Cellular and Organismal Toxicity of Nanoparticles and Its Associated Health Concerns

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Abstract

The demand for nanotechnology in biomedical science is escalating rapidly as novel nanomaterials help in rebuilding the life of patients suffering from serious health conditions. Nanomaterials are widely used for biomedical applications such as drug delivery carriers, diagnostic agents, image-contrasting agents, tissue engineering, targeted cancer therapy, and so on. However, due to poor understanding of mechanisms at the nanoscale, nature had to deal with the negative face of the nanotechnology broadly called as nanotoxicity. Nanotoxicology is therefore the study of the toxicity of nanomaterials at the cellular, organism, and environmental levels. Variety of nanoparticles (NPs) prepared from sources like metals, semiconductors, polymers, and lipids behave differently in cells due to the difference in their surface functionality, size and shape anisotropy, charge and dispersity in polar or nonpolar solvents, etc. Therefore, since the last decade, the scientific community has shown keen interest to understand the NPs toxicity at different biological levels of the organization. Cellular toxicity is mainly due to the intervention of NPs in cellular processes leading to oxidative stress, altered signaling, proliferation, and death pathways. Nanotoxicity in organism level causes defects in physiological functioning, behavior, and reproduction. Herein, this chapter enlightens various effects of commonly used NPs at cellular level as well as in organisms that may have implications linked to serious abnormal conditions such as cancer, diabetes, neurodisorders, cardiovascular, and hepatotoxicity.

Keywords

Nanoparticles · Nanotoxicity · Cellular and organismal toxicity · Disease

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Abbreviations

Ag	Silver
Al_2O_3	Aluminum oxide
ALCL	Anaplastic large cell lymphoma
Au	Gold
Bi_2O_3	Bismuth oxide
Ca	Calcium
CAT	Catalase
CdSe	Cadmium selenide
CeO_2	Cerium oxide
CNP	Carbon nanoparticles
CNT	Carbon nanotube
Cu	Copper
CuO	Copper oxide
DNA	Deoxyribonucleic acid
Fe_3O_4	Iron oxide
GPx	Glutathione peroxidise
GSH	Glutathione
HaCaT	Human keratinocyte cell line
Hb	Hemoglobin
HepG2	Liver hepatocellular carcinoma cells
Hsps	Heat shock proteins
IL-6	Interleukin 6
JNK	c-Jun N-terminal kinase
MCN	Mesoporous carbon nanoparticles
miRNA	MicroRNA
MRC-5	Medical Research Council cell strain-5
mRNA	Messenger ribonucleic acid
MSN	Mesoporous silica nanoparticles
MT	Metallothionein
NPs	Nanoparticles
p38MAPK	p38 mitogen-activated protein kinase
pax	Paired box gene
PCL	Polycaprolactone
PEG	Poly ethylene glycol
pH	Potential of hydrogen
PLA	Polylactic acid
PLGA	Polylactic-co-glycolic acid
PNIPAM	Poly(N-isopropylacrylamide)
QD	Quantum dot
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TiO_2	Titanium dioxide

TLRs	Toll-like receptor signaling
TNFα	Tumor necrosis factor α
WC-Co	Tungsten carbide cobalt
ZnO	Zinc oxide
ZrO_2	Zirconium dioxide

21.1 Introduction

Today with emerging trends, the transformation of technology overlooks harmful effects aggravated by the exposure of nanotoxicants that normal eyes fail to pick in a day's routine. Advances in nanotechnology in the field of health and biomedical science have improved the quality of life of patients suffering from various dreadful diseases. Molecules in the nanodimension interact with cells and their microenvironment and induce a therapeutic effect. Currently, there is no concurrence among the scientific community regarding what feature is most important in highlighting response for each type of nanomaterial even though a range of findings is available. Various nanoparticles (NPs) have been successfully used for several biomedical applications such as drug delivery carriers (Koo et al. 2005), tissue engineering (Gorain et al. 2017), cancer therapy (Peer et al. 2007), contrasting imaging agents (Koo et al. 2005), gene delivery (Xiao et al. 2019), biosensing, and environmental applications (Sanvicens et al. 2009). Using the bottom-up approach, bulk materials are chemically reduced into smaller nuclei followed by growth results in nanomaterials. Due to the high surface to volume ratio, individual NPs can able to interact with each biomolecule independently which aids to enhancement in functional attributes essential for biomedical applications. Further, various material properties including solubility, scattering, fluorescence, magnetization, reflectance, drug targeting, and thermal properties are significantly affected. Biomedical applications entail interaction of nanodrug carriers with target tissues. Therefore, desirable properties of nanocarriers should oblige a) encapsulation or entrapment of drug molecules in a nanosystem, b) biocompatibility and biodegradability of NPs, c) long circulating drug delivery with minimal burst effect, d) site-specific and selective tumor targeting, e) stability of NPs in aqueous solvents, f) high surface area for enhanced accumulation into the tissue site, and g) controlled drug delivery which includes ultrasound, pH, magnetic hyperthermia, and photothermal and enzyme-triggered drug release (Brigger et al. 2012; Cao and Wang 2011; Chen et al. 2018; Cuenca et al. 2006; Koo et al. 2005; Logothetidis 2006; Mohanraj and Chen 2006; Patravale et al. 2004; Peer et al. 2007).

