Nanoparticle-Mediated Gene Expression Modulation: Mechanism and Clinical Translation

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ABSTRACT

Nanoparticles (NPs) are used extensively in nanomedicine, as drug carriers to actively influence the cellular and molecular processes. Due to their unique physicochemical properties such as nanoscale size and high surface reactivity. The gene expression can be modulated through NPs active direct interaction with the biomolecules such as DNA, RNA, and proteins. These effects occur through several mechanisms, including epigenetic alterations like DNA methylation and histone changes and non-coding RNA regulations.

The oxidative stress and signaling pathway activation induced by nanoparticles can influence the cell mechanisms such as cell proliferation, apoptosis, and immune responses. Their valuable properties make them suitable in biomedical applications, especially in gene therapy and cancer treatment, due to their enhanced activity in drug delivery and therapeutics.

Despite their several potentials in gene expressions, challenges such as toxicity and off-target effects remain a serious concern. This review suggests an overview of molecular mechanisms of gene expression and their importance in precision medicine.

Key words: Nanoparticles; Gene expression modulation; Epigenetics; Oxidative stress; Signal transduction; Gene therapy; Cancer therapy; Precision medicine; Toxicity.

1.INTRODUCTION

Nanoparticles (NPs) have potentially entered essentially all areas of everyday life, especially in the human body. They invade the human body through the usual inhalation or ingestion processes. The process is so smooth due to its unique properties such as size, shape, and concentration. The size of a nanoparticle is a key parameter; it is referred to as the diameter [1]. The size of the nanoparticle is usually in the range of 1 – 100 nm; the nano-sized property enhances the surface energy and spatial confinement and increases the fraction of surface atoms [2]. This nanosized feature allowed them to physically interface with the DNA of 2 nm diameter. According to references, the surface interactions are made between the nanoparticles and the biomolecules such as proteins and nucleic acids. The proteins can have various binding sites due to their specific and non-specific adsorption. There are two factors considered for the interaction, i.e., the nanoparticle should be surrounded with biomolecules to modify or saturate the surface and the method of nanoparticle entering the human body [3].

Initially, the nanoparticles were considered drug carriers in the fields of biomedicals and pharmaceuticals [4]. But the researchers are identifying the nanoparticles as active ligands capable of interacting directly with the receptors and triggering the signaling pathway. The nanoparticles with targeting ligands can sometimes lose their specificity and mask the surface ligands, also preventing receptor recognition. Despite the increase in cellular uptake, the ligand and receptor interactions are reduced, highlighting their challenges. Thus, intrinsic nanoparticle cell interaction serves as an alternative mechanism [5].

The viral vectors have specific properties to cross the dense barriers easily—unlike the viral vectors, the nanoparticles are non-viral vectors for gene delivery that can be engineered to enhance their transport across the barriers, especially the blood-brain barriers present in the CNS. This enables the active delivery of therapeutic agents in the nervous system, making it serve as a suitable alternative for long-term genetic therapy in the main areas like the brain. This will enable targeted results in a protective site. The nanoparticles must be engineered to bypass the immune system in the body. This will help the nanoparticle to enter the target site for delivering the drug in the right place. There is new ongoing research based on nanoparticles to serve as carriers for delivering the genetic material, peptides, and drugs in the nervous systems. There are several works relating to nervous system therapeutics using the nanoparticles that are being processed [6,7].

The engineered nanoparticles have higher potential to revolutionize the therapeutical and treatment processes. Specifically, the targeted drug delivery is allowed to reach the cell through this modified or engineered nanoparticle. Although these potentials do not resolve every challenge, such as surmounting all the biological barriers. It is necessary to understand the importance of the characteristics of the nanoparticles, such as size, shape, and surface properties, for the enhanced activity. The nanoparticles need to be rationally designed to acquire high potential [8].

In recent findings, the nanoparticles temporally regulate the gene activity rather than altering the genome permanently. This is enabled through the active delivery of nucleic acids such as siRNA or mRNA. Therefore, nanoparticles reverse and control the modulation mechanism of gene expression. Thus, the nanoparticles act as a switch-like control over the genes [9].

