.2 Carbon nanoparticles

Carbon nanoparticles are used extensively in biomedical applications due to their excellent biocompatibility and relatively low toxicity [24]. Carbon nanoallotropes like fullerenes, carbon dots, graphene sheets, graphene oxide, carbon nanotubes, and nano-diamonds have been used in the medical field with applications in pharmacy and medicine for drug delivery system in therapeutics, cancer therapy, regenerative studies [25–28]. In spite of these applications, some studies have reported the toxicity of carbon nanoparticles. Ref. [29] reported that multiwalled carbon nanotubes induced various degrees of cytotoxicity in human macrophages in vitro. Similarly Ref. [30] observed cytotoxicity in HeLa cells exposed to carbon nanoparticles. They further reported that cytotoxicity could be attenuated by adsorbing serum proteins onto the nanoparticles. Carbon nanotubes have been reported to affect the epithelial cells of lungs in a number of studies. For instance, Ref. [31] compared the toxicity of multiwalled carbon nanotubes and onion-like shell-shaped carbon nanoparticles in human bronchial epithelial cells and found that the carbon nanotubes were more toxic. Similarly Ref. [32] reported that carbon nanotubes induced higher cytotoxicity than carbon nanoparticles in human epithelial cell line A549. Single-walled carbon nanotubes were also found to induce fibrosis in the lungs of mice as well as elevated production of inflammatory cytokines [33]. The essential mechanisms by which carbon nanotubes induce toxicity include oxidative stress by generating ROS, inflammatory responses, malignant transformation, DNA damage and mutation (errors in chromosome number as well as disruption of the mitotic spindle), the formation of granulomas, and interstitial fibrosis [34].

Other carbon nanoparticles such as fullerenes (C60) also have applications in drug and gene delivery as well as in dermatology [35,36]. However, their toxicity has been reported by several researchers in lungs [37–39] (Marchione et al., 2007). The possible mechanisms of toxicity of fullerenes in lung cells include induction of ROS and DNA damage [40].

13.2.3 Metallic nanoparticles

Metallic nanoparticles have a number of biomedical applications depending on the type of metal used. The most commonly employed metals used in biomedical applications are gold, silver, zinc, iron, and manganese and have been extensively studied with regard to their toxicity and biocompatibility. A number of these nanoparticles are regularly used as drug carrier molecules in the treatment of neoplastic malignancies [41]. Metallic NPs allow effective conveyance of anticancer drugs into the tumors by utilizing the pathophysiology of the neoplastic cells, thereby modifying the therapeutic outcomes [42]. These metallic nanoparticles are used by targeting ligands with specific receptors on tumor cells thus offering targeted delivery to the tumor cells thereby evading the nonneoplastic cells [43,44]. Metallic nanoparticles also accumulate in various cells such as macrophages and other immune cells and various strategies are adopted to avoid uptake by these cells for effective drug delivery [45–47]. The size, density, surface charge, and chemistry of metal NPs play a crucial role in generating an immune response and renal clearance, thus increasing the circulation time and bioavailability for the target organs [48–50]. Once administered, they accumulate in immune cells, detoxifying and excretory tissues such as the liver, spleen, lymph nodes, bone marrow, adrenal glands, and kidneys [51–54].

In the recent years, gold nanoparticles are receiving much recognition and attention in medical research due to its unusual physical properties such as high resistance to corrosion which makes it biocompatible for medical applications like diagnosis and treatment of several diseases such as cancer, skin ulcers HIV, smallpox, measles, and rheumatoid arthritis and also has possible promising applications as an anticancer, antibacterial, and bio-diagnostic material [55–57]. Gold nanoparticles are also valued in the medical field due to their relative chemical stability that makes the preparation and fabrication methods modest, straightforward, and less dangerous. Gold nanoparticles are known to be less toxic compared to other metal nanoparticles (although not completely nontoxic), this is the reason they are more appropriate for biological/medical applications. Some studies have reported the toxicity of gold nanoparticles. Ref. [58] injected various sizes of gold nanoparticles in mice and observed sickness and altered pathology of organs in mice injected with gold nanoparticles with a size range of 8–37 nm. The size, concentration, and exposure conditions of gold nanoparticles have been reported to influence their

cytotoxicity. For instance, gold nanoparticles were observed to enter human dermal fibroblast cells via clathrin-mediated endocytosis and accumulate in vacuoles where they can exert cytotoxicity [59]. Surface charge, whether charged or neutral, may also be an important factor for the mechanism of toxicity of gold nanoparticles [60].