The general synthesis of NPs involves two approaches: the top-down approach and the bottom-up approach. Generally, the top-down approach is a technique where large materials are broken down by external forces into small nanoscale structure in a precise pattern, whereas in bottom-up approach, the force of chemical oxidation or reduction is in total control with the formation of nanoparticle. Here crystal growth takes place, growth species like atoms, ions, and molecules impinging on

the surface assemble into crystal structures. Hence this approach is building up of materials from the bottom. In general bottom-up approach involves the principle of supersaturation and nucleation followed by growth. Supersaturation involves an increase in concentration as a function of time. Nucleation does not occur even above equilibrium. Nucleation would start when the minimum supersaturated concentration is attained that overcomes the critical energy barrier. Uniform monodispersed nuclei formed grows subsequently. When the solute concentration decreased below supersaturated concentration, no new nuclei would form, and growth proceeds further (Cao and Wang 2011). Thus, NPs formed in solution are monodispersed. However, size, shape, and dispersion in aqueous or organic solvents can be controlled by varying the concentration of solvents, temperature, types of surfactants, and pH. Major challenges in synthesis are huge surface energy, acquiring mono-dispersed particle, stabilization, and prevention of agglomeration.

Depending on the specific applications, NPs are fabricated into metallic, semiconductor, lipid, protein, and polymeric structures. For example, metallic gold (Au), silver (Ag), and copper (Cu) NPs have plasmonic characteristics which upon excitation with laser induce surface plasmon resonance (SPR). Therefore, surface functionalization with monoclonal or polyclonal antibodies can be probed for the detection of biomolecules such as cells, proteins, enzymes, growth factors, and so on. Further, the bactericidal activity of AgNPs makes them a prominent player in developing antimicrobial surfaces. The semiconductor quantum dots (QDs), also known as "zero-dimensional" NPs, display inherent fluorescence with high photostability and high quantum yield. The photoluminescent QDs encapsulated in biocompatible polymeric NPs have been widely used for bioimaging and fluorescent resonance energy transfer (FRET) applications (Beija et al. 2012; Kini et al. 2018, 2019; Van Vlerken and Amiji 2006). Use of biocompatible polymers like polylactic acid (PLA), poly(N-isopropylacrylamide) (PNIPAM), chitosan, alginate, polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and respective copolymers is highly promising and demanding for therapeutic applications (Uhrich et al. 1999). Nanocarriers fabricated from such polymeric materials for drug delivery not only induce the therapeutic efficacy but also enable selective targeting and enhance the cellular uptake efficiency. Other nanocarriers including liposomes (lipid-based NPs), dendrimers (hyperbranched polymeric macromolecules with the central core from where polymeric branches originated for drug entrapment), polymeric micelle formed by oil in water or water in oil emulsions, and fullerenes (spheroidal carbon nanostructures) are used as drug carriers for drug delivery applications. NPs such as QDs (semiconductor-based fluorescent nanocrystals), iron oxide-based superparamagnetic NPs (IO for magnetic hyperthermia), Au NPs (for photothermal therapy), AgNPs (for water disinfectant), and titanium oxide (TiO_2) and zinc oxide (ZnO) NPs are mainly used for imaging and diagnostic purposes (Beija et al. 2012; Van Vlerken and Amiji 2006), and carbon-based NPs like graphene and carbon nanotubes (CNTs) are extensively used for drug delivery and biosensing applications. Liposome-based doxorubicin (Doxil) (Mousa and Bharali 2011) and albumin-based paclitaxel (Abraxane) are clinically approved and marketed for cancer treatment (Hawkins et al. 2008; Li and Wallace 2008). Some of the PLGA NPs for the delivery of anticancer agents such as leuprolide acetate,

buserelin acetate, and triptorelin pamoate were successfully used for prostate cancer therapy (Mundargi et al. 2008).

Nanotoxicology deals with the study of the toxicity of nanomaterials at the cellular, organism, and environmental levels. So the serious concern is about the effects of NPs exposure because individual NPs are highly reactive due to high surface energy which means a significant mass of NPs can pose a serious threat to health compared to the equivalent mass of bulk material. Earlier evidence and current knowledge on NPs suggest that one of the main reasons for nanotoxicity in cells is oxidative stress (Aguilar 2012; Stone and Donaldson 2006). Tiny NPs such as carbon black, fullerenes, CNTs, asbestos, etc. causing ambient pollution in the atmosphere generate radicals with unpaired electrons which makes them highly reactive species (Elsaesser and Howard 2012; Oberdörster 2010). Therefore, the interaction of such free radicals with cells disturbs the balance maintained by antioxidants such as vitamins, glutathiones (GSH), and peroxidases. Industrial production of NPs derived from metals and semiconductors like silicon, titanium, gold, zinc, silver, and their respective oxides has shown a link between oxidative damage and diseases like asthma, cancer, cardio- and hepatotoxicity, and immune-related disorders (Baky et al. 2013; Chen et al. 2018; Gaiser et al. 2013; Khanna et al. 2015; Lanone and Boczkowski 2011).

