

FUNCTIONALIZED NANOPARTICLES AND THEIR INFLUENCE ON ANIMAL CELL PHYSIOLOGY, OXIDATIVE STRESS AND CHROMOSOMAL STABILITY

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ABSTRACT

Objective: Functionally modified nanoparticles (FNPs) have emerged as pivotal vectors in biomedical nanomedicine, offering tailored physicochemical attributes that enhances drug delivery, diagnostic imaging, targeted gene transport and oncological therapeutics. Surface Functionalization utilizing synthetic or biological macromolecules-including polymers, monoclonal antibodies, functional peptides, lipids and biomolecules-impares colloidal stability, prolongs systemic circulation, and maximizes bio-distribution and cellular uptake efficiency. This review critically evaluates the primary structural classes of FNPs, their endocytic internalization pathways, and subcellular distribution, while elucidating the toxicological paradigms governing nanoparticle-induced cellular and genomic perturbation in mammalian systems. This review uniquely integrates nanoparticle surface functionalization profiles with microRNA dysregulation, chromatin remodeling, and structural chromosomal instability (CIN) mechanisms, while providing a critical evaluation of methodological artifacts and predictive computational models. **Mechanism:** Cellular processing of FNPs initiates specific biological cascades dictated by surface architecture and particale kinetics. Intracellular toxicity is predominantly driven by excess production of reactive oxygen species(ROS), which overwhelms endogenous antioxidant, defenses and triggers mitochondrial membrane depolarization, repiroatary chain disruption, lipid peroxidation, and protein carbonylation. At the nuclear level, toxic events proceed via direct and indirect pathways: ultra-small particles penetrate nuclear pore complexes or interact with naked chromatin during mitosis, whereas cytoplasmic oxidative cascades induce single- and double-strand DNA cleavage, alter DNA methyltransferase (DNMT) dynamics, dysregulate oncogenic microRNAs(e.g. miR-21 and miR-155), and disrupt spindle assembly checkpoints (SAC). **Finding in brief:** Exposure to reactive FNPs induces systemic intracellular distress, culminating in structural membrane destrabilization, chronic pro-inflammatory signaling, telomeric guanine oxidation, and micronucleus formation- a primary biomarker of clastogenic and aneugenic chromosomal instability(CIN). Conversely, strategic surface modification enables localized hyperthermic, photothermal and redox- responsive therapeutic interventions. Recent advances in safe-by-design (SbD) nanotechnology, biodegradable polymeric matrices, provide viable pathways to decouple therapeutic efficacy from cellular injury. **Conclusions:** While surface-functionalized nanoparticles offer transformative clinical utility, significant translational challenges persist regarding chronic bio-accumulation, off-target biodistribution, environmental ecotoxicity, and long term genomic instability. Comprehensive multi-omics profiling, predictive computational toxicology, and physiologically relevant three- dimensional (3D) tissue models are imerative to advance safe clinical translation.

KEYWORDS: nanotechnology, nanoparticles, microRNA, nanomedicine, Chromosomal Stability nanotoxicology, oxidative DNA damage.

1. INTRODUCTION

Nanotechnology has emerged as a primer domain within contemporary biomedical science, offering advanced paradigms for disease diagnostics, targeted drug oncology. Nanoparticles are defined as particulate materials possessing at least one dimension in the 1-100nm size regime. At this spatial scale, they exhibit unique physicochemical attributes distinct from their bulk counterparts, including a high surface-area-to-volume ratio, enhanced catalytic reactivity, tunable optical properties, and tailorable surface chemistry. Consequently, nanomaterials have been widely adopted across industrial and biomedical application. Over the past decade, functionalized nanoparticles strategies that optimize colloidal stability, targeted accumulation, cellular uptake, therapeutic efficacy, and biocompatibility. Surface functionalization involves conjugating ligands- such as polymers, surfactants, peptides, antibodies, polysaccharides, nucleic acids, proteins, or therapeutic agents- onto the nanoparticle substrate. These modifications prolong systemic circulation, minimize particle aggregation, attenuate immunogenicity, and enhance site-specific delivery to diseased tissues. Accordingly, FNPs represent a cornerstone of modern nanomedicine, exemplified by PEGylated gold nanoparticles for oncology, mRNA-loaded liposomes, antibody-drug conjugates for targeted tumor therapy, and polymeric drug delivery platforms.^[1]

Reactive oxygen species (ROS), such as superoxide anion, hydroxyl free radical, singlet oxygen, and hydrogen peroxide are continuously generated during physiological metabolic processes in aerobic organisms. Under physiological homeostasis, endogenous antioxidant networks- comprising superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), thioredoxin, and reduced glutathione (GSH)-maintain cellular redox balance. However, nanoparticle exposure disrupts this defense architecture via surface catalytic ROS generation and mitochondrial electron transport chain impairment. Sustained intracellular ROS accumulation causes extensive oxidative damage to structural proteins, membrane phospholipids, mitochondrial integrity, and genomic DNA.^[2]

Chromosomal Instability (CIN) represents a primary downstream consequence of nanoparticle-mediated oxidative stress. CIN as one of the most significant effects of oxidative damage caused by nanoparticles. Chromosomal instability can be defined as alterations in the structure and/or number of chromosomes, which include chromosome breakage, aneuploidy, genomic rearrangements, micronuclei disrupt DNA replication fidelity, mitotic spindle assembly, centrosome biogenesis, telomere maintenance, and DNA repair pathways. Such genomic instability is strongly implicated in oncogenesis, tissue dysplasia, and acquired therapeutic resistance. Furthermore, nanoparticles modulate epigenetic homeostasis and microRNA (miRNA) expression profiles by altering DNA methylation patterns, post

translational histone modifications, and chromatin architecture, thereby dysregulating gene expression and cellular differentiation. Concurrently, aberrant miRNA signaling amplifies pro-inflammatory cascades, apoptotic pathways, and systemic oxidative stress.^[3,4]

In this review, the implications of nanoparticle functionality on the physiological functions of cells, with a special focus on oxidative stress, mitochondrial dysfunction, epigenetics, chromosomal instability, and genotoxicity, are analyzed in a critical manner. In addition, this review focuses on potential therapeutic uses of engineered nanoparticles as well as safety issues in nanomedicine.

2. CLASSIFICATION OF FUNCTIONALIZED NANOPARTICLES

Nanoparticles functionalized by some specific chemicals may be categorized based on their chemical nature, physical nature, morphology, and application in biomedical science. Surface functionalization has an impact on nanoparticle biodistribution, pharmacokinetics, efficacy, cellular uptake, and cytotoxicity profile.

2.1. Metal Nanoparticles

Metals in the form of nanoparticles are some of the most studied nanomaterials in the field of biomedical research owing to their distinct optical, catalytic, and antibacterial properties. Among the metallic nanoparticles used in medicine and biotechnology include gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), platinum nanoparticles, and copper nanoparticles. AuNPs have shown high biocompatibility, surface plasmon resonance, and chemical stability. The AuNP functionalized forms are used in biosensing, bioimaging, targeted drug delivery, and photothermal cancer treatment applications. PEGylation, peptide conjugation, antibody conjugation, or aptamer functionalization increase the targeting ability and minimize clearance by the immune system. But their toxicity varies significantly based on the nanoparticle size, shape, dose, and surface modifications. Small AuNPs can even enter cell nuclei and undergo interactions with the chromosomal DNA leading to DNA oxidative damage and genomic instability. Silver nanoparticles are extensively utilized due to their potent antimicrobial efficacy, localized surface plasmon resonance, and catalytic activity. Firstly, AgNPs exhibit potent antibacterial, antifungal, and antiviral activities. Silver nanoparticles are used in wound dressings, coatings for medical devices, textiles, and cosmetics. However, silver nanoparticles can cause oxidative stress, inflammation, mitochondrial malfunction, and apoptosis in mammalian cells. The Ag⁺ ions' liberation is assumed to be responsible for cytotoxicity and genotoxicity.^[5,6]