Silver nanoparticles, another widely used metal nanoparticle, are present in several personal care products owing to their excellent antimicrobial activities. However, several studies have concluded that they are toxic both in vivo and in vitro which may be dependent on their size, shape, surface coating, and surface charge [61–63]. Ref. [64] orally gavaged rats with silver nanoparticles and observed several toxic effects such as decrease in body weight, alterations of alkaline phosphatase and cholesterol, and liver damage. Silver nanoparticles were found to be retained in the brain and testes of rats even 8 weeks after a 28-day exposure which could lead to probable long-term toxic effects [65]. In another study, silver nanoparticles were found to leach silver ions when dispersed in water which was found to influence toxicity in murine macrophages [66]. The probable mechanisms of silver nanoparticle toxicity include generation of ROS, interaction with cell membranes and subsequent damage, protein and nucleic acid interaction triggering various cell signaling pathways [67]. Silver nanoparticles have also been reported to impair mitochondrial function such as uncoupling of oxidative phosphorylation [68].

Zinc oxide is generally recognized as safe (GRAS) by the FDA [69], but at nanoscale level, they are known to attain novel properties which are not present in the micro or larger sizes. Studies carried out in mice reveal the potential of ZnO nanoparticles to accumulate in organs like the liver, spleen, heart, bone, and the pancreas [70]. The toxicity of ZnO NPs on mammals has been demonstrated both in vitro and in vivo. Inhalation of these nanoparticles are known to cause potent yet reversible pulmonary inflammation [71]. Intratracheal delivery of ZnO NPs into the lungs of rats induced eosinophilia, propagation of airway epithelial cells, goblet cell hyperplasia, and pulmonary fibrosis [72]. It is believed that the mechanism of ZnO nanoparticle toxicity is through production of ROS [69] and dissolution of lysosomal membranes [72]. A three-tier model of ROS oxidative stress is described by Ref. [73]. Tier one includes increases in antioxidant enzymes to start the initial antioxidant defense, followed by Tier two which includes an increase in potent proinflammatory cytokines leading to inflammation, while Tier three is characterized by mitochondrial perturbation resulting in cellular death by apoptosis or necrosis. All three tiers have been observed for ZnO nanoparticles in immortalized phagocytic or bronchial epithelial cells leading to damage of lipids, proteins, and DNA, increased release of lactate dehydrogenase, and death by either necrosis or apoptosis [21,73–77].

Several in vivo and in vitro studies have been carried out to study the toxicity of manganese oxide (MnO) nanoparticles. Manganese as an important component of the antioxidant enzymes namely superoxide dismutase but literature has cited that manganese compounds among micronutrients cause neurotransmitter anomalies, elevate ROS level,

and promote protein misfolding and aggregation, and the mechanisms contributing to the Parkinson's disease model [78–81]. MnO nanoparticles were reported to induce moderate toxicity as seen from mitochondrial reduction activity in PC-12 cells from PC-12 cell line cultured neuronal phenotype [82]. Studies have shown that MnO nanoparticles affect the reproductive system of rats having chronic exposure, decrease in the number of sperms, spermatogonia, spermatocytes, diameter of seminiferous tubules, and also bring down the motility of sperms [83]. At lower doses MnO nanoparticles induce genotoxicity, biochemical, and histopathological alterations as compared to microparticles of MnO. Biodistribution investigations have revealed the presence and accumulation of MnO NPs in the gastrointestinal tract and in the organs and tissues. The concentrates of MnO NPs were also found in the liver, spleen, kidney, heart, blood, brain, and lungs. The bulk of NPs were found in the liver, kidney, as well as spleen [84].