Toxicological aspects of NPs are chasing technological developments like a shadow as by-products of nanosynthesis process, tissue accumulation, unpredictable and adverse consequences after exposure, systemic toxicity, enhanced reactivity due to high surface area, and toxic degradation products cause adverse health effects. Therefore, toxicological data of NPs at cellular as well as organ level is a prerequisite before taking into the field and also useful for safety and risk assessment. In vitro studies are conducted in the presence of antioxidants present in the serum which may neutralize the oxidative effect of NPs leading to false positive estimation of biocompatibility. Nevertheless, there are several physical, chemical, and biological factors of NPs that influence the toxicity. For example, ultrafine particles with size <100 nm can penetrate the skin; deposit in the lungs, liver, and kidney; and cause chemical and physical effects in cells (Borm et al. 2006; Buzea et al. 2007). Chemical effects include solubility, reactive oxygen species (ROS) generation, lipid peroxidation, catalytic oxidation and reduction of functional proteins, ionic imbalance, and change in intracellular pH. Physically NPs can cause disruption of the membrane, protein aggregation and DNA damage, and barrier formation for cellular communications. Though these effects are dependent on the size, shape, charge, surface energy, and ligand functionalization, there is no accurate pattern in physicochemical parameters which could predict the toxicity of neither NPs nor epidemiological data available. For example, different NPs having the same structural backbone may cause variable toxicity due to different surface functionalization. Sometimes lack of awareness about handling prepared NPs may cause direct exposure of NPs to human body or environment as most of the bottom-up methods do not require well-equipped clean rooms and aseptic conditions. Similarly, by-products of purified nanomaterials also contain nanomolecules which contaminate water and air resources. Apart from physicochemical and cellular factors,

assessment of doses; systemic administration including nanodrug delivery to intravenous, transdermal, and blood-brain barrier; and pulmonary routes and biodistribution are contributing to systemic toxicity. To counter such problems, internationally standardized protocols for handling NPs and safety protocols need to be developed and validated. However, monitoring long-term effects of engineered NPs which are already commercialized for applications like cosmetics, electronics, food additives, clothing, sports materials, etc. becomes challenging. Therefore, it requires strong earnestness to understand the basic scientific mechanism of toxicity of various anisotropic NPs at cellular levels both in vitro and in vivo before toxicants reach the alarming level. Further, accurately determining the toxicity limit of physicochemical parameters of NPs used for clinical studies could allow researchers to design nanomaterials in the future.

Considering the above facts, assessment of various NPs toxicity at cellular as well as organism level is indispensable. This knowledge of nanotoxicology would help the researchers and clinicians to set safety parameters for the usage of NPs in various biomedical applications. Herein, this chapter describes the toxic effects of various NPs on cellular processes involving signaling, proliferation, growth, division, and death pathways. Similarly, the toxicity of NPs is associated with the physiological functioning of the organisms such as development, reproduction, and behavior. Furthermore, it is well documented that cellular and organism toxicity leads to various lifestyle diseases. Henceforth, this study focuses on the potential dangers of diverse NPs and their associated health risks like cancer and other problems as described in the following (Fig. 21.1).