2.Physiochemical Determinants for Genomic Entry:

2.1 Size-dependent nuclear entry: The size of the nanoparticle is the key parameter; even the nanoparticle-mediated in vivo and in vitro responses are highly dependent on the size. An experiment was conducted to identify the penetration ability of metal nanoparticles and their potential use as ultrasmall modified nanoparticles in gene therapies. It is confirmed that the smaller nanoparticles, less than 10 nm, enter the nucleus, and the larger ones are present in the cytoplasm [10]. The smaller nanoparticle can penetrate the nucleus through the nuclear pore complex, and the larger NPs need the nuclear localization signals (NLS) for importin proteins to recognize [11].

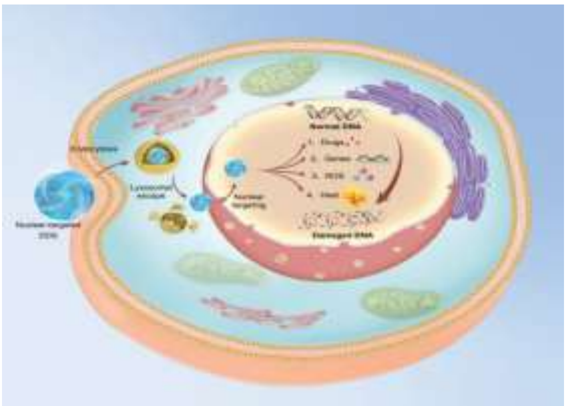

Fig. 1: Nuclear targeted drug delivery systems (DDS) [11]

2.2 Surface charge and chromatin affinity: The nanoparticles' surface charges, DNA's base content of oligonucleotides, and their length are the crucial parameters for active absorption. The experiment conducted by Sara Abbasian et al. (2014) proved that the adsorption of DNAs to Ag nanoparticles depended on the surface charge of nanoparticles. Also, the increase in adenine base percentage in the oligonucleotide sequence increased the adsorption rate. It was confirmed that the length of the oligonucleotide can positively influence the adsorption when it is preheated. This consequently increases the protective effect against salt-induced aggregation [12].

2.3 Protein Corona as Key: The cationic and anionic surface of nanoparticles extensively adsorbs the serum proteins. The protein structure can be altered through the adsorption process, where the cationic polystyrene NPs modify due to the secondary structure of BSA changing. The anionic NP change can be observed in the carboxylate-modified quantum dots. Despite the alterations in NP structure and the surface, the protein and NP complex remain even during the cellular internalization and transport. Corona proteins formed from the nanoparticle binding with the protein will have dedicated cell surface receptors for the internalization of the complex [13].

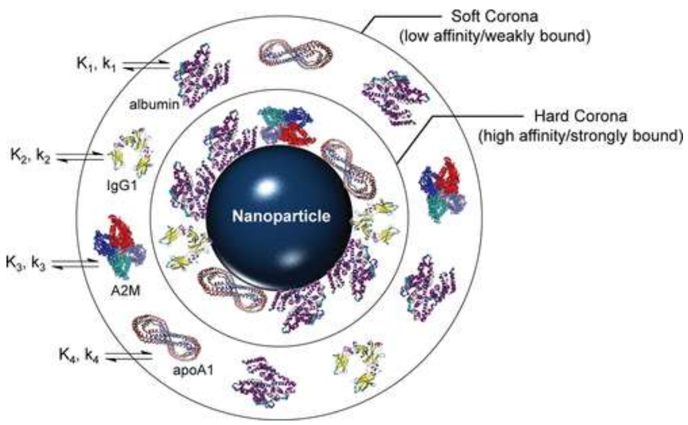

Fig 2: Protein corona formation around nanoparticles [13]

3.Molecular Mechanisms-Direct genomic interactions:

The gene expression can be influenced by the direct interaction of nanoparticles and genomic material through various molecular mechanisms. These interactions move beyond the indirect signaling and alter the physical and biochemical properties of DNA and the transcriptional processes. In which one important mechanism is transcriptional inhibition, it blocks the process by interfering with the transcriptional machinery progression with the DNA strand. An experiment was conducted to suggest that the gold nanoparticles, when functionalized with the promoter-specific oligonucleotides that bind to the target DNA regions, had disrupted the transcription processes. The RNA polymerase functioning is affected through the steric hindrance of the nanoparticle and the sequence-specific binding, which leads to mutation, i.e., gene silencing. Furthermore, the translation process is simultaneously inhibited by the nanoparticle-DNA conjugates through the antisense interaction. This mechanism strongly demonstrates a dual-level activity at both transcriptional and translational stages [14].