13.2.4 Magnetic nanoparticles

Magnetic nanoparticles mainly incorporate metal nanoparticles, metal oxide nanoparticles, and metal alloy nanoparticles. Magnetic nanoparticles have a great specific surface area, which is ideal for carrying large amounts of DNA fragments, drugs and modified compounds. Additionally, most modified magnetic nanoparticles have excellent biocompatibility and superparamagnetism which make them excellent vehicles for targeted drug delivery [85]. Iron oxide nanoparticles are the most studied and commonly used magnetic nanoparticles for biomedical applications, due to their unique chemical, biological, and magnetic properties such as chemical stability, biocompatibility, high saturation magnetization, and high magnetic susceptibility. Iron oxide nanoparticles have been studied for the use in magnetic hyperthermia treatment, targeted drug delivery, and contrast agents in magnetic resonance imaging (MRI). Furthermore, a number of studies prove that magnetic nanoparticles, coated or uncoated, are not toxic which is useful for further development of their biomedical applications [86–91]. However, some magnetic nanoparticles have been proven to be toxic. The toxicity of magnetic nanoparticles depends on their size, shape, coatings, and nature of magnetically responsive components such as iron, nickel, cobalt, etc. [92]. For instance, composite iron oxide nanoparticles with silica core or nanoflakes induced significant cytotoxicity in human umbilical vein endothelial cells [91]. On the other hand, magnetic nanoparticles coated with amorphous silica were found to be protective against the toxicity of uncoated magnetic nanoparticles in human bronchial epithelium–derived BEAS-2B cells, in vitro compared to bare magnetic nanoparticles [93]. Careful administration of magnetic nanoparticles in the body is important because unintended inhalation or ingestion of these nanoparticles could possibly result in the distribution of nanoparticles in different parts of the body leading to toxicity [94–96]. The possible mechanisms of magnetic nanoparticle toxicity include oxidative stress by generation of free radicals, lipid peroxidation, and elevation of

antioxidant enzymes [97–99]. This mechanism can be considered ambiguous in the sense that these nanoparticles can induce cytotoxicity and cell death in cancer cells as well as normal cells and thus careful targeting is of utmost importance [100].

13.2.5 Polymer and liposome-based nanoparticles

Polymer-based nanoparticles are colloidal carriers composed of natural polymers such as starch, polypeptides, chitin, cellulose, and polyhydroxyalkanoates (PHAs) or synthesized polymers such as polyethylene glycol (PEG), poly-lactic-acid-co-glycolic-acid (PLGA), polybutylcyanoacrylate (PBCA), and polyvinyl alcohol (PVA). They are known to effectively carry drugs, proteins, and DNA to target cells and tissues and hence synthesized as polymer nanospheres and nanocapsules. Certain disadvantages of using synthesized polymers in medical applications include nonbiodegradability and presence of toxic residues which are not properly removed during the manufacturing process [101,102]. High concentrations of polybutylcyanoacrylate nanoparticles were reported to be toxic to cell cultures but were found to be nontoxic to rats in vivo [103]. In another study, the cytotoxicity of PLGA nanoparticles coated with various stabilizers such as chitosan, PVA, and poloxamer 188 was evaluated in human-like THP-1 macrophages [104]. The PLGA nanoparticles coated with these stabilizers at high concentrations induced significant cytotoxicity while the stabilizers themselves did not induce significant cytotoxicity. One study attributed the in vitro toxicity of polymeric nanoparticles to generation of reactive oxygen species and expression of tumor necrosis factor alpha [105].