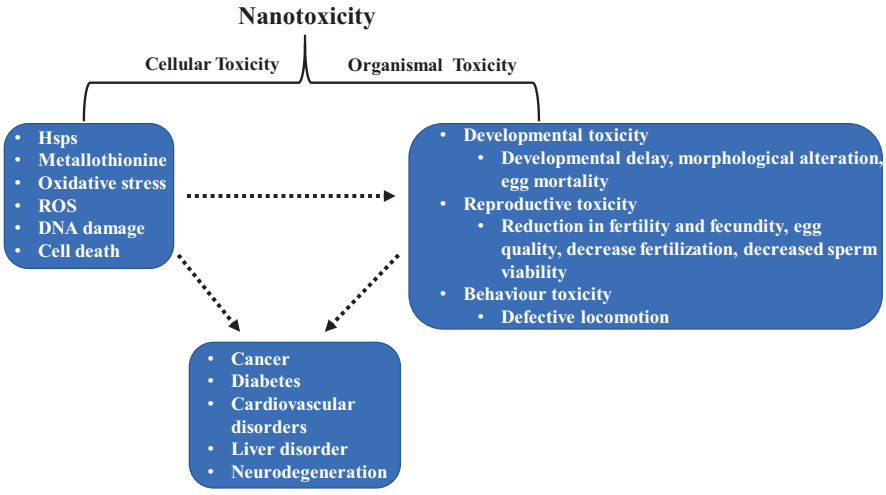

Fig. 21.1 Schematic representation of nanotoxicity

21.2 Cellular Nanotoxicity

Responses at the cellular level are one of the earliest reactions which help the cells to defend and recover from stressful events. The interaction of NPs with cells could trigger various cytotoxic effects (Table 21.1). Therefore, illustrating the effect of NPs at the cellular level is a critical aspect of human risk assessment and has been receiving great interest in the process of implementation of NPs. NPs are different in nature due to their composition and conformation; therefore cellular toxicity could be assessed at the different level of regulations. Among the multiple cellular responses, upregulation of heat shock proteins (Hsps) is considered as an early toxicity biomarker (Gupta et al. 2010). Increased Hsps level in the cell prevents protein aggregation and other protein modifications (Chatterjee and Burns 2017; Takalo et al. 2013). Since the last decade, modulation in Hsps has been considered as an early sensor of NPs toxicity. Recently, Masouleh et al. (2017) and Krishnaraj et al. (2016) observed an increase in *hsp70* mRNA levels in Ag NPs-exposed juvenile *Caspian kutum* and zebrafish, respectively. Similar upregulated levels of Hsp70 were observed with ZnO and silica NPs exposure in *Drosophila*, TiO_2 NPs in Caribbean reef-building coral, Au NPs in *Daphnia magna*, Cu NPs in *Takifugu fasciatus*, and IONPs in mice (Dominguez et al. 2015; Jovanovic and Guzman 2014;

Table 21.1 Nanoparticles toxicity at cellular and organismal levels

Nanoparticles	Cellular effect	Organismal effect
Ag NPs	Hsp70, metallothionein, oxidative stress and ROS	Decrease body proportion and depigmentation
MSN and silica NPs	Hsp70, Hsp22, Hsp27, Hsp60, Hsp90, metallothionein, oxidative stress and ROS	Sperm abnormalities, malformation, and impairment in swimming activity
ZnO NPs	Hsp70, metallothionein, ROS, DNA, and protein damage	Decreases the developmental stage, increases egg mortality, and small size of organism
TiO_2 NPs	Hsp70, apoptosis and TLR signaling, ROS, and JNK activation	Defective larval crawling and climbing behavior
Au NPs	Hsp70, Hsp90, apoptosis, inflammatory response	Inhibition of ectodermal differentiation, abnormal embryonic development and abortion, abnormal reproduction, reduced swimming activity
Fe_3O_4NPs	Hsp 70, cytokine production, oxidative stress	Embryo mortality, delay in hatching and malformation
QD NPs	Metallothionein, oxidative stress, and ROS	Decrease heart and hatching rate, pericardial and yolk sac edema
CuO NPs	Hsp70, metallothionein, and oxidative stress	Developmental delay and structural changes such as skeletal rods and shorter arms
Bi_2O_3	Hsp70, metallothionein, and oxidative stress	
ZrO_2	Glutathione peroxidase and oxidative stress	Reduction in the climbing activity

Pandey et al. 2013; Siddique et al. 2014; Sundarraj et al. 2017; Wang et al. 2018b). Such upregulation of Hsp70 has been proposed as an early bioindicator of cellular stress. Nevertheless, researchers raised the concern that one class of gene/protein cannot work as universal bioindicator as chemicals are different in nature (de Pomerai 1996; Gupta et al. 2010). In accordance with this concern, significant induction in the other class of *hsps* such as *hsp22* in *Drosophila* larvae after exposure to silica NPs has been observed (Pandey et al. 2013). Similarly, increased Hsp90 expression along with Hsp70 has been recorded after polystyrene nanoplastic and Au NPs exposure in *Daphnia pulex* and *Sparus aurata*, respectively (Liu et al. 2019; Teles et al. 2018). However, Petrache Voicu et al. (2015) observed downregulation in Hsp27, Hsp60, and Hsp90 protein expression in silica NPs-treated MRC-5 cell lines. Along with Hsps, metallothionein is also considered as a prominent biomarker of cellular toxicity. Metallothioneins are intracellular cysteine-rich, metal-binding proteins found from bacteria to human (Ruttkay-Nedecky et al. 2013). Increased metallothionein levels in the cell enhance detoxification, scavenge free radicals, and inhibit pro-apoptotic mechanisms (Thirumoorthy et al. 2007). Thus, the expression of metallothionein was examined in the metal NPs. Horie et al. (2018) and Miyayama and Matsuoka (2016) showed upregulation of metallothionein 2A (MT2A) in ZnO, copper oxide (CuO), bismuth oxide (Bi_2O_3), and AgNPs-exposed A549 cells due to release of metal ions in the cell. Rocha et al. (2018) investigated the effect of QDs on metallothioneins (MTs) isoforms (mt10IIIa and mt20IV) expression using mussel *Mytilus galloprovincialis*. Same group observed concentration and time-dependent changes in mt20IV mRNA levels and suggested its role in QDs metabolism. Parallel to Hsps and metallothionein induction, antioxidant defense mechanism and generation of ROS of an organism have been also used as an indicator of cellular toxicity (Auten and Davis 2009; Fu et al. 2014). ROS are unstable molecules containing unpaired oxygen (superoxide anion, hydroxyl radicals, peroxynitrite) atom. This unstable form of oxygen is collectively called free radicals. Excess formation of ROS due to the stressor toxicants may cause protein, lipid, and DNA damage in the cell that may lead to many disease conditions (Schieber and Chandel 2014; Sharma et al. 2012). As a protective mechanism, cells have universal conserved enzymatic (e.g., superoxide dismutase (SOD), catalase (cat), glutathione reductase, glutathione peroxidase (GPx)) and nonenzymatic (e.g., glutathione, vitamins C and D) antioxidant defense mechanism that helps in ROS detoxification. In this line, an ample number of reports highlight oxidative stress due to NPs exposure. Zhang et al. (2018b) studied the effect of AgNPs on soil nitrogen-fixing *Azotobacter vinelandii* bacteria. AgNPs exposure caused oxidative cellular damage to bacteria due to excess ROS and hydroxyl radical generation. Rossner Jr. et al. (2018) studied the effect of inhalation of acute and sub-chronic ZnO NPs by mice using next-generation sequencing and found modulation of splice junction genes associated with oxidative stress, immunity, and DNA repair. Similarly, increased ROS level was observed in ZnO NPs-exposed human umbilical vein endothelial cell line (Qiao et al. 2018b). Mesoporous silica NPs (MSNs) are extensively used as a drug delivery carrier. Hozayen et al. (2019) found that MSNs exposure to rats for 30 days causes cardiac and pulmonary toxicity due to increase