2.2. Metal Oxide Nanoparticles

Metal oxide nanoparticles find application in various areas due to their catalytic, magnetic, photocatalytic, and antioxidant characteristics. Titanium dioxide

nanoparticles (TiO₂NPs) have a wide range of applications including sunscreen products, drug production, food additives, and paint products. Titanium dioxide nanoparticles can produce ROS under ultraviolet light due to the photocatalytic nature of these nanoparticles. There are ongoing investigations on the use of functionalized TiO₂NPs in photodynamic therapy and antibacterial applications. ZnONPs have antimicrobial and anticancer activities. Functionalization increases their dispersibility, stability, and targeted nature. Nevertheless, the release of Zn²⁺ from ZnONPs might result in mitochondrial dysfunction, oxidative stress, and chromosome aberrations. Fe₃O₄NPs have multiple applications in MRI, targeted drug delivery systems, and hyperthermic treatment. The magnetic features of these nanoparticles assist in their specific localization in desired organs and tissues. Nevertheless, Fe³⁺ and Fe²⁺ ions released from these nanoparticles might induce ROS production via Fenton chemistry and damage DNA by oxidative stress. Ceria nanoparticles (CeO₂NPs) constitute a special type of antioxidant nanomaterials. Due to the redox cycle between Ce³⁺ and Ce⁴⁺, CeO₂NPs act as ROS scavengers and mimic some natural antioxidant enzymes, such as catalase and SOD. Cerium oxide nanoparticles have shown protective effects against oxidative injuries and neuronal pathologies.^[7,8,9]

2.3. Carbon-Based Nanoparticles

Carbon nanomaterials encompass carbon nanotubes (CNTs), graphene oxide nanoparticles, fullerenes, and carbon quantum dots. Carbon-based nanoparticles show remarkable electrical conductivity, heat resistance, and high tensile strength. CNTs have numerous applications in biosensing, tissue engineering, and drug delivery platforms. Nonetheless, research shows that CNTs cause sustained inflammation, oxidative damage, fibrosis, and genetic mutations due to their fibrous form and biopersistence. Graphene oxide nanoparticles demonstrate great ability to load drugs and functionalize surfaces. However, they can compromise membrane permeability and trigger toxicity owing to their edge shape and oxidation nature.^[10,11]

2.4. Lipid Nanoparticles

The significance of lipid nanoparticles (LNPs) was highlighted after their success in delivering mRNA vaccines. Lipid nanoparticles increase the stability of nucleic acids, enable cellular entry, and prevent the breakdown of RNA molecules by enzymes. While LNPs generally demonstrate reduced intrinsic oxidative toxicity and increased biocompatibility relative to metal nanoparticles,^[12] their safety profile is highly dependent on formulation parameters. Specifically, biocompatibility, cytotoxicity, and oxidative responses vary according to lipid composition, ionizable lipid structure, surface charge, dose, tissue distribution, and degradation behavior.

2.5. Polymeric Nanoparticles

Polymeric nanoparticles, including PLGA nanoparticles, chitosan nanoparticles, dendrimers, and nanocapsules, find broad applications in drug delivery and genetic engineering. Their biodegradable nature and modifiable surfaces enhance their effectiveness and reduce systemic toxicity.^[13]

2.6. Quantum Dots

Quantum dots refer to semiconductor nanocrystals with exceptional fluorescent and photochemical stability. They have found extensive applications in imaging, diagnostic tests, and biological sensing. Unfortunately, most quantum dots consist of hazardous heavy metals like cadmium and selenium, causing oxidative stress, mitochondrial dysfunction, neurotoxicity, and cell death.^[14]

3. CELLULAR UPTAKE MECHANISMS

The biological function of nanoparticles depends heavily on how they are taken up inside the cell and distributed within (Fig. 1, Table1). These nanoparticles internalize via multiple cellular entry pathways, including endocytosis, phagocytosis, macropinocytosis, receptor-mediated uptake, and passive diffusion.^[15,16,17]

3.1. Endocytosis and Receptor Specificity

Endocytosis is the main mechanism for nanoparticles entry into mammalian cells. The mechanisms of clathrin-mediated, caveolae-mediated, and clathrin/caveolae-independent endocytosis are highly influenced by the size, shape, surface charge, and surface modifications of nanoparticles. Positive nanoparticles bind well with negative phospholipids in plasma membranes, leading to enhanced electrostatically mediated cellular uptake. To achieve targeted internalization, nanoparticles are surface-functionalized with specific ligands (such as transferrin, folate, epidermal growth factor, or monoclonal antibodies) that display high receptor specificity. Surface-bound ligands recognize target cell surface receptors (e.g., transferrin receptors [TfR], folate receptors [FR- α] or integrins like $\alpha_v\beta_3$), initiating localized receptor clustering, plasma membrane invagination, and selective internalization.

3.2. Phagocytosis and Micropinocytosis

Phagocytosis plays a primary role in nanoparticle clearance by professional phagocytes, such as macrophages, monocytes and neutrophils. Large clusters or micron-scale aggregates of nanoparticles are preferentially phagocytosed following opsonization. Micropinocytosis mediates the non-specific fluid-phase internalization of solute molecules and suspended nanoparticles via actin-driven membrane ruffling and macropinosome formation.

3.3. Intra-Cellular Localization: Following endocytic internalization, nanoparticles undergo dynamic endosomal sorting and intracellular trafficking.

3.3.1. Early-to-late Endosomal Maturation

Internalized particles within primary endocytic vesicles are routed along the endo-lysosomal pathway. Early endosomes (pH $\approx$ 6.0-6.5) mature into late endosomes (pH $\approx$ 5.0-5.5), driven by Rab GTPase switching (e.g., Rab5 to Rab7 transition) and progressive acidification via vacuolar-type H⁺ ATPase.

3.3.2. Lysosomal sorting and Escape

Late endosomes fuse with hydrolase-rich lysosomes (pH $\approx$ 4.5-5.0). In lysosomes, acidic enzymatic breakdown promotes functional degradation or, in the case of metallic nanoparticles, accelerates toxic metal ion leaching (e.g., Ag⁺, Zn²⁺). To avoid degradation, engineered nanoparticles utilize endosomal escape mechanisms (such as the proton-sponge effect displayed by cationic polymers, membrane disruption, or pH-responsive lipid destabilization) to translocate into cytosol.

3.3.3. Retrograde and Direct Organelle Trafficking

Certain surface coatings permit nanoparticles to bypass lysosomal destruction via retrograde transport through the Golgi apparatus and endoplasmic reticulum(ER), utilizing Rab9 or Rab 11 recycling networks to access cytosolic and organellar compartments directly.

3.4. Protein Corona Formation

Following cytosolic entry or organelle targeting nanoparticles localize to lysosomes, mitochondria, the nucleus, endoplasmic reticulum, or cytosol. Lysosomal entrapment leads to localized enzymatic degradation and ion leaching. Mitochondrial uptake disrupts membrane potential, triggering ROS generation and ATP depletion. Ultra-small nanoparticles (< 10-15nm) can penetrate nuclear pore complexes or interact directly with naked chromatin during mitosis, elevating risks of genotoxicity, structural chromosomal aberrations, and chromosomal instability.

3.5. Protein Corona Formation

On entering biological systems, serum proteins rapidly absorb onto the nanoparticle surface to form a dynamic protein corona (hard and soft corona). The protein corona fundamentally dictates the nanoparticle's biological identity, cellular uptake routes, biodistribution, and immune systems recognition. Functionalization of the nanoparticle surface alters corona composition; for instance, PEGylation reduces complement opsonization and phagocytic clearance, prolonging systemic circulation time, whereas strongly cationic coatings promote non-specific protein binding and enhance membrane disruption and toxicity.