Liposome-based nanoparticles consist of cationic lipids in a bilayer that has a vesicular structure. Drugs of interest are encapsulated in the aqueous core of these liposomes for subsequent delivery to target tissues/cells. Thus, liposomes are highly biocompatible and biodegradable allowing for their extensive in biomedical applications such as targeted drug delivery [106]. Some of the disadvantages of liposome nanoparticles include low rate of encapsulation of water-soluble drugs and poor stability of the liposome. To solve the problem of stability, PEGylation of lipid nanoparticles have been used to further stabilize the nanocarriers for drug delivery [107]. However, a few studies have reported the toxicity of liposome nanoparticles. For instance, various concentrations of cationic liposomes, when injected in rats, were found to induce DNA strand breaks in the cells of the lung and spleen [108]. The expression of cytokines was also found to be elevated in the lungs, spleen, and liver of these rats. In another study, Ref. [109] reported the cytotoxicity and genotoxicity of cationic liposomes in human hepatocyte cells (HepG2) and lung epithelial cells (A549) in vitro. In an attempt to understand drug efficacy with liposomes Ref. [110] administered liposomal doxorubicin in Walker 256 tumor-bearing rats. When compared with rats administered with dendrimer doxorubicin, the liposomal formulation induced significant systemic toxicity and cardiotoxicity although both formulations displayed similar antitumor efficacy.

13.3 Genotoxic biomarkers

Genotoxicity tests are routinely used to assess the DNA damaging effects of nanoparticles before they are used for their potential applications. Two commonly used tests for assessing genotoxicity are the micronucleus test and the single cell gel electrophoresis assay (comet assay) (Fig. 13.2).

13.3.1 Micronucleus test

The micronucleus test is a rapid and easy test to assess clastogenicity (chromosomal damage) in cells. In eukaryotic cells, the chromosomes exist within a compact nucleus. However, the presence of DNA damaging agents can affect the integrity of these chromosomes such that they can cause breaks or fragmentation. Furthermore, the toxicants may also affect the spindle apparatus of cells and may not allow proper segregation of chromosomes during mitosis. This eventually leads to a broken chromosomal fragment or a whole chromosome persisting in the cytoplasm near the main nucleus, hence termed micronucleus. Thus, higher the incidence of micronuclei in cells, higher is the DNA damaging potential of the toxicant. The micronucleus test has been used as a biomarker of genotoxicity in several studies involving nanoparticle toxicity. Ref. [111]. used the in vitro cytokinesis block micronucleus assay in Chinese hamster lung fibroblast cells (V79) to test the genotoxic potential of zinc oxide nanoparticles and reported significant induction of micronuclei at higher nanoparticle concentrations. In another study, cerium

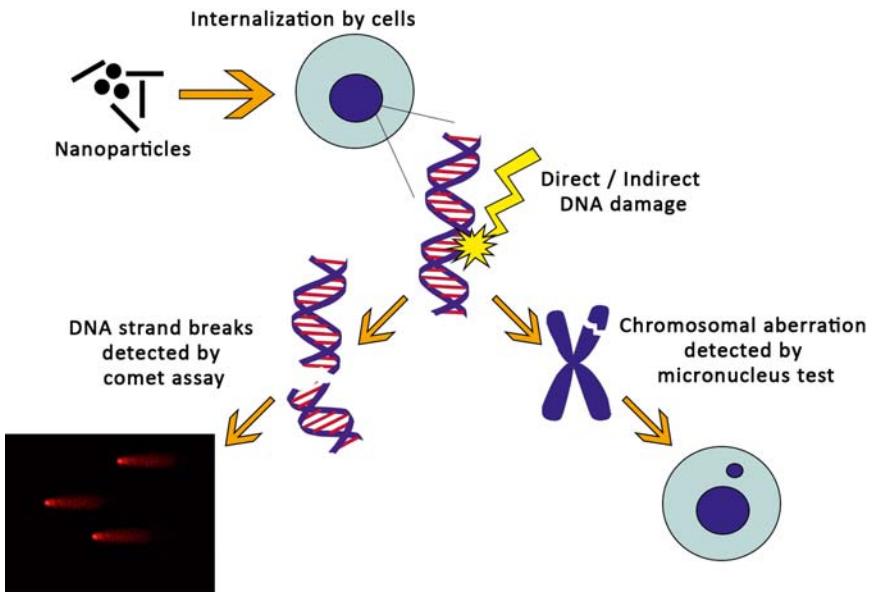

Figure 13.2 DNA damage mechanisms measured by the comet assay and micronucleus test.