in ROS generation and malondialdehyde and decline in antioxidant defense mechanism in the heart and lung of rats. Likewise, several other NPs have been shown oxidative stress (changes in antioxidant enzyme activities) and ROS generation in various in vivo and in vitro model systems (Abdelhalim et al. 2018; Gallo et al. 2018; Kong et al. 2019; Soltani et al. 2018; Yue et al. 2018). The immune system provides the first-line defense against infection. In addition immune toxicity is the sensitive area under chemical toxicants exposure (Vos et al. 1989). Dhupal et al. (2018) exposed RAW 264.7 cells (macrophage) to TiO_2 NPs and observed concurrent induction of macrophage-mediated apoptosis and Toll-like receptor (TLR) signaling through ROS-mediated JNK and p38MAPK pathways. Similarly, apoptosis and inhibition of TNF-α and IL-6 were found in T lymphocytes after exposure to mesoporous carbon NPs (MCN) (Li et al. 2018). Another study by Shah et al. (2018) showed human T lymphocytes exposed to IONPs decreased the cytokine production and proliferation of mitogen-activated T cells due to a redox imbalance. The effect of ZnO NPs was assessed by Abass et al. (2017) on albino mice spleen and thymus. The group observed an increase in total leucocytic count and decrease in RBCs, platelet counts, and Hb % due to the oxidative or inflammatory pathway. Recently, Manzo et al. (2017) exposed sea urchin with nanosized ZnO via food and observed DNA damage (through comet assay) in their coelomocytes (immune effector cells). Alaraby et al. (2015) examined the effect of cadmium selenide (CdSe) QDson *Drosophila* hemocytes. They found CdSeQDs cross the intestinal barrier and cause oxidative stress and DNA damage in hemocytes. Asadpour et al. (2014) found reduction in cell viability and glutathione peroxidase activity in ZrO2-exposed N2a and PC12 cells. Similar to immunotoxicity, NPs also interfere with hematopoiesis that leads to several blood disorders. Due to high metabolic activity, the hematopoietic system is highly prone to biological and physical stress. In this line, several reports underline the negative impact of NPs on hematopoiesis process such as inhibition of erythrogenesis process in zebrafish after exposure to AgNPs (Cui et al. 2016). Liu et al. (2014) demonstrated the shrinkage and apoptosis of hematopoietic organs via an increase in ROS due to cadmium QDs exposure to *Bombyx mori*. However, melanin NPs exposure restores hematopoietic homeostasis in γ-radiation-treated mice (Rageh et al. 2015). Toxicomics study gives a broad idea to understand the toxicity in totality and to unravel the associated molecular mechanism. Analysis of global gene, protein, and metabolic changes associated with NPs helped environmental researchers to predict adverse responses to NPs. In this context, transcriptomic data identified differentially expressed genes associated with oxidative stress, detoxification, endocytosis, intestinal integrity, and iron homeostasis in IONPs-exposed *Caenorhabditis elegans* (Gonzalez-Moragas et al. 2017). In another toxicogenomic study, AgNPs exposed HepG2 cells revealed misregulation of genes related to metabolism, stress response, cell differentiation, cell death, and development (Sahu et al. 2015). Kumar Babele (2019) did the total protein and metabolite profiling in ZnO NPs-exposed budding yeast and found changes in 40% of total proteins and metabolites involved in energy metabolism, oxidative stress, DNA and protein damage, and membrane integrity. Mirzajani et al. (2014) studied AgNPs toxicity in *Oryza sativa* L. through proteomic approach. The results revealed that

AgNPs exposure to *O. sativa L.* root affects oxidative stress tolerance, Ca^{2+} regulation and signaling, cell division, apoptosis, and nucleic acid damage. Yang et al. (2010) identified 16 differentially expressed proteins in silicon dioxide NPs-exposed HaCaT cells that were linked to oxidative stress, cytoskeleton, energy metabolism, apoptosis, and tumor-associated proteins. In the past decade, miRNA has been established as a promising biomarker for toxicological studies. In this line, Qiao et al. (2018a) identified miRNAs associated with inflammation and vesicle-mediated transport, oxidative stress, apoptosis, and autophagy in ZnO NPs-exposed rats. Similarly, 202 microRNAs were differentially expressed in Au NPs-exposed human dermal fibroblast cells. These microRNAs are involved in 71 different biological pathways such as metabolic process, cell-cell communication, cell cycle, apoptosis, and inflammatory response (Huang et al. 2015). In conclusion, risk assessment of NPs has been found to be crucial as they can affect the cellular homeostasis in different ways.