3.6. Determinant of Nanoparticle Toxicity and Sources of Experimental Discrepancy

The biological response to functionalized nanoparticles (FNPs) is governed by a complex interplay between intrinsic physicochemical characteristics and extrinsic

exposure conditions^[18] A major challenge in nanotoxicology is that studies evaluating apparently identical nanomaterials often report conflicting toxicological outcomes.^[19] These discrepancies primarily arise because nominal particle parameters in stock suspensions differ significantly from the effective parameters experienced by cells in biological matrices.^[18] **Intrinsic Physicochemical Parameters**

3.6.1. Particle Size and Aspect Ratio

Hydrodynamic diameter dictates subcellular localization and uptake routes.^[20] While larger nanoparticles are preferentially cleared via phagocytosis, ultra-small particles (< 10-15 nm) penetrate nuclear pore complexes, leading to direct chromatin binding and genotoxicity.^[20] High-aspect-ratio nanomaterials cause "frustrated phagocytosis" in macrophages, triggering chronic inflammatory signaling and mitotic spindle disruption that differs significantly from spherical counterparts.^[18]

3.6.2. Surface Charge and Coating Stability

Positively charged (cationic) FNPs bind electrostatically to negatively charged cell membrane phospholipids, enhancing cellular uptake but also inducing non-specific plasma membrane destabilization.^[21] Furthermore, organic surface coatings and functional ligands can undergo enzymatic cleavage or degradation over time, exposing the reactive underlying core and altering toxicity profiles during prolonged exposure.^[19]

3.6.3. Dissolution Kinetics and Ion Leaching

For metallic FNPs, toxicity is a dual function of particle-mediated ROS generation and intracellular ion release.^[3] Acidic endo-lysosomal environments (pH 4.5-5.0) drastically accelerate metal ion leaching (Ag⁺, Zn²⁺), causing rapid mitochondrial membrane depolarization and nuclear damage that may be absent in neutral extracellular environments.^[22]

3.6.4. Extrinsic Exposure and Methodological Variables Protein Corona Dynamics and Media Composition

Upon entry into biological fluids, FNPs adsorb serum proteins, forming a dynamic "protein corona" that redefines their biological identity, target receptor binding, and cellular clearance.^[23] Variations in fetal bovine serum (FBS) batches, protein concentrations, or culture media formulations across laboratories alter corona composition, resulting in inconsistent cellular uptake rates and toxicity readouts.^[23]

3.6.5. Aggregation and Effective Dosing

Nanoparticles frequently undergo agglomeration in high-ionic-strength cell culture media.^[24] Aggregation alters settling velocity, hydrodynamic diameter, and the effective dose delivered to cell monolayers, causing significant discrepancies between administered concentration and actual cellular exposure.^[18]

3.6.6. Cell Model Sensitivity and Assay Interference

Metabolic activity, antioxidant defense levels, and phagocytic capacities vary widely across primary cells, non-cancerous lines, and immortalized tumor models.^[25] Additionally, FNPs frequently absorb light or bind

directly to optical dyes used in standard colorimetric assays (e.g., MTT, WST-1, LDH), generating false-positive or false-negative cytotoxicity results if appropriate cell-free controls are omitted.^[26, 27]

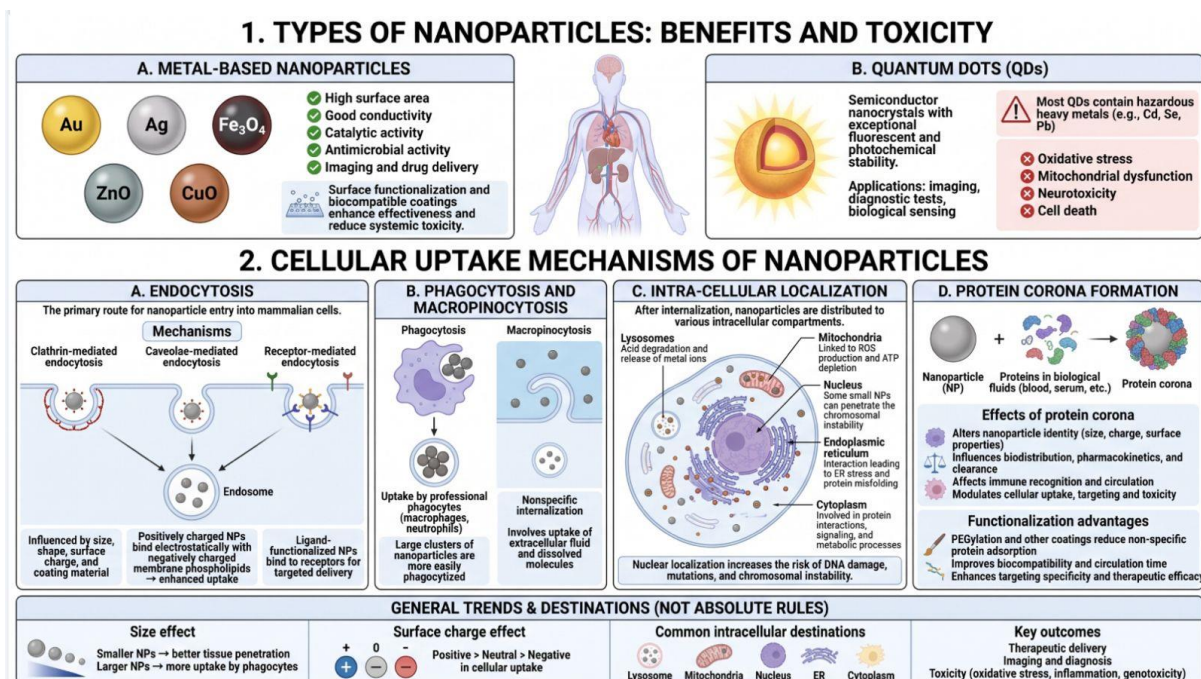


Fig. 1: Cellular Uptake Mechanisms.

4. NANOPARTICLES AND OXIDATIVE STRESS

Nanoparticles cause toxic effects through oxidative stress. Reactive oxygen species are produced constantly within living organisms via metabolism and are involved in normal cellular signaling pathways. In a physiological state, there is a system for defending against oxidative stress. Nevertheless, nanoparticles might affect this balance and lead to excess ROS production.^[16]

4.1 Mechanisms of ROS Generation

Nanoparticles induce ROS formation through several mechanisms: Electron leakage from mitochondrial electron transport chains, surface catalytic reactions, metal ion release, activation of inflammatory cells, NADPH oxidase activation, and Fenton and Haber-Weiss reactions (Fig. 2). Transition-metal nanoparticles are particularly efficient in ROS generation because of their catalytic redox properties.^[28]

4.2 Lipid Peroxidation

ROS attacks membrane phospholipids and initiates lipid peroxidation. Oxidative degradation of lipids disrupts membrane fluidity, ion transport, receptor signaling, and membrane integrity. Malondialdehyde (MDA) and 4-hydroxynonenal are major biomarkers of oxidative lipid injury.^[29]

4.3 Protein Oxidation

Nanoparticle-induced oxidative stress promotes protein carbonylation, oxidation, nitration, and crosslinking reactions. Protein oxidation impairs enzyme activity, cytoskeletal organization, signal transduction, and membrane transport systems.^[30]

4.4 Oxidative DNA Damage

ROS-mediated DNA damage comprises single-strand breaks, double-strand breaks, oxidized nitrogen bases, and DNA-protein cross-links. Oxidative DNA damage accumulates when excessive intracellular ROS production overwhelms cellular antioxidant defenses and surpasses DNA repair capacity, which can cause mutations, cell death, and cancer development.^[21]

4.5 Inflammatory Amplification of Oxidative Stress

There exists a strong relationship between oxidative stress and inflammation. The reactive oxygen species trigger signaling pathways involved in inflammation, such as NF-κB, MAPK, and inflammasome signaling pathways, resulting in the generation of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. Inflammation exacerbates oxidative damage and promotes genomic instability.^[30, 31]