Nanoparticles are engineered to serve as artificial transcription factors (ATFs) that directly regulate the gene expression at the transcriptional stage. An important example determines the efficiency to mimic the multidomain structure of the natural transcriptional factors. The functions of the domains are regulated effectively by the gold nanoparticle-based platform called Nanoscript. It activates the nuclear localization signal for nuclear entry, initiates an interaction of the DNA-binding domain with promoter regions, and activates the transcriptional machinery. The process is initiated during the localization of ATFs into the nucleus. The nanoparticle-based ATFs are bound to target DNA to begin the transcription process by recruiting the RNA polymerase II and the other cofactors. The nanoparticle always serves in delivering the particle or transcriptional factors in the cell, but instead it acts as a functional replica to prove that nanoparticles are capable of directly altering the regulatory molecules. The nanoparticle has become a powerful tool to activate the targeted gene and cellular modifications [15].

The Cys2His2-type zinc finger protein (ZEP) plays an important role as a DNA binder. It has approximately 30 amino acids and serves as a common DNA-binding motif. They contain unique qualities like binding as monomers to their DNA targets and having several finger domains. This makes the zinc finger protein act as a promising candidate for the ATFs domain formulation. This particularly identifies the targeting sites in chromosomes and regulates gene expression both in vitro and in vivo [16].

Another mechanism involves the reactive oxygen species (ROS)-mediated signaling. The silica nanoparticle is used in many industries; despite its use in commercial products, it is extensively used in regulating the gene. The silica nanoparticle elevated generation of reactive oxygen species, high-end production of malondialdehyde, and the downregulation of glutathione peroxidase that results in induced oxidative stress. The SiNPs triggered the gene activation, i.e., the Nrf2-mediated antioxidant system. The activation was due to the induced effect of nuclear factor-kB and the regulation of the MAPK pathway. The gene alteration eventually leads to vascular endothelial dysfunction [17].

The molecular crowding condition occurs due to the high space occupancy of various biomolecules in the cell. The biomolecules are either soluble or insoluble particles like proteins, nucleic acids, saccharides, lipids, and metabolites. This condition plays an important role in regulating the structure of nucleic acids and changing the functions of hydration dynamics, thermal stability, and interaction of molecules. Due to the crowded environment, the water activity is reduced, eventually stabilizing non-canonical DNA structures. It also influences the permeability of transcriptional factors into the genomic areas by destabilizing canonical B-form DNA. Furthermore, binding and hybridization activity are affected, leading to altered gene expression levels. In this case, the nanoparticle entry will rapidly increase the condition to the next level and enhance

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overpopulation in the cellular or nuclear environment. This highlights the high chances to affect transcriptional factor mobility, interaction, and gene regulation dynamics [18].

Intercalation is a crucial aspect to notice; the small molecules can modify the structure of DNA through insertion between the base pairs. This will significantly result in unwinding and expanding the DNA helix. For instance, ethidium bromide (EtBr) is a molecular intercalator proved to significantly regulate a change in the DNA structure. The increase in inter-base distance and thermal stability increase was observed. Through these findings, the DNA conformation and external agents' susceptibility are well understood. On extending beyond the cellular level, the nanoscale and nanoclusters may interfere with the DNA activity and alter the gene regulation [19].

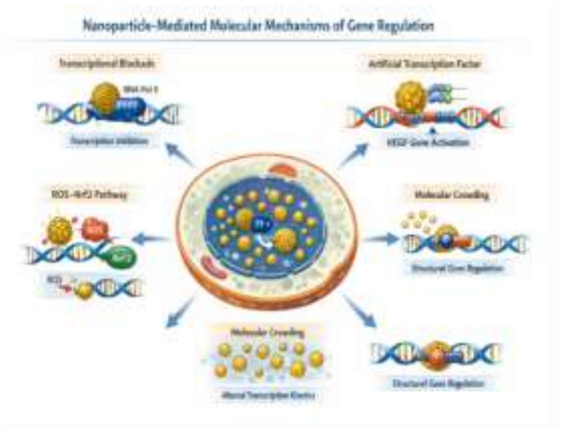

Fig 3: Mechanism of nanoparticle-mediated gene regulation

4.Applications in precision medicine:

Oncogenic gene silencing:

The nanotechnology in the biomedical field is well explored by researchers and used in several aspects. The cancer is the main area to be focused on the use of nanotechnology to regulate gene expression. The growth and progression of cancer is due to the overexpression of oncogenes through its signaling events to induce uncontrolled proliferation, metastasis and the prevention of apoptosis. The oncogenes such as KRAS, MYC, BCL2, EGFR, HER2, and ALK are the primary genes to promote cell growth. The traditional treatment shows high resistance, off-target toxicity and tumor heterogeneity. These setbacks made the small interfering RNAs (siRNAs) a potential candidate for the gene-silencing at the post-transcriptional stage. The siRNAs are short and double stranded RNA molecules with 21-23 nucleotides. The siRNA induces sequence-specific degradation of target mRNA by incorporating into the RNA-induced silencing complex (RISC) reflecting in post-transcriptional gene silencing. The mechanism helps in downregulating the oncogene expression leading to control tumor progression. The siRNAs also target any gene virtually with known sequence, including the undruggable targets like transcription factors and non-enzymatic scaffolding proteins. The siRNAs delivery is mediated by the variety of delivery systems; they are engineered for the improved bioavailability and specificity. The lipid nanoparticle is one of the delivery systems to enhance a targeted delivery [20].

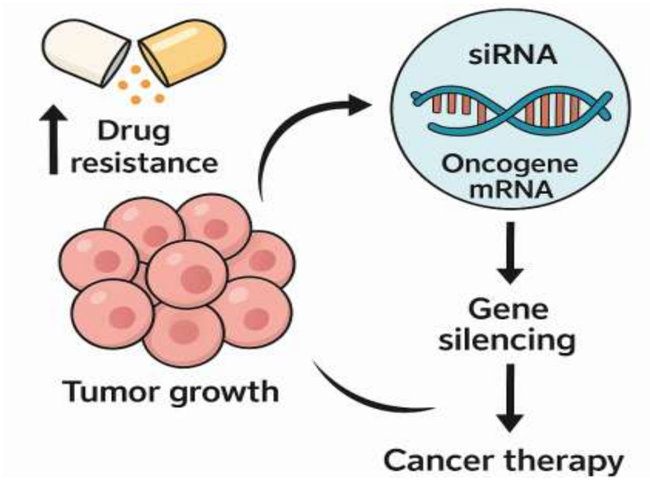

Fig 4: use of siRNA to silence oncogenes [20]

Neuro-genetic repair:

Neurodegenerative diseases (NDs) cause major impact on the nervous systems and spinal cords. The blood brain barrier plays a pivoted role in preventing the entry of molecules, they are protective and prohibits the entry of chemicals. Thus, the effectiveness of traditional treatments is reduced by the barriers. The serious brain diseases include amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD). The nanoparticles with the tiny and unique characteristics can cross the barrier to deliver the drugs. Through the capability of crossing the blood-brain barrier using nanoparticles can do neuro-genetic repair by actively targeting neurodegenerative pathways. In Parkinson's disease, a specific nanoparticle graphene quantum dots interacts with misfolded proteins especially, alpha-synuclein to promote fibrillar structures disassembly by preventing their aggregation. Furthermore, nanoparticle-based systems are engineered for the regulation of gene expression related to protein misfolding extending to offer a multifunctional therapeutic strategy [21].

Cardiovascular Gene tuning:

The cardiovascular disease is causing increased death rate worldwide, in which myocardial infarction (MI) are the primary cause of death. The irreversible necrosis of cardiac tissue caused due to the ischemia results in MI and followed with coronary artery occlusion. As myocardium cannot regenerate and damaging the extensive myocardial which leads to cardiac remodelling and causing to heart failure or sudden death. The traditional treatment methods have adequate side-effects, necessitating the use of nanomaterials as faster and more efficient approaches. The nanoparticles release the angiogenic factors in the targeted site of myocardial infarction area. The growth factors like Basic fibroblast growth factor (bFGF) promotes the angiogenesis process. The nanoparticles like CNT, carbon nanofibers and graphene oxide can directly promote angiogenesis and repair tissue [22].

Diagnostic theranostics:

Nanoparticles can be used widely in theranostic platforms by emitting fluorescent signals in real-time through binding to specific targets. They prove to show simultaneous imaging and therapeutic delivery of drugs. For example, nanoparticles release drugs like doxorubicin with fluorescence for detecting active drug release and target interaction. The quantum dot-based nanoparticles are conjugated with antibodies to selectively bind to cancer biomarkers. Through this mechanism, the clinicians see and treat disease in precised and controlled manner [23].