21.2.1 The Organismal Nanotoxicity

Toxicity of acute exposure at the cellular level is usually associated with cells/tissue and used to establish the safety levels of toxicants (Gormley and Teather 2003). Moreover, accumulation of damage at cellular and tissue levels may pose a negative impact at the organismal level. However, sometimes due to physiological complexity, changes at cellular do not reflect at organismal levels. Thus, evaluating long-term/chronic effects on the basis of these acute tests may be multifaceted. Therefore, systemic studies of NPs at organismal levels are essential to deciphering the long-term impact on the organisms fitness such as reproduction, development, and behavior (Table 21.1). Abnormal development due to chemical exposure such as malformation, growth retardation, low birth weight, and behavior deficit are the important defects in biomedical research which needs to be explored. In this line, Maisano et al. (2015) investigated the effect of CuO NPs on the development of sea urchin embryo. They observed that CuO NPs exposure causes developmental delay, morphological alteration such as absent of skeletal rods, and shorter arms in the exposed organism. Embryonic exposure of CuO NPs to zebrafish showed shorter body axis, smaller eyes, underdeveloped liver, and a delayed retinal neurodifferentiation along with reduced locomotory ability. A similar study in zebrafish decreased the expression of *pax2* and *pax6* genes which are involved in neural differentiation and decreased sizes of neural structures. Studies involving cerium oxide (CeO_2) NPs exposure in zebrafish larvae showed growth inhibition, decreased body weight, and delayed vertebral calcification (Lin et al. 2014). The effect of ZnO NPs on development was investigated in amphibians by Spence et al. (2016). The result showed that ZnO NPs decrease the developmental stages, increase egg mortality, and reduce the body size of an organism. In another case, Hao et al. (2017) studied the effect on offspring of ZnO-exposed hens and found that ZnO NPs cause liver dysfunction due to inadequate lipid synthesis (15 genes were found downregulated after ZnO exposure). Developmental exposure of Ag NPs to Drosophila larvae

resulted in delayed and reduced developmental success and decreased body proportion (Panacek et al. 2011; Posgai et al. 2011). Phenotypic defects such as depigmentation and soft cuticle was also found when AgNPs were exposed in *Drosophila* (Gorth et al. 2011; Posgai et al. 2011). Administration of Au NPs to pregnant mice for over 3 days resulted in inhibition of ectodermal differentiation, uncharacteristic embryonic development, and abortion (Yang et al. 2018). Likewise, Hong et al. (2016) observed that TiO_2 exposure to mice during pregnancy/lactation time poses negative effect on the development of the central nervous system (diminishing of cerebral and cerebellar cortex, reduction in neurons, edema, nuclear condensation, and decrease in learning and memory capacity) in mice offsprings. Another report by P et al. (2018) showed ZrO_2NPs induced embryonic mortality, delay in hatching, axis and tail bent, and other malformation in zebrafish. In summary, these results show that exposure to NPs cause severe developmental problems, which might be responsible for various health adversities such as reproduction, neurological, and behavior abnormalities. In the last decade, several publications have shown the reproductive adversities of NPs. These include the effect on fertility and fecundity, fertilization, and egg quality, disrupting the balance of sex hormones and many more. Preaubert et al. (2016) investigated the effect of low CeO_2NPs concentration on in vitro fertilization in mice and found decrease in fertilization along with oxidative stress and DNA damage to spermatozoa and oocytes. However, supplementation of CeNPs at low concentration enhanced in vitro embryo production of prepubertal ovine oocytes (Ariu et al. 2017). A study involving female mice exposed to Cu NPs showed adverse changes in the reproductive biology of the organism (Zhang et al. 2018a). Researchers exposed human extravillous trophoblast cells and mice to Cu NPs and found an imbalance in sex hormones and also induced apoptosis and cell cycle arrest at cellular levels. In another study CuO NPs exposure to sea urchin showed sperm toxicity. This effect could be linked to decreased sperm viability, defective mitochondrial activity and increased ROS levels, lipid peroxidation, and DNA damage (Gallo et al. 2018). In *Paracentrotus lividus*, ZnO NPs exposure causes morphological alteration in the offspring, which may be due to sperm DNA damage. Wang et al. (2018a) observed lesser reproduction phenotype in Ag NPs-exposed *Daphnia similis*. This could be associated with downregulation of fatty acid contents after Ag NPs exposure to the organism. Hong et al. (2015) demonstrated that TiO_2 NPs cross the blood-testis barrier, accumulate in the testis, and negatively affect spermatogenesis process in mice. The authors found downregulation in the expression of several testis-specific genes (*Cdc2*, *Cyclin B1*, *Dmcl*, *TERT*, *Tesmin*, *TESP-1*, *XPD*, and *XRCCI*), which may be responsible for the reduced spermatogenesis process in TiO_2-exposed mice. In addition to that, TiO_2 NPs exposure (5–30μg/mL) in Sertoli cells showed cell inhibition, lactate dehydrogenase release, and induction of apoptosis (Hong et al. 2016). Kim et al. (2013) evaluated a multigenerational transfer effect of Au NPs using *C. elegans* and observed no signification effect on the survival rate of the organism. However, their reproduction rate was significantly decreased and caused abnormalities in the bag of worms. Evaluation of an organismal behavior is an important rule to determine physiological homeostasis which is crucial for proper body functioning. Among various behavior, locomotion

