Gene–Cellular and molecular Interactions of Nanomaterials.

Nanomaterials interact with cellular systems at multiple levels, leading to a cascade of molecular and genetic responses that can alter cell function, trigger inflammation, or induce cell death. Their unique physicochemical properties influence how they are internalized, transported, and engage with key cellular components like membranes, organelles, proteins, and the cell's genetic material.

Cellular interactions

Nanoparticles (NPs) interact with cells and cellular components in a dynamic and multi-step process, determined largely by their properties and the cellular environment.

Cellular uptake and internalization

- **Endocytosis:** Most NPs are internalized by energy-dependent endocytic mechanisms. The specific pathway depends on NP size, shape, and surface properties. For example, smaller NPs may enter through clathrin-coated pits, while larger ones use caveolae-mediated processes.
- **Direct membrane penetration:** Extremely small or sharp NPs (e.g., carbon nanotubes, graphene nanosheets) can directly penetrate the cell membrane, potentially causing localized damage and leakage of cellular contents.
- **Binding:** Before internalization, NPs often bind to the cell surface. Positively charged NPs are generally attracted to the negatively charged cell membrane, leading to a stronger interaction and higher uptake than negatively charged NPs.

Intracellular localization and transport

Once inside the cell, NPs can follow various paths:

- **Escape endosomes:** Many NPs, after being taken up by endocytosis, are trapped in endosomes. If they can escape into the cytoplasm, they can interact with intracellular structures.
- **Targeting organelles:** NPs can accumulate in specific organelles. Some, for example, have shown a tendency to localize in mitochondria or the endoplasmic reticulum.
- **Nuclear translocation:** Only very small NPs (<20 nm) can cross the nuclear envelope to interact directly with DNA. This is a critical factor for genotoxicity.

Molecular interactions

The effects of nanomaterials are driven by their interaction with various biological molecules.

Protein corona formation

When NPs enter a biological fluid, proteins immediately adsorb to their surface, forming a layer known as the "protein corona".

- **Altered identity:** The corona effectively cloaks the NP, determining its new "biological identity." The cellular recognition of the NP is then mediated by the proteins in the corona, not the NP itself.
- **Modifying function:** The corona influences everything from cellular uptake to the NP's toxicity and therapeutic efficacy. It can either reduce toxicity by hindering cell entry or enhance it by altering protein function.

Enzyme inhibition and activation

NPs can interact with cellular enzymes, altering their function.

- **Inhibition:** Certain NPs can bind to the active sites of enzymes, inhibiting their activity and disrupting normal cellular metabolism. Silver ions released from silver NPs, for instance, can bind to sulfhydryl groups on proteins, inactivating them.
- **ROS generation:** The high catalytic reactivity of NPs' surfaces can lead to excessive production of reactive oxygen species (ROS). This can disrupt the redox balance and damage proteins, lipids, and DNA.

Gene-level interactions

Nanomaterial exposure can lead to significant changes in gene expression and epigenetic modifications, affecting long-term cellular function and fate.

Alterations in gene expression

- **Upregulation and downregulation:** Nanoparticles can induce or repress the expression of specific genes. For example, metal NPs can affect genes related to oxidative stress, DNA damage, and metal homeostasis.
- **Activation of signaling pathways:** By disrupting cell membranes or generating ROS, NPs can trigger signaling cascades, such as the mitogen-activated protein kinase (MAPK) pathway or NF-κB, which regulate a wide range of cellular processes, including inflammation and proliferation.

- **Immunomodulation:** Nanomaterials can influence gene expression in immune cells, leading to either stimulatory or suppressive effects on immune responses. Some carbon nanotubes, for example, have been shown to either upregulate or negatively control genes involved in immune pathways.

Epigenetic modifications

- **DNA methylation:** Nanoparticle exposure can cause epigenetic alterations, such as changes in DNA methylation patterns. This can have lasting effects on gene expression without altering the underlying DNA sequence.
- **Histone modification:** Carbon nanoparticles have been shown to alter histone modification, a process that controls gene expression by changing chromatin structure.

Genotoxicity

- **DNA damage:** Nanomaterials can damage DNA, either directly by interaction or indirectly through ROS production. This can lead to mutations and potentially contribute to cancer development.
- **DNA fragmentation:** Carbon NPs can induce chromatin condensation and DNA fragmentation, affecting the cell cycle and viability.