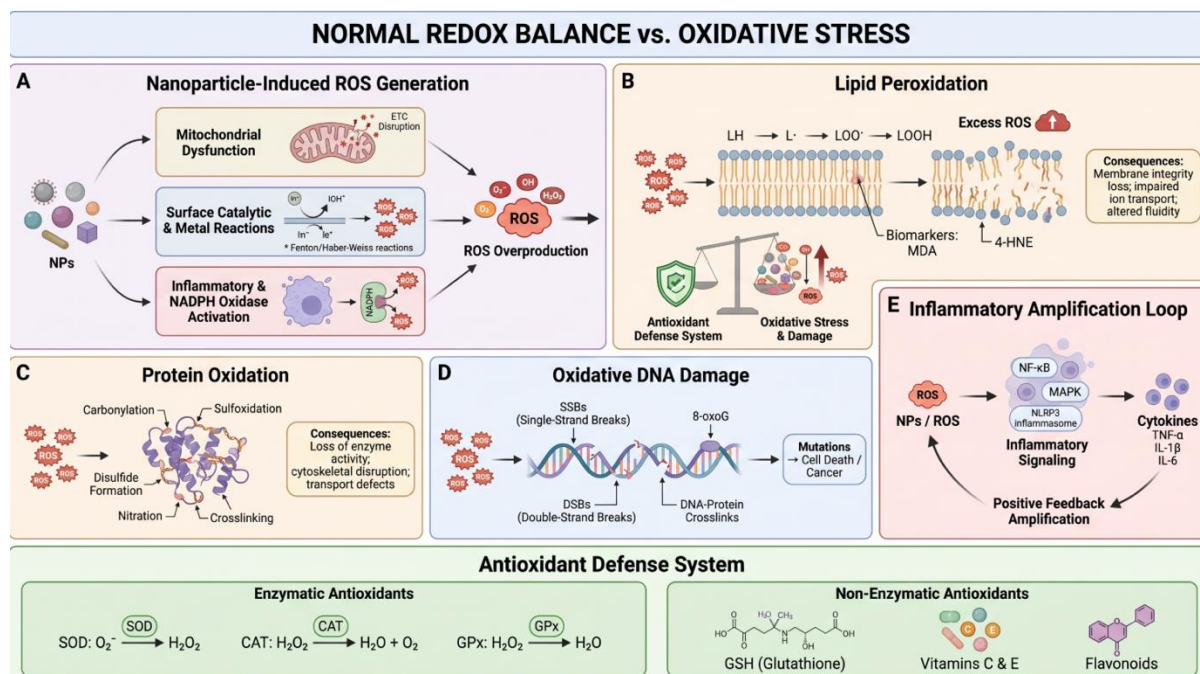


Fig. 2: Nanoparticles and Oxidative Stress

5. MITOCHONDRIAL DYSFUNCTION

Nanoparticles can cause serious damage to mitochondria, which are involved in the production of ATP, the regulation of calcium balance, apoptosis, and ROS formation. Consequently, mitochondrial impairment is viewed as a primary pathway through which nanoparticles lead to oxidative stress and cell death.^[22]

5.1. Mitochondrial Accumulation

Because of their nanometer-sized structure and electrochemical characteristics, nanoparticles may localize preferentially inside mitochondria. Upon localization, nanoparticles disrupt the complexes of electron transport chains and facilitate electron leakage.^[9]

5.2. ATP Depletion

Mitochondrial dysfunction limits oxidative phosphorylation and ATP production. An ATP shortage limits transport across membranes, ion balance, protein synthesis, and cellular metabolism.^[32]

5.3. Mitochondrial Membrane Depolarization

Nanoparticles impair the mitochondrial membrane potential and raise the membrane permeability. This causes cytochrome c release and subsequent activation of caspase-dependent apoptosis.^[33]

6. CALCIUM IMBALANCE

Damage to mitochondria leads to a calcium imbalance within cells. This aggravates oxidative stress and permeability transition within mitochondria. An increase in intracellular calcium activates cell injury-related proteases and phospholipases. Silver nanoparticles, zinc oxide nanoparticles, and copper oxide nanoparticles are specifically known for inducing mitochondrial swelling,

reduction in ATP production, increased oxidative stress, and apoptosis of mammalian cells.^[5, 6, 1]

7. EPIGENETIC AND MIRNA ALTERATIONS

In recent times, significant progress has been made in the area of nanotoxicity, establishing that functionalized nanoparticles affect not only redox status and cellular metabolism, but also epigenetics and post-transcriptional gene regulation.

Epigenetic modifications govern gene expression without altering the primary DNA sequence through mechanisms including DNA methylation, post-translational histone modifications, chromatin remodeling, and non-coding microRNA (miRNA) regulation. The epigenome is highly sensitive to nanoparticle-induced oxidative stress, which alters DNA methyltransferase (DNMT) dynamics and leads to promoter-specific hypermethylation or global hypomethylation. Such epigenetic shifts have been widely observed following exposure to silver, titanium dioxide, and carbon-based nanomaterials.^[34] MicroRNAs (miRNAs) are small, noncoding RNA molecules (18-25) that regulate post-transcriptional gene silencing by binding to target messenger RNAs (mRNAs). Functionalized nanoparticles trigger significant shifts in miRNA expression profiles, driving pathways associated with oxidative stress, apoptosis, DNA repair, and chronic inflammation:

miR-21: Upregulated across metallic and metal oxide nanoparticles (such as silver and iron oxide), suppressing tumor suppressor networks (e.g., PTEN, PDCD4) and promoting pro-survival pathways under acute oxidative stress conditions.^[25]

miR-34a: Regulated by gold and functionalized polymeric nanoparticles, altering p53-dependent apoptotic pathways, cell cycle arrest checkpoints, and mitochondrial outer membrane permeability.^[25]

miR-155: Dysregulated upon exposure to metal oxide nanoparticles and carbon-based nanomaterials, serving as a primary driver of pro-inflammatory cytokine expression (TNF- α , IL-6) and macrophage activation cascades.^[3, 25]

miR-146: Dysregulated upon exposure to metal oxide (ZnO, TiO₂) and polymeric nanoparticles; acts as a key negative feedback regulator of NF- κ B inflammatory signaling by targeting TRAF6 and IRAK1.^[3, 25]

miR-200c: Downregulated following carbon-based and metallic nanoparticle exposure, inducing epithelial-to-mesenchymal transition (EMT), loss of E-cadherin expression, and cellular migration.^[11, 25]

miR-125: Modulated during nanoparticle-induced oxidative distress, regulating p53 crosstalk, mitochondrial apoptosis cascades, and inflammatory cytokine release.^[25, 34]

Targeted miRNA Therapeutics: Optimized lipid and polymeric nanoparticle systems allow for therapeutic miRNA delivery and post-transcriptional regulation with minimal intrinsic ROS generation.^[12, 34] Nanoparticle-mediated generation of reactive oxygen species (ROS) disrupts key transcription factors and epigenetic processing machinery, leading to widespread miRNA dysregulation. These altered miRNAs subsequently dictate downstream physiological responses, including antioxidant enzyme expression, mitochondrial respiratory efficiency, inflammatory cascades, and chromosomal stability.^[25]

7.1. CHROMOSOMAL INSTABILITY AND GENOTOXICITY

Chromosomal instability (CIN) is considered to be one of the serious effects resulting from long-term nanomaterial exposure (Fig. 3). CIN is defined by higher frequencies of changes in the structure and number of chromosomes during cell division. These changes are represented by chromosome breaks, aneuploidy, chromosomal aberrations, micronuclei production, chromosomal translocation, sister chromatid exchange, and missegregation of chromosomes. Continuous genomic instability is significantly linked to carcinogenesis, tissue degeneration, aging, and drug resistance. Genotoxicity can be induced directly or indirectly by nanoparticles. Direct genotoxicity involves the physical interaction of nanoparticles with DNA molecules, chromatin, and mitotic proteins. Indirect genotoxicity, on the other hand, is mostly induced via oxidative stress, inflammation, and interference with DNA repair processes.^[35]

Oxidative DNA Damage: Exposure to nanoparticles stimulates intracellular ROS generation, inducing oxidative DNA damage and yielding modified bases such as 8-hydroxy-2'-deoxyguanosine (8-OHdG)—an established biomarker of oxidative stress. Other forms of DNA damage include DNA strand breakage, DNA double-strand breakage, DNA cross-linking, base modifications, and formation of DNA-protein cross-links.^[36]