oxide nanoparticles were found to induce significant micronuclei in lymphocytes in vitro as measured by the cytokinesis block micronucleus test barely 3–24 h after nanoparticle exposure [112]. The micronucleus test has also been used to report the genotoxicity of silver nanoparticles in vitro [113,114] and in vivo [51,115]. Engineered nanoparticles with potential industrial applications have also been evaluated for genotoxicity using the micronucleus test [116]. A number of studies have suggested that micronuclei formation may be attributed to oxidative stress induced by the nanoparticles [117–119].

13.3.2 Single cell gel electrophoresis assay (comet assay)

In contrast to the micronucleus test, the comet assay measures DNA damage in the form of single- or double-stranded DNA breaks. The protocol for comet assay is a bit more laborious, but is highly sensitive and allows for the visualization of DNA strand breaks in cells. In this test, cells are embedded on agarose gel–coated slides and subject to lysis. The lysis buffer degrades the membranes and cytoplasmic contents of the cell leaving only the nucleus intact. The DNA are then unwound using an alkaline or neutral unwinding buffer so as to liberate the broken DNA fragments. After a brief period of unwinding, the slides are subjected to electrophoresis where the broken DNA fragments migrate out from the nucleus under the influence of the electric field (since DNA is negatively charged). The slides are then placed in neutralization buffer and stained with a nuclear fluorescence dye such as ethidium bromide or SYBR green and observed under a fluorescence microscope with appropriate filters. Cells with a large amount of breaks show the appearance of a "comet" (the head resembling the intact DNA and tail representing broken DNA fragments which migrated out during electrophoresis). Thus, longer the tail, larger is the extent of DNA damage. Cells with no breaks resemble only the head of the comet with no tail. The tail length can be measured using visual scoring methods or with the help of software and can be recorded. DNA damage induced in this way may be due to direct effects of the nanoparticle or indirect effects mediated by free radicals. The comet assay is thus a suitable test for measuring the extent of DNA damage induced by nanomaterials [120]. Ref. [112] reported significant DNA damage in human lymphocytes in vivo measured by the alkaline comet assay. Ref. [121] also reported DNA strand breaks and DNA oxidation by various nanoparticles. They further reported that this DNA damage was brought about due to increased levels of reactive oxygen species and reduced DNA repair capacity. Similarly, the comet assay was also used to detect the genotoxicity of titanium dioxide intra-tracheally instilled in rats where they reported no genotoxicity [122]. Consequently, DNA damage measured by the comet assay was reported in human peripheral blood cultures exposed to titanium dioxide nanoparticles in vitro [123]. The comet assay was also used to detect DNA damage in human keratinocytes exposed to citrate-coated silver nanoparticles in vitro indicating the probable genotoxicity of cosmetic products [124].

13.4 Safety against toxic effects

13.4.1 Biocompatibility

Biocompatibility is a general term used to define the compatibility of biomaterial (biological compound, nanoparticle, or implantable devices) to perform its specific function in the living tissue or a living system with respect to a medical therapy without inducing any undesirable effects, that will assure minimal toxic effects, potential to cause injury, or physiological/immunological reactivity [125]. No compound/particle can be claimed to be completely biocompatible, but the research is continued to design and establish sufficiently biocompatible particles along with the benefits that it offers. To study NPs biocompatibility, there are several aspects which need to be explored, which include evaluation of cell viability, cytotoxicity, proliferation, apoptosis/necrosis, cellular morphology alteration, oxidative stress, inflammatory response, and hemotoxicity. The biocompatibility of certain nanoparticles depends closely on various several factors, which include physicochemical properties of the nanoparticles, the impact of their size, shape, and surface charge state, their formulation, biological target, dose, the methodology employed to evaluate their toxicity, and how they are delivered into the body (Huang et al., 2017) (Fig. 13.3).