is a vital behavior of an organism which affects various physiological processes such as reproduction, food intake, and predation. When the two *Daphnia* species *Daphnia similis and Daphnia pulex* were exposed to CeO_2 NPs, they exhibited a decreased swimming velocity by 30% and 40%, respectively (Artells et al. 2013). The author also found some morphological changes like presence of reliefs on the cuticle and longer distal spine in *D. similis*, which may be the cause of CeO_2 aggregation. Michalec et al. (2017) observed a decreased swimming activity and lower velocity in Au NPs-exposed calanoid copepod. Sabat et al. (2016) demonstrated that TiO_2 exposure to Drosophila larvae resulted in defective larval crawling and climbing behavior due to impaired brain physiology. Similar reduced (25%) climbing activity was recoded in zirconium dioxide (ZrO_2) NPs-exposed *Drosophila* (Mishra et al. 2017). Administration of silica NPs to mice showed negative effect on male reproductive biology such as damaged seminiferous epithelium, decreased sperm quality, and sperm abnormality (Zhang et al. 2016). Another study on zebrafish demonstrated that silica and Fe_3O_4 NPs exposure causes tail and head malformation and delayed hatching along with impaired swimming behavior (Duan et al. 2013; Zhu et al. 2012). The effect of carbon QD was investigated by Xiao et al. (2016). They exposed rare minnow embryos/larvae to carbon QD and found decreased movement in minnow embryo, increased heart rate, decreased hatching rate, pericardial and yolk sac edema, and malformation. The group suggested that these phenotypes might be mediated by increased oxidative stress and misregulation in development-associated genes.

21.3 Nanoparticles Affecting the Health

Recently emerging studies specifically concerning the behavior and toxicity of NPs that mediates health complications are gravitating. Moreover, not all toxicological studies to date deal with NPs. Hence, the pessimistic side of NPs is overlooked due to its huge impact on improving the technology. Health challenges are many; however, difficulties with inhalation, carcinogenicity, cardiovascular, neurodegenerative, and hepatotoxicity are the main problems associated with toxic NPs. Further, the specificity of nanotoxicants that eventually effect health is described.

21.3.1 Nanoparticles Linked to Cancer Development

According to a report submitted by the American Association for Cancer Research, it is prudent to limit the introduction of NPs into the environment until we understand which NPs are potentially harmful. For instance, Au NPs at an optimum nanosize range is pertained to photochemically damage tumor cells (Khanna et al. 2015). However, the rogue size of Au NPs can cause adverse effects at the cellular level for normal cells by interacting with cellular components and damaging the DNA (Alkilany and Murphy 2010). Additionally, exposure and inhalation of tungsten carbide cobalt (WC-Co) dust composed of NPs in metal manufacturing, drilling, and

mining facilities can cause an increased risk of lung cancer (Armstead and Li 2016). Further, polyurethrane NPs-based breast implants are associated with causing anaplastic large cell lymphoma (ALCL), a rare form of cancer (Keith et al. 2017). Epidemiological research concerning leukemia-specific cancer and bladder cancer reports that low-cost commercial hair dyes slog by the formation of nanocrystals from lead sulfide (Towle et al. 2017; Turati et al. 2014). With emerging concerns over NPs safety, the application of inorganic ceramic NPs such as silica, titanium, and alumina is not being used in cancer therapy due to their non-biodegradable nature. Hence, the inability to molecularly decompose ceramic NPs in the environment limits its extent of application.

21.3.2 Nanoparticles Linked to Diabetes

Recently, CeO_2NPs have been implicated in diabetes-induced testicular sperm damage by attenuating hyperglycemia oxidative damage in different organs (Artimani et al. 2018). In contrast to the results of the study, it is reported that the administration of different doses of CeO_2NPs in healthy individuals causes oxidative damage in testes resulting in diminutive sperm quality, disruption of the endocrine system, and inflammation (Adebayo et al. 2018). In another approach, insulin-loaded aquasomes are fabricated with self-assembled nanocrystalline carbohydrate-coated calcium phosphate dihydrate ceramic core to optimize blood glucose in the targeted site using parenteral delivery system (Cherian et al. 2000; Umashankar et al. 2010). However, intrinsic biophysical constraints of the three layered conformations of aquasome can lead to an adverse or allergic reaction with suboptimal pharmacological activity (Collen et al. 2010).