7.2. Micronucleus Formation

Micronuclei are defined as extra nuclear structures that contain chromatin derived from either lagging chromosomes or broken chromosome segments during cell division. Micronuclei have been identified as one of the important biomarkers that indicate genomic instability and genotoxicity. Some nanomaterials such as silver nanoparticles, titanium dioxide nanoparticles, zinc oxide nanoparticles, and quantum dots have shown an increase in micronuclei production within mammalian cells. Small-sized nanoparticles possess more genotoxicity due to greater nuclear access.^[37]

7.3. Mitotic Spindle Disruption

The other important mechanism by which nanoparticles induce chromosomal instability includes the interference with the mitotic machinery. The proper segregation of chromosomes depends upon the correct assembly of spindles, centrosomes, and kinetochores and also on the control of checkpoints. Nanoparticles can disrupt the process of microtubule assembly, centrosome duplication, spindle assembly checkpoints, and kinetochores. All these lead to chromosome segregation and aneuploidy. Carbon nanotubes and some metal nanoparticles have fibre-like effects on spindle microtubules.^[35]

7.4. Spindle Assembly Checkpoint Dysfunction

The spindle assembly checkpoint (SAC) guarantees that chromosomes segregate properly before entering anaphase. The oxidative stress caused by nanoparticle exposure can affect the checkpoint's function through MAD2, BUBR1, and Aurora kinase proteins. Abnormal SAC function means that cells with abnormal chromosomes undergo mitosis.^[1]

7.5. Telomere Dysfunction

Telomeres are repetitive DNA sequences found at the end of chromosomes that help maintain genomic stability during replication. Telomeric DNA is very vulnerable to oxidation due to high levels of guanine. The nanoparticle-induced generation of reactive oxygen species causes rapid depletion of telomeres and telomerase function. Telomere dysfunction causes Chromosome fusion, Chromosomal aberrations, Cellular senescence, and Carcinogenesis. Antioxidant nanoparticles exemplified by cerium oxide nanoparticles confer cytoprotection to telomere integrity by eliminating ROS.^[38]

However, the biological behavior of CeO₂ nanoparticles is strictly context-dependent. Under standard physiological conditions with a high Ce⁺³ / Ce⁺⁴ surface valence ratio, CeO₂ nanoparticles exhibit antioxidant and superoxide dismutase-mimetic activity. Conversely, under acidic microenvironments (such as in tumor cells or lysosomal compartments) or with elevated Ce⁺⁴ surface states, they exhibit pro-oxidant, oxidase-like activity that promotes ROS generation and cytotoxicity.^[19, 21]

7.6. DNA Repair Inhibition

DNA repair pathways such as homologous recombination, non-homologous end joining, and base excision repair can be inhibited by the use of nanoparticles. Inhibiting the DNA repair pathways will enhance the mutation load and genomic instability. Eventually, this could lead to cancerous transformation.^[36]

7.7. Nuclear Penetration and Direct DNA Interaction

Nanoparticles of very small sizes have the capability to pass through the nuclear membrane and affect the

chromosomal DNA. Positively charged nanoparticles have greater chances of having an effect due to the electrostatic interactions between them and the negatively charged DNA molecules. Gold nanoparticles and quantum dots are examples of nanoparticles that are good at entering nuclei based on their size and surface chemistry.^[39]

7.8. Relationship between Chronic Inflammation and Genotoxicity

Nanoparticles have been found to be capable of generating genotoxicity through the joint effects of oxidative stress and inflammation. The chronic state of inflammation is seen to increase the levels of nitric oxide, ROS formation, and oxidative DNA damage. The persistent state of inflammation also promotes proliferation and remodeling, which are factors that may aid the onset of cancer.^[35]

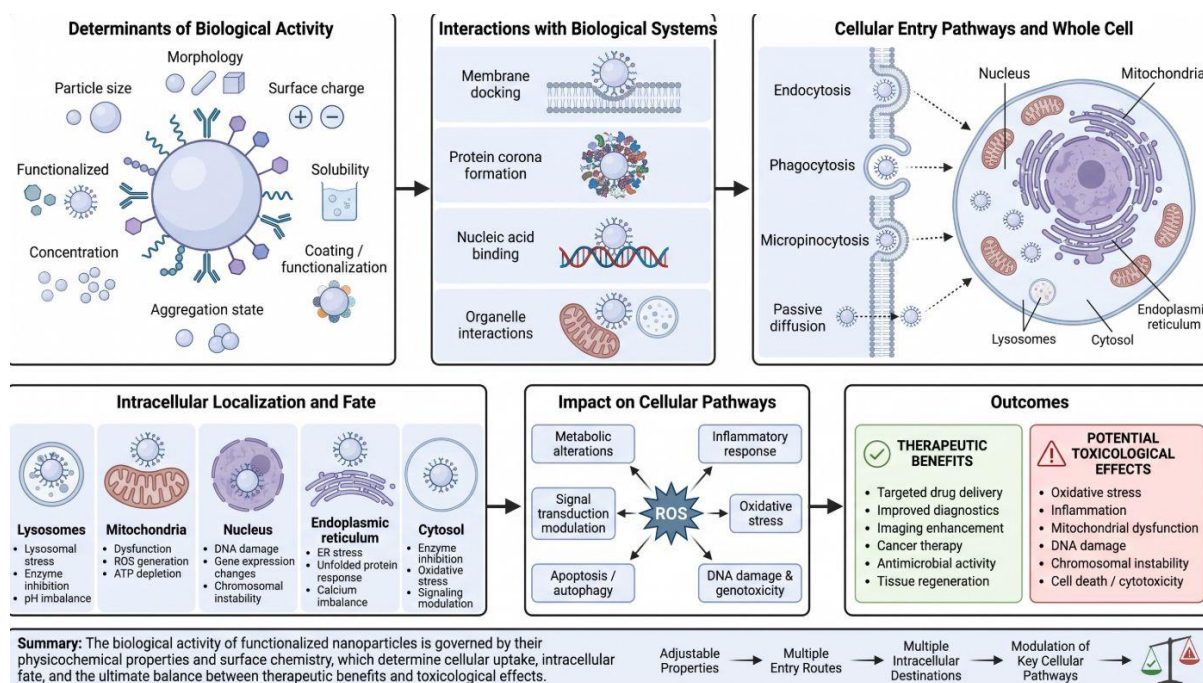


Fig. 3: Chromosomal Instability and Genotoxicity of Nanoparticles.

8. THERAPEUTIC APPLICATIONS

In spite of worries about the toxic effects of nanoparticles, functionalized nanoparticles demonstrate therapeutic potential across nanomedicine, oncology, regenerative medicine, diagnostic, and targeted drug delivery. Through surface modifications, nanoparticles can increase the effectiveness of therapeutic approaches while limiting systemic toxicity. When it comes to targeted drug delivery, one of the major roles played by functionalized nanoparticles is that of targeted drug delivery. In many cases, conventional chemotherapy is

not very selective, involves significant toxicity, and is associated with the fast degradation of drugs. The ability of functionalized nanoparticles to promote the accumulation of drugs in diseased tissues is due to either passive or active targeting (Fig. 4).^[10, 40]

8.1. functionalized nanoparticles

Have been widely used in cancer treatment due to the fact that the tumors have an abnormal permeability to blood vessels and an oxidizing environment.^[41,40] The nanoparticles can specifically target tumors and

discharge the drugs by means of biological signals from their surroundings.^[40] Gold nanoparticles have been extensively researched in photothermal therapy for the reason that they are able to absorb the infrared rays and produce heat to kill tumor cells.^[16] Iron oxide nanoparticles are also applied in magnetic hyperthermia therapy.^[40]

8.2. The Redox-Responsive Nanoparticles

Are intended to take advantage of the high levels of ROS and glutathione in the tumor environment. These nanoparticles will specifically release the drugs in the oxidizing environment to improve the tumor targeting efficiency and reduce the toxicity to other body parts.^[42] In the Ferroptosis-Inducing Nanoparticles area, Ferroptosis represents a controlled mode of cell death that features iron-dependent lipid peroxidation and ROS generation. Some engineered nanoparticles can selectively trigger ferroptosis in cancer cells by targeting

the antioxidant defense mechanisms and raising the concentration of intracellular iron. Iron oxide nanoparticles and redox-sensitive nanomaterials have been found to possess high therapeutic efficacy against malignancies via the induction of ferroptosis.