Green synthesis for biocompatibility:

Nanoparticles are proved to show greater inducing quality in transcriptional modifications in the microbial systems, specifically in activating stress-response pathways. For example, the genes are upregulated when E. coli is exposed to AgNPs results leading to indicate that nanoparticles can be used in cellular defence mechanisms as well. In addition, the nanoparticle-mediated delivery is more effective than the ionic silver to regulate gene expression. The nanoscale interactions are more crucial in determining biological properties. The green-synthesized nanoparticles with the plant biomolecules create more retaining capacity for the activation of stress-response mechanisms. This is the most biocompatible approach as the cytotoxic effects are reduced [24].

5. Challenges of Nanoparticle:

- One of the major challenges faced by nanoparticle-based drug delivery is the inconsistency of enhanced permeability and retention (EPR) effect in different individuals and tumor types. The enhanced permeability of the tumor mediates the transport of macromolecules into the tumor sites and enabling to stay suppressed in lymphatic filtration. This phenomenon forms the basis for nanoparticle platform to release the drug in targeted way. Even through surplus demonstration in preclinical models, EPR shows variability. In addition, tumor accumulation does not only translate into enhanced therapeutic outcomes, but their tumor response is also not either related with the patient survival. These challenges limit the passive targeting strategies and showcase the necessity of next-generation nanoparticles that utilize active targeting method for the precise and targeted delivery [25].

- Nanoparticles are constantly accumulating in the liver after introduction into the body, creating major concern about the toxicity and safety. Some NPs exhibit strong effects related to physical parameters and strongly affects liver function [26]. Studies reveal that the silver nanoparticles tend to accumulate in various tissue, including the intestine and liver leading to multigenerational toxicity through their trophic transfer of food chain. They widely affect their physiological, regenerative effect and gene expression mechanisms [27].

- In the field of nanotechnology, translating from lab scale to pilot scale remains a complex situation mainly due to their unique physiochemical properties. This condition produces a varying results in the pre-clinical testing, clinical trial runs, and quality checks. These many disputes lead to inconsistencies, reduced safety and efficacy in manufacturing. However, the alterations in size, surface charge and stability can be a major cause of the issues in scaling up process. Even the minor changes in cellular uptake and biodistribution can modify the batch results. In this case, nanoparticles must be engineered with proper regulatory and manufacturing strategies for the successful production [28].

6. Future Directions:

The recent advances in nanotechnology have developed the smart nanoparticles for their potential use in biomedical applications. They are primarily designed to work in diverse conditions like varied pH, surface charge and microenvironment. The smart nanotechnology allows responding to both the stimuli internal as well as external such as magnetic fields, temperature and light. Through these stimuli responsiveness the drug release will be precise and controlled. The smart nanotechnology develops the nanocarriers like micelles, nanogels, and graphene-based systems to enhance a dual or multi-stimuli activation. The knowledge in recent advancement delves us into further establishment and creates a promising future in nanomedicine and drug delivery [29].

7. CONCLUSIONS

In conclusion, nanotechnology is a powerful tool in various aspects of life. The nanoparticles are useful in major fields like biomedical engineering, industrial and therapeutical. Nanoparticles widely modulate gene expression via both direct genomic interactions and indirect signalling mechanism. Their unique properties remark them as suitable candidate to interact with biomolecules like DNA, RNA and proteins to influence transcriptional modification, epigenetic regulation and cellular mechanisms. Nanoparticles regulate gene expression through transcriptional inhibition, ATF activity, Ros-mediated signaling and molecular crowding.

The nanoparticles are applied in precision medicine, neurogenetic repair, cardiovascular gene tuning, diagnostic theragnostic and demonstrates their ability in therapeutical potential. Furthermore, the green biosynthesis approach maintains functional efficacy by enhancing biocompatibility. Despite these potential uses, challenges such as toxic activity, bioaccumulation, differences in EPR effect, and piloting large-scale production hurdles remain significant. These challenges can be mitigated using improved regulatory frameworks and advanced standards. The future prospect in smart nanotechnology delves further into combining artificial intelligence and bioinformatics with biotechnology. The combination would revolutionize genomic medicine and continue research works will hold nanotechnology a promising solution.

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