21.3.3 Nanoparticles Linked to Cardiovascular Diseases

A leading cardiovascular disease, atherosclerosis is causing an increase in the mortality rate worldwide. This is also promoted by certain calcifying NPs (calcium phosphate). These mineral chaperones augment calcification of arterial vascular smooth muscle cells in vitro as suggested by many studies (Barba et al. 2012; Hunter et al. 2014). Another in vitro study has also revealed that engineered carbon NPs (CNPs) and single-walled nanotubes induce the aggregation of platelets, thus enhancing vascular thrombosis in rat carotenoid artery (Radomski et al. 2005). Recently Zhou et al. (2018) found the accumulation of CNPs in zebrafish after a long exposure. The study exhibited that the accumulation of CNP is responsible for structural changes in myocardial tissue and expression of inflammatory cytokines. Another study by El-Hussainy et al. (2016) showed that Al_2O_3 NPs exposure to rat for 14 days (30 mg/kg) altered ECG, disturbed serum markers, and enhanced inflammation and oxidative stress in myocardium. Altogether all these changes lead to myocardial dysfunction in the organism. Further, ceramic NPs used commonly for drug delivery exhibit carcinogenic effect as well as oxidative stress or cytotoxic

activity in the heart, lungs, liver, and brain (Grundmann et al. 1989; Singh et al. 2016).

21.3.4 Nanoparticles Linked to Liver Diseases

The effect of ZnO NPs has been studied on a specific population of mice with inflammatory bowel disease induced by indomethacin. Histopathological examination shows high hepatic zinc detection postexposure that causes punitive lesions in the liver (Du et al. 2018). Jia et al. (2017b) investigated the effect of TiO_2 NPs on mice liver tissue and found adverse effects such as bulgy hepatocytes along with nuclear condensation and apoptosis. This could be associated with increased ROS levels and decreased expression of cytoprotective genes. Yu et al. (2017) demonstrated that SiO_2 NPs exposure in mice causes liver fibrosis. Further they explained SiO_2 NPs cause oxidative stress and activate TGF-β1/Smad3 signaling, which promotes liver fibrosis. Oral exposure of nontoxic doses of Ag NPs to normal and obese mice was studied by Jia et al. (2017a). The group found that AgNPs deposits only in the liver of obese mice which induce liver inflammation and suppresses fatty acid oxidation lead to steatohepatitis. Moreover, an evaluation of the toxic potential of AgNPs shows significant endoplasmic stress response in the liver, kidney, and lungs that can be avoided by rational use within safe dose (Huo et al. 2015).

21.3.5 Nanoparticles Linked to Neurodegeneration

The most common neurotoxic element on earth is aluminum with a plausible link to Alzheimer's disease (Tomljenovic 2011). Incremental acquisition of aluminum NPs (Al_2O_3) over a lifetime favors selective accumulation in sufficient amounts to cause brain damage (Krewski et al. 2007). In another study, a single-dose of oral ingestion of TiO_2, ZnO, and Al_2O_3NPs shows translocation of NPs to the central nervous system. The accumulation of NPs leads to axillary toxicity, subsequently damaging the normal metabolism of the brain (Shrivastava et al. 2014). Pathological effects such as destruction of blood-brain barrier, cellular edema, and brain tissue necrosis are observed in the presence of differently sized TiO_2 NPs in rat astrocytes (Liu et al. 2013). Moreover, the learning abilities of rats are affected due to dopaminergic neuronal dysfunction in the presence of manganese dioxide (MnO_2) NPs (Li et al. 2014). A study reveals that susceptibility of pregnant mice to neuroendocrine changes intensifies twofold in the presence of NPs compared to a nonpregnant female. Here, QDs are transferred across the placental barrier with increasing dose, suggesting the transplacental transfer potential of NPs (Chu et al. 2010; Wick et al. 2010). Further, neuropsychiatric complication was observed among patients due to flaking off of the metal shavings of the faulty hip implant followed by the release of chromium and cobalt toxicants into blood streams indicating possible dementia (Green et al. 2017).

21.4 Conclusions

The use and production of NPs have been grown worldwide from the last decade, and their exposure to human beings and other organisms has created an alarming situation. Moreover, there are no accepted occupational and environmental levels of NPs causing toxicity. Therefore, the rapid risk assessment of NPs is very much essential in the present scenario. In this context, researchers have explored various biomarkers or readouts for early and rapid risk assessment of NPs exposure. These include induction of Hsps, metallothionein, ROS generation, DNA damage, and different developmental, behavioral, and reproductive parameters (Table 21.1). Moreover, all these changes at the cellular and organismal levels might be responsible for various health emergencies. However, the mechanistic insight of NPs-induced health adversities is still open for an investigation. We hope that the ongoing studies across the world might be helpful to decipher the molecular mechanisms associated with NPs-induced toxicity. Apart from this, the promotion and execution of nanosafety programs at social, academic, and economic levels might be helpful to render the NPs-associated health risks.

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