8.3. The Antioxidant Nanoparticles

Are promising therapeutic agents for neurodegenerative diseases, Ischemia-reperfusion damage, inflammatory conditions, and radiation-related tissue damage. Some nanoparticles have inherent antioxidant actions that allow them to protect from oxidative stress. As discussed in Antimicrobial Applications, silver nanoparticles and zinc oxide nanoparticles show antibacterial, antifungal, and antiviral properties. Various functionalized antimicrobial nanoparticles have wide applications ranging from wound dressings to coatings and medical devices. Environmental impact on microbial resistance is an area of major concern.^[43]

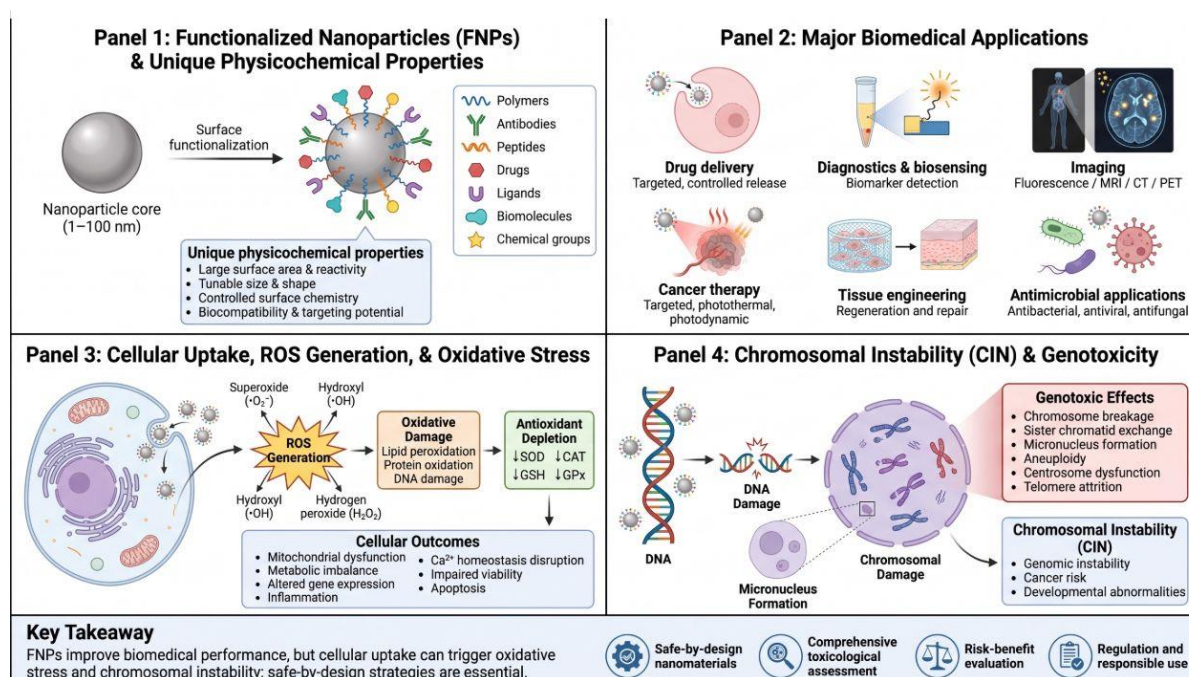


Fig. 4: Therapeutic Applications.

9. SAFE-BY-DESIGN NANOTECHNOLOGY

The growing concern about nanoparticle toxicity has led to the emergence of design-to-safety technologies that would ensure maximal treatment benefits and minimal biological side effects. Biodegradable nanoparticles will decrease toxicity by promoting degradation through metabolic pathways. Nanomaterials, including PLGA, chitosan, and liposomes, have better biological safety compared with toxic metals.

9.1. Green synthesis approaches use plant extracts, microbial metabolites, natural polymers, and biogenic reducing agents. They offer environmentally friendly synthesis techniques, which lower the risk of chemical toxicity and

enhance the biocompatibility of nanoparticles. Other differences include.

9.2. Surface Functionalization Strategies such as surface coatings that determine nanoparticle toxicity. PEGylation decreases opsonization, while biomimetic coatings increase nanoparticle affinity with cell membranes. Antioxidant functionalization can also be used to avoid ROS formation and oxidative damage.^[44]

9.3. In Advanced Toxicological Models, the traditional monolayer cell culture is often inadequate in predicting the in vivo behavior of nanoparticles. Advanced models like organoids, three-dimensional cultures, microfluidic chips, and organ-on-a-chip offer better models to study nanoparticle toxicology.

On the other hand, in Omics Technologies, Nanotoxicology increasingly relies on the use of Transcriptomics, Proteomics, Metabolomics, and Epigenomics. This offers a platform for the assessment of molecular events associated with nanoparticle-cell interaction and toxicity mechanisms. Finally, under Regulatory Considerations, Standardized guidelines are necessary for evaluating oxidative stress markers, genotoxicity, biodistribution, chronic toxicity, and environmental effects of nanoparticles.^[11]

10. CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Though functionalized nanoparticles have tremendous biomedical applications, several issues need to be addressed.

10.1. Chronic Exposure, Dose-Kinetics, and Long-Term Genotoxicity

Current research predominantly focuses on acute toxicity assessments, leaving long-term biological impacts and organ accumulation poorly understood. The cellular response to functionalized nanoparticles follows non-linear kinetic profiles dependent on exposure duration and intracellular persistence. While acute, low-dose exposures trigger adaptive antioxidant signaling via the Keap1-Nrf2 pathway, chronic exposure leads to antioxidant depletion and sustained intracellular ROS generation. This persistent oxidative stress drives cumulative oxidative DNA damage (e.g., 8-OHdG base modifications), converting single-strand breaks (SSBs) into double-strand breaks (DSBs) during replication cycles. Furthermore, chronic exposure during mitosis impairs centrosome duplication and spindle assembly checkpoint (SAC) fidelity, escalating structural chromosomal aberrations into persistent genomic instability and potential carcinogenesis.

10.2. Methodological Limitations of Current Models and Standardization Issues

A major bottleneck in clinical translation stems from the limitations of conventional testing models. Static 2D *in vitro* monocultures fail to simulate physiological shear stress, tissue architecture, and systemic clearance mechanisms. Additionally, functionalized nanoparticles frequently cause assay interference—interacting with optical dyes and reagents in standard MTT, WST-1, and LDH assays through light absorbance overlap or surface adsorption, yielding false-positive or false-negative readouts. Variations in synthesis protocols, surface characterization, and exposure modes further make cross-study comparisons difficult.^[45] Establishing standardized testing protocols and adopting dynamic microfluidic platforms (e.g., organ-on-a-chip) are critical imperatives for reliable safety evaluations.

10.3. Biodistribution Challenges and Protein Corona Dynamics

Predicting *in vivo* biodistribution and elimination remains complex due to particle size, aspect ratio, surface charge, and species-specific clearance differences. Rodent reticuloendothelial system (RES) kinetics and renal clearance dynamics differ substantially from human physiology. Moreover, upon entering biological fluids, nanoparticles immediately adsorb host proteins and lipids to form a dynamic "protein corona." Static *in vitro* media containing fetal bovine serum (FBS) fail to replicate the human plasma corona, altering cellular targeting, uptake pathways, and localized genotoxic responses *in vivo*.

10.4. Environmental Ecotoxicity and Biological Transfer With the increasing usage of

Nanoparticles across industrial and biomedical sectors, concerns regarding environmental contamination and ecotoxicity have gained critical prominence. Nanoparticles that enter waterways and soil can contaminate environments, bioaccumulate across food chains, and ultimately induce systemic oxidative damage in living organisms.^[24,19]

10.5. Personalized Nanomedicine

In the future, personalized nanomedical therapy based on artificial intelligence, computational toxicology, and omics will enable patient-tailored delivery platforms with targeted efficacy^[24, 41] (de la Harpe et al., 2019; Kukowska-Latallo et al., 2005).