One of the ways of protecting the body against the toxic effects of nanoparticles is by using a protective coating against the uncontrolled release of metal ions into the cells and tissues. A number of studies have compared the toxicity of uncoated and coated nanoparticles. For instance, Ref. [126] reported that uncoated iron oxide nanoparticles induced significant cytotoxicity in A549 and HeLa cells. However, the nanoparticles coated with a thin shell of silica reduced their toxicity rendering them more stable within biological environments. Magnetic nanoparticles used in hyperthermia treatment have also been made biocompatible with various surface modifications/coatings such as

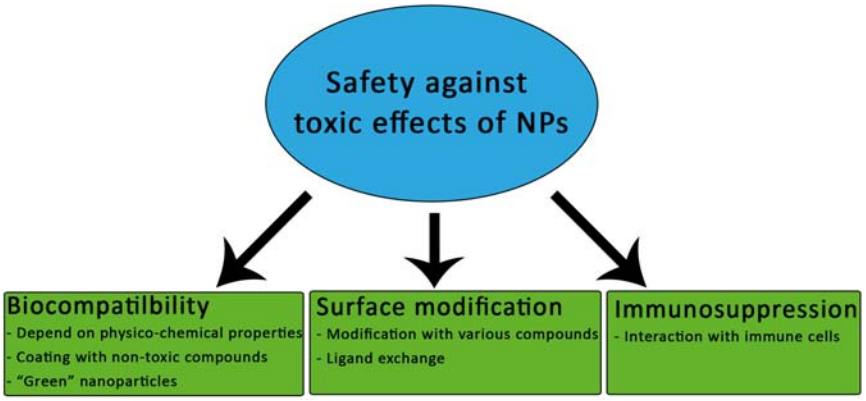

Figure 13.3 Safety against toxic effects of nanoparticles in biomedicine.

PEGylated curcumin, aptamers (small single-stranded DNA or RNA), polycations, and amino acids, to name a few [127–130].

Ref. [131] reported that gold nanoparticles loaded with doxorubicin hydrochloride (drug delivery system) were found to be cytotoxic in A549 cells. However, when they stabilized the nanoparticle–drug complex with xanthan gum, cytotoxicity was found to be significantly reduced. Similarly silver nanoparticles used in antibacterial or antifungal applications were stabilized with type I collagen and this composite was found to be nontoxic to fibroblasts and keratinocytes while exhibiting toxicity to bacteria [132]. In another study, zinc oxide nanoparticles, which are known to be toxic, were incorporated with nanostructured hydroxyapatite, were found to be nontoxic when administered to rats in vivo [133]. With such biocompatibility, this nanoparticle composite has potential applications in bone regeneration in orthopedics and dentistry while also acting as an antibacterial agent.

Carbon nanoparticles have been used in several biomedical applications such as bioimaging and drug carriers, but are known to induce toxicity. Thus the biocompatibility of carbon nanoparticles should be assessed before being used in biomedicine. Ref. [134] synthesized carbon dots hybridized with plasmonic nanostructures for potential applications in diagnostic bioimaging and were found to be biocompatible with Vero epithelial kidney cells in vitro. In another study, nitrogen-doped carbon nanoparticles were found to be biocompatible for bioimaging of histidine detection in cells [135]. Carbon dots have also been coupled with aspirin to be used dually as an antiinflammatory agent and fluorescent biomarker and have also found to be nontoxic in vitro [136]. Carbon nanotubes/poly(lactic-co-glycolic acid) composites synthesized by Ref. [137] were reported to be biocompatible for bone and tissue regeneration in rats. No significant toxicity was observed probably due to the lower concentration of the carbon nanotubes. Furthermore, this biocompatibility was similar to that of poly(lactic-co-glycolic acid) administered alone.