10.6. Improved Safety and Next-Generation Nanomaterials

Future research will be oriented towards creating biodegradable nanoparticles, nanoparticles with antioxidant coatings, biomimetic nanomaterials, green nanotechnology, and stimuli-responsive platforms that minimize off-target cytotoxicity.^[24,11]

Computational and Machine Learning Frameworks in Nanotoxicology

To overcome the time constraints and experimental variability of conventional *in vitro* and *in vivo* toxicity testing, computational and machine learning (ML) models have become vital components of predictive nanotoxicology. Advanced algorithms—such as Random Forests, Artificial Neural Networks, and deep generative architectures—leverage key physicochemical descriptors (e.g., hydrodynamic size, surface charge, zeta potential, and core chemistry) to forecast critical toxicological endpoints, including reactive oxygen species (ROS) generation, membrane disruption, and cellular uptake. Furthermore, open-access nanoinformatics platforms (such as the NanoSolveIT e-platform and the OECD QSAR Toolbox) integrate biological descriptors and multi-omics datasets. These tools enable quantitative

structure-activity relationship (nano-QSAR) modeling and mechanism-informed Safe-by-Design (SbD) strategies, providing a robust alternative that reduces reliance on animal testing.

10.7. Limitations of *In Vitro* Models, Animal-to-Human Translation, and Chronic Exposure Challenges

Despite rapid advancements in nanotoxicology, converting experimental safety data into clinical translation remains bottlenecked by fundamental methodological and physiological discrepancies:

10.8.1. Limitations of Conventional *In Vitro* Models

The majority of nanotoxicological literature relies on static, two-dimensional (2D) monocultures of immortalized or transformed cell lines. While cost-effective and amenable to high-throughput screening, 2D monolayers lack physiological architecture, cell-extracellular matrix (ECM) interactions, multicellular crosstalk, and dynamic fluid shear stress. Furthermore, static *in vitro* systems suffer from particle sedimentation artifacts—where gravitational settling artificially accelerates nanoparticle transport to the cellular monolayer—resulting in overestimations of effective intracellular dosing and cytotoxicity compared to dynamic *in vivo* vascular flow.^[18,20]

10.8.2. Interspecies Differences and Animal-to-Human Translation

Preclinical animal models (predominantly rodents) frequently fail to predict human toxicological outcomes due to species-specific physiological variations. Differences in mononuclear phagocyte system (MPS) clearance rates, renal filtration thresholds, capillary bed architecture, serum protein profiles (which dictate dynamic protein corona evolution), and metabolic rates alter the tissue biodistribution, half-life, and accumulation of FNPs in humans relative to small animal models. Moreover, rodent models lack the immunological complexity and heterogeneous disease pathology present in human patient populations.^[40]

10.8.3. Challenges of Chronic, Low-Dose Exposures

Most toxicological evaluations focus on acute, high-dose exposure regimes over 24 to 72 hours. However, real-world biomedical and environmental exposures typically involve chronic, low-dose accumulation over months or years. Non-biodegradable nanomaterials (e.g., carbon nanotubes, quantum dots, and metallic cores) persist within reticuloendothelial organs (liver, spleen, lymph nodes), leading to chronic lysosomal overload, low-grade persistent inflammation, latent organelle stress, and cumulative genotoxicity. These sub-lethal chronic insults can cause progressive telomere attrition and subtle spindle assembly checkpoint (SAC) impairment that escape detection in acute 2D screens, eventually manifesting as permanent chromosomal instability (CIN) and potential tumorigenesis.^[35]

11. CONCLUSION

Functionalized nanoparticles stand among the top technological innovations in the domains of nanomedicine and biomedical sciences owing to their special physicochemical properties and applications for therapeutic purposes. The surface modification of nanoparticles has helped enhance their stability, targeting capability, cellular penetration capacity, and efficacy as well as contributed towards groundbreaking advances in drug delivery, medical imaging, gene therapy, biosensors, and cancer therapy. Nevertheless, it is evident from current research findings that nanoparticles might also affect biological functions within animal cells and tissues in a significant way. Oxidative stress has been identified as the main biological process involved in the toxicity caused by nanoparticles and has linked the production of ROS to several processes such as mitochondrial dysfunction, inflammation, apoptosis, epigenetic alterations, DNA damage, and chromosomal instability.

The biological effects of nanoparticles strongly depend on their size, shape, concentration, surface charge, aggregation state, ion release, and functionalization. Functionalization can reduce or increase toxicity depending on physical-chemical features of coating materials and biological systems. On the other hand, the application of engineered nanoparticles offers numerous therapeutic prospects in the form of targeted delivery, redox-based treatments, ferroptosis, gene delivery, antioxidant therapy, and regeneration medicine. The design of less harmful nanotechnologies, biodegradable nanoparticles, new methods of toxicity evaluation, and environmental synthesis approaches will become important directions for mitigating biological hazards. Future studies combining nanotechnology, molecular biology, genomics, epigenetics, toxicology, and artificial intelligence are expected to shed light on the mechanisms underlying nanoparticle-cell interactions.

Table 1: Functionalized Nanoparticles and Their Influence on Animal Cell Physiology, Oxidative Stress, and Chromosomal Stability.

Nanoparticle Type	Particle Size (nm) & Surface Charge	Surface Coating / Functionalization	Cell Biological Model	Exposure Dose & Duration	Assay Method Used	Major Biological & Toxicological Outcomes	Reference
Manganese Dioxide (MnO ₂ NPs)	20-50nm, Negative	Bare / Uncoated	Human Neuronal Cells (HN-h)	10-100 µg/mL, 24h	DCFH-DA, MTT, Comet Assay	Intracellular ROS generation, mitochondrial membrane depolarization, caspase-dependent apoptosis, DNA damage	[3] Alarifi et al. (2017)
Bare vs. Surface-Modified Metallic NPs	Sub-100nm, Variable	Polymer / Ligand coatings vs. Bare	Mammalian Cell Lines	Broad concentration range	MTT Assay, LDH Release, DCFH-DA	Surface modification prevents plasma membrane lysis, blunts reactive oxygen species generation, and lowers intrinsic toxicity	[19] El-Ansary & Al-Daihan (2020)
Functionalized NPs	Broad size range, Positive/Neutral	Surface-conjugated targeted ligands	Mammalian Cell Lines	Dose-dependent series	ICP-MS, Flow Cytometry, Confocal Microscopy	Surface functionalization dictates uptake pathway selection, subcellular organelle localization, ROS kinetics, and cytotoxicity thresholds	[21] Gao et al. (2023)
Zinc oxide nanoparticles (ZnONPs)	15-35nm, +18mV	Polymeric coating / Bare	Human Epithelial / Immune Cells	5-50µg/mL, 24h	Sister Chromatid Exchange, MTT	Altered antioxidant-related miRNAs, sister chromatid exchange, genotoxicity, rapid intracellular Zn ⁺² leaching	[3, 19] Alarifi et al. (2017); El-Ansary & Al-Daihan (2020)
Cerium oxide nanoparticles (CeO ₂ NPs)	5-15nm, Near-neutral	Antioxidant functionalization	Neuronal & Endothelial Models	10-50µg/mL, 48h	Catalase-like Assay, DCFH-DA	Regulation of oxidative pathways, reduced oxidative DNA damage, catalase-mimetic activity, cytoprotection	[19, 21] El-Ansary & Al-Daihan (2020); Gao et al. (2023)
Iron oxide nanoparticles (Fe ₃ O ₄ NPs)	10-50nm, Neutral	Dextran / PEG functionalization	Diagnostic / Theranostic Models	Imaging dosage range	MRI, TBARS, Colorimetric Assays	Oxidative signaling alterations, DNA fragmentation, Fenton-reaction mediated ROS generation at high concentrations	[40] Dadfar et al. (2019)
Quantum dots	2-10nm, Negative	Polymer shells / Silica coating	Neural / Primary Cell Lines	1-20µM/mL, 24h	Flow Cytometry, Fluorometry	miRNA dysregulation linked to neurotoxicity,	[19, 21] El-Ansary & Al-Daihan (2020);