In recent years, nanoparticles synthesized from plants have gained attention due to their eco-friendly approach and ease of production [138,139]. These "green" nanoparticles are usually preferred over engineered ones due to their biological origin and higher biocompatibility [140]. A number of studies have proven that nanoparticles synthesized from plant sources were found to be less toxic than chemically synthesized ones and thus, more biocompatible. Ref. [141] reported that silver nanoparticles synthesized from the leaf extracts of *Nigella sativa* did not induce significant cytotoxicity in mouse mesenchymal stem cells compared to chemically synthesize silver nanoparticles. Similarly Ref. [142] also reported that silver and selenium nanoparticles synthesized from various plant extracts did not induce significant toxicity in mice in vivo. In another study, gold nanoparticles synthesized from reducing gold salts by phytochemicals in tea leaves did not induce significant toxicity in cells probably due to the phytochemicals forming a coating over the gold nanoparticles [143].

13.4.2 Surface modification

Apart from the increase in biocompatibility, NPs surface modification can be a very important tool for the modulation of the body's immune response against the specific particles as well as to fix or attenuate issues related to NPs toxicity. After NPs are injected in the blood stream, they interact with a lot of specific proteins like opsonin, complement proteins, immunoglobulins, fibronectin, and apolipoproteins (protein corona). Such interactions can modify the behavior of NPs and can trigger an immune response (Barbero et al., 2017). The NP's surface modification can be exploited to promote their escape from the immune system and to increase their half-life in blood by reducing the clearance due to macrophages of the mononuclear phagocyte system (MPS). Conversely, in the next-generation vaccines, NP surface modifications can trigger the immune response toward a specific antigen (Ahmad et al., 2019; Cappellano et al., 2019; Gu et al., 2019). Furthermore, surface modification also allows nanoparticles to be taken up by cells for effective drug delivery [144].

Surface modifications usually involve ligand exchange or ligand adsorption to improve the functionalization and prevent toxicity of engineered nanoparticles [145]. Various types of nanomaterials have characteristic chemical properties and functional groups exposed on their surface to be used in the first steps of functionalization. Superparamagnetic iron oxide nanoparticles can be easily modified by using a ligand exchange strategy based on the substitution of the original surfaces with functional groups such as a diol, amine, carboxylic acid, and thiol to improve hydrophilicity and stability which would be beneficial in biomedical applications such as imaging (Korpany et al., 2016). Conversely, in another study by Ref. [146] superparamagnetic iron nanoparticles which were amine-surface-modified, though not cytotoxic, were found to alter the osteogenic and chondrogenic differentiation of human mesenchymal stem cells in vitro. Ref. [147] reported that polydopamine surface modification of CdSe quantum dots did not induce significant in vivo toxicity in rats compared to unmodified CdSe. Another nanoparticle used in drug delivery is polylactic-co-glycolic acid (PLGA), gets opsonized by the reticuloendothelial system, and thus requires surface modification using various compounds such as human serum albumin, potassium dichromate, and oxygen plasma [148–150].

13.4.3 Immunosuppressants

The immune system of humans is a complex and important series of defense mechanisms against harmful foreign substances and pathogens. Nanoparticles in biomedical research can stimulate the immune system in an undesirable or desirable way [151]. For instance, many nanoparticles induce inflammation in the body; the same property can be used for the treatment of certain diseases like cancer. On the other hand a number of nanoparticles are known to cause immunosuppression which can be used in the treatment of inflammatory disorders or autoimmune diseases. A number of mechanisms exist on how

nanoparticles achieve immunosuppression such as interaction with macrophages, antigen presenting cells as well as B and T cells [152]. However, immunosuppression by nanoparticles can also render the body susceptible to various infections that ultimately cannot be combatted by the immune system [153].

A number of nanoparticles have been synthesized for use as immunosuppressants for biomedical applications. Such nanoparticles maybe used directly to induce immunosuppression or indirectly when it serves as a drug delivery vehicle [152]. Ref. [154] prepared polylactide-cyclosporine A nanoparticles and found that they induced immunosuppression by suppressing T-cell proliferation. These nanoparticles could also be directed to lymph nodes to induce immunosuppression during drug delivery. In another study, rapamycin-loaded chitosan/polylactic acid nanoparticles were reported to induce immunosuppression during corneal transplantation in rabbit models [155]. Carbon nanoparticles and other metal nanoparticles have also been extensively used as immunosuppressants in targeted drug delivery [156–159]. Immunosuppression can also be brought about by tumors which allow them to proliferate in the body. A number of nanoparticles have been synthesized to reverse immunosuppression as a way to destroy tumors. For example, Ref. [160] synthesized self-stabilized hyaluronic acid nanoparticles to deliver chemotherapy drugs to osteosarcoma sites and reported that these nanoparticles reverse immunosuppression brought about by the tumor. A significant decrease in the growth of the tumors was observed as a result of the synergistic effect of immunotherapy and chemotherapy. In another similar study, modified phenylboronic acid nanoparticles inhibited pancreatic tumors and simultaneously alleviated the tumour-induced immunosuppression [161]. Ref. [162] synthesized poly lactic-co-glycolic acid nanoparticles which were coated with PD-L1 (programmed cell death-ligand 1) overexpressed mesenchymal stem cells and induced immunosuppression when administered at a tumor site in the liver of mice. Such nanoparticles have been found to be promising to induce immunosuppression for treatment of tumors and cancers and for effective drug delivery and therapy.

13.5 Summary and conclusions

Nanoparticles are important in a number of biomedical applications. However, nanoparticles such as carbon nanotubes, metallic nanoparticles, and magnetic nanoparticles have been proven to be toxic inducing oxidative stress, DNA damage, decreasing cell viability, and histopathological alterations. These particles can also be translocated to different nontarget organs in the body such as the brain, liver, testes, etc., where they can accumulate and possibly exert toxic effects. The mechanism of toxicity of most nanoparticles is via the generation of free radicals which in turn affect various biomolecules in cells. Therefore, the toxicity of these particles needs to be tested prior to their use. Various biomarkers can be used to test the toxicity of nanomaterials in vivo and in vitro such as the micronucleus test and the comet assay. The use of biocompatible nanoparticles, surface

modification, and immunosuppression are some strategies which can be used to minimize potential toxic side effects of nanoparticles. The green synthesis of nanomaterials also appears to minimize toxicity compared to the chemically engineered ones.

13.6 Challenges and future outlook

The progress of nanomaterial research in biomedicine has been profound over the recent years which is evident in successful treatment of a variety of diseases including certain cancers. The availability of variegated form of nanotechnology has fast tracked many medical procedures and treatments which otherwise were time intensive. The rapid blooming of nanoallotropes of different materials gives us great promise in the medical future as drug vectors, as well as being the drugs themselves with their acquired novel chemical and optical properties at the nanoscale level. However enough data regarding the safe and regular usage of certain nanoparticles is still scarce and wanting. Issues with biocompatibility and surface modifications could still potentially arise and studies on long-term effects of these nanoparticles are lacking. Although nanoparticles can be degraded/removed from the body after completing their therapeutic effects, they may still remain accumulated in different tissues and cause toxic side effects. Contradictory findings make it arduous for the researcher and user to build stable formulations for various therapies. The biggest challenge while using NPs is that at different nanoscales, the NP of the same material may exhibit different properties making it difficult to label their action and behavior toward a procedure. The use of animals and cell cultures also may show contrasting results where toxicity of a particular nanoparticle may manifest in either model and not in both.

The use of green chemistry is promising in the field of nanomedicine as nanoparticles are synthesized from natural sources such as plants and are more biocompatible than chemically engineered nanoparticles. Additionally, toxic residues may not be present in green nanoparticles thus making them suitable for use in various biomedical applications. Biocompatibility of nanoparticles should also be tested for all types of toxicity in animal models particularly pertaining to the nervous system and reproductive system in order to fully understand long-term effects.

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