						heavy metal ion release ($\text{Cd}^{+2}/\text{Se}^{2+}$), DNA oxidation, apoptosis	Gao et al. (2023)
Lipid nanoparticles	80-100nm, pH-dependent	Ionizable Lipid Bilayer encapsulation	In vitro / In vivo mRNA Models	Transfection dose series	Luciferase / GFP Transfection, LDH	Therapeutic miRNA delivery, low genotoxicity, rapid lysosomal escape, minimal intrinsic oxidative stress	^[12] Cullis & Hope (2017)
Polymeric nanoparticles	50-200nm, Neutral/Negative	Polymeric Shell (PLGA / Chitosan / PEG)	In vitro / In vivo Tumor Models	Target therapeutic doses	Fluorometric Assays, HPLC	Regulation of inflammatory miRNAs, EPR targeting, sustained drug release, reduced off-target organ toxicity	^[13] Beach et al. (2024)
Carbon nanotubes	High aspect ratio(> 1 μm length), Variable	Carboxylated / Functionalized carbon surfaces	Macrophages / Lung Models	5-50 $\mu\text{g/mL}$, 48h	Micronucleus Assay, ELISA	miRNA-associated inflammation, chromosome missegregation, frustrated phagocytosis, persistent ROS generation	^[19, 21] El-Ansary & Al-Daihan (2020); Gao et al. (2023)
Titanium Dioxide (TiO_2)	20-40nm/ Negative	Polymer coating / PEGylation	Lung Epithelial Cells	20-100 $\mu\text{g/mL}$, 12-24 h	TBARS, Western Blot, RT-qPCR	miR-155 dysregulation, photocatalytic ROS production, lipid peroxidation, DNA damage, chromosome aberrations	^[19, 21] El-Ansary & Al-Daihan (2020); Gao et al. (2023)
Engineered Nanoparticles	Broad range/ Anionic	Surface-modified variations	Human Erythrocytes & Blood Models	Blood-concentration exposures	Hemolysis Assay, Aggregation Assays	Surface charge-dependent hemocompatibility, red blood cell lysis, platelet activation, blood coagulation modulation	^[24] de la Harpe et al. (2019)
Size-Adjustable NPs	Switchable size, Variable	Stimuli-responsive surface shell	Macrophages & Endothelial Cells	Plaque-targeting doses	Fluorescence Imaging, ELISA	Dual cell-targeting capabilities, enhanced vascular plaque accumulation, anti-inflammatory therapeutic effects	^[31] Deng et al. (2025)
Gold nanoparticles (AuNPs)	15-30nm, +22mV	PEG, antibodies, peptides / <i>Ceratonia siliqua</i> extract	Cancer cell lines / Human Erythrocytes	10-100 $\mu\text{g/mL}$, 24h	Hemolysis Assay, DCFH-DA, Comet Assay	miR-34a modulation, apoptosis signaling, DNA strand breaks, chromosomal instability, dose-dependent ROS scavenging	^[25] Brzóška et al. (2019)

Silver nanoparticles (AgNPs)	<20nm, -18mV	Protein coating, PVP, polysaccharides	HepG2 cells / Cancer models	5-25µg/mL, 48h	TRAP Assay, Q-FISH, Annexin V, RT-qPCR	miR-21 upregulation, intracellular Ag ⁺ leaching, micronuclei formation, DNA oxidation, telomerase inhibition	[25, 38] Brzóska et al. (2019); Chen et al. (2018)
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Table 2: Comparative Analysis of Nanoparticle Classes: Advantages, Toxicity Mechanisms, Biomedical Applications, and Safe-by-Design Strategies.

Nanoparticle Class	Key Advantages	Primary Limitations	Primary Toxicity Mechanisms	Biomedical Applications	Safe-by-Design & Safety Considerations
Metal Nanoparticles (e.g., AuNPs, AgNPs)	Surface plasmon resonance, high catalytic activity, potent antimicrobial properties, tunable surface chemistry.	Ion leaching, size-dependent nuclear penetration, concentration-dependent genotoxicity.	Ag ⁺ ion leaching, catalytic ROS generation, mitochondrial electron transport chain disruption, oxidative DNA strand breaks, micronucleus formation.	Photothermal therapy, biosensing, targeted drug delivery, wound dressings, antimicrobial coatings.	Biocompatible surface functionalization (e.g., PEGylation, peptide conjugation) to minimize immune recognition and prevent non-specific cellular uptake.
Metal Oxide Nanoparticles (e.g., TiO ₂ , ZnO, Fe ₃ O ₄ , CeO ₂)	Magnetic guidance, photocatalytic activity, redox-cycling and intrinsic ROS-scavenger capabilities CeO ₂	Cation release (Zn ⁺² , Fe ⁺² , Fe ⁺³), photocatalytic injury under light/UV, risk of persistent oxidative stress.	Fenton and Haber-Weiss reactions, lipid peroxidation, loss of mitochondrial membrane potential $\Delta\Psi_m$, dysregulation of pro-inflammatory microRNAs (e.g., miR-155).	MRI contrast agents, magnetic hyperthermia, photodynamic cancer therapy, neuroprotective antioxidant therapy.	Polymeric or biomimetic coatings to suppress unwanted metal ion dissolution; utilization of redox-responsive linkages for controlled intra-tumoral release.
Carbon-Based Nanoparticles (e.g., CNTs, Graphene Oxide, QDs)	High mechanical strength, electrical conductivity, high surface-area-to-volume ratio for drug loading.	Fibrous aspect ratios (asbestos-like kinetics), long-term biopersistence, membrane piercing by sharp edges.	Membrane integrity disruption, chronic granulomatous inflammation, mitotic spindle perturbation, centrosome dysregulation leading to chromosomal instability (CIN).	Tissue engineering scaffolds, biosensors, high-capacity drug/gene delivery platforms.	Surface hydrophilic functionalization (carboxylation, PEGylation) to improve dispersion, reduce biopersistence, and mitigate inflammatory cascades.
Lipid Nanoparticles (e.g., LNPs, Liposomes)	High biocompatibility, low intrinsic toxicity, efficient encapsulation and cytosolic delivery of nucleic acids.	Risk of rapid hepatic or splenic clearance if unshielded, limited stability in gastric/acidic environments.	Transient endosomal membrane destabilization; minimal intrinsic ROS production under optimized dosing.	mRNA vaccines, siRNA delivery, targeted miRNA gene therapy, oncological targeted drug delivery.	Surface modification with stealth polymers (PEG) and biomimetic lipid coatings (e.g., cell membrane camouflaging) to extend systemic circulation and

					prevent opsonization.
Polymeric Nanoparticles (e.g., PLGA, Chitosan, Dendrimers)	High biodegradability, tunable drug release kinetics, versatile functionalization schemes.	Cationic polymers may induce electrostatic cell membrane disruption or endosomal swelling.	Endoplasmic reticulum (ER) stress, transient oxidative imbalance, high-dose DNA damage.	Controlled sustained drug release, non-viral gene therapy, targeted cancer chemotherapy.	Utilizing FDA-approved, fully biodegradable polymers (e.g., PLGA, polylactic acid) that hydrolyze into non-toxic metabolic intermediates.
Quantum Dots (e.g., CdSe, CdTe)	Superior fluorescence yield, quantum stability, multiplexed bioimaging capability.	Heavy metal core leaching (e.g., Cd ²⁺ , long-term bioaccumulation, intrinsic cytotoxicity.	Heavy metal ion release, mitochondrial damage, dysregulation of p53-dependent apoptotic pathways (via miR-34a modulation), telomere attrition.	Diagnostic imaging, cellular tracking, fluorescence-guided surgery, biosensing.	Synthesis of core-shell architectures (e.g., ZnS shells) and thick polymer/silica encapsulation layers to prevent toxic heavy metal leaching.

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