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Nanobiomaterial: Hybrid Gold and Silver Nanoparticles (AuNPs and AgNPs) as Non-viral Gene Delivery Vehicles

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Hybrid gold and silver nanoparticles (AuNPs and AgNPs) are known as chemically or biologically engineered nanomaterials that have size dimension in the range of 1-100 nm. Nanosized materials are exhibited various novel properties like site-specific reactivity, greater sensing capability and increased mechanical strength which offered their easy, safe, fast, efficient and cost effective synthesis. Previously, various nanosized formulations and dispersions of conjugated or hybrid gold and silver metals have been proposed for targeted drug delivery by well known pharmaceutical companies. These hybrid nanobiomaterials have also been used in tissue engineering, protein detection, cancer therapy, multicolour optical coding for biological assay at genome level. Recently, nonviral gene therapy is going to be proposed as a promising therapeutic modality for the treatment of genetic, metabolic and neurodegenerative disorders. Their nonviral approaches has been found to be an excellent and safe alternative gene transferring vehicles to the popular viral vectors due to having significant favourable properties such as non-immunogenicity, low toxicity, and potential tissue specificity and effective targeted drug delivery. As well as, these hybrid nonviral mediated clinical and genetic approaches have been tested in preclinical studies and human clinical trials

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over the last decade which may prove more potent drug and safe gene/drug/nucleic acid delivery carriers for combating various types of cancers and epidemics worldwide.

Keywords: Nanbiomaterials; nonviral gene delivery vehicles; gold nanoparticles; silver nanoparticles; nanoscaffold.

1. INTRODUCTION

Nanobiomaterials are known as chemically or biologically engineered nanomaterials having dimension in the range of 1-100 nm, high site-specific reactivity, non-immunogenicity, low toxicity, potent sensing capability and high mechanical strength. Previously, colloidal silver nanoparticles, titania nanoparticles, carbon nanotubes, nanoscaffold and gold nanoparticles and other metallo nanoparticles dispersions had been used for drug as nonviral approaches to carry out safe tissue engineering, protein detection, cancer therapy as well as also successfully used in the treatment of genetic, metabolic & neurodegenerative disorders [1-3].

Earlier, various proposed viral gene delivery methods were found to cause pathogenesis in host cell/genome during the delivery of desired loaded components. So, fabrications of new multifunctional conjugated or hybrid nanobiomaterials are becoming more promising and safe choice for gene delivery over others conventional viral-vector delivery systems. Direct nonviral gene therapies have been proposed to increase the delivery potency of current plasmid DNA vectors [4,5].

Hence, these nonviral vector designs were found to be safe and efficient to load the desired protein or antibiotic resistance genes in the host at site specific targeted delivery [6,7]. Hence, designing of new advanced multifunctional non-viral nano-devices are become more promising choices for gene delivery over others proposed viral vector delivery methods [8-10]. Use of non-viral gene vectors have also been used for neuronal transfection via siRNA delivery mediated including the use of *E. coli*, Lentil virus, Adenovirus, Herpes virus, Retro viruses, lipoplexes, liposomes, polyplexes, calcium phosphates, lipids, and cationic polymers, polyplexes, lipoplexes, lipopolyplexes, chitosan, polyethylenimine, polyamidoamine dendrimers, poly(lactide-co-glycolide), Gold Nanoparticles, Magnetic nanoparticles, Quantum dots, Silica nanoparticles and Fullerenes, carbon nanotubes (CNTs) [11]. The use of hybrid gold and silver nanoparticles can facilitate development of new advanced nucleic acids-based nanotherapies for alleviation of various disorders [12,13].

Use of non-viral gene delivery using polyethylenimine-coated magnetic nanoparticles, cell-penetrating peptides (CPPs) and potential nanoscaffolds exogenous DNA were also reported for impregnation of desired loading constituents into host genome for efficient gene/ nucleic acid delivery to combat genetic disorders such as severe combined immunodeficiency, cystic fibrosis and Parkinson's disease [14-18].

In past, non-viral gene delivery systems have been proposed as a more safer alternative over viral vehicles by using synthesized water-soluble aminoethyl-chitin (AEC) complex conjugated with DNA and AEC/DNA nanoparticles. There are further tested for their transfection efficiency in host genome; human embryonic kidney cell line (HEK293) to improve transfection efficiency of AEC/DNA nanoparticles as compare to naked DNA [19].

2. AuNPs (GOLD NANOPARTICLES) AS HYBRID NONVIRAL GENE DELIVERY VEHICLE

AuNPs (Gold nanoparticles) were found to be an attractive nanoscaffold as nontoxic gene delivery vehicle system which prepared by decorating the surface of nano-biovehicles with specific antibodies or oligonucleotides/ small interfering RNA.

Their grafting with fabrication of active functional groups e.g. polyethylene glycol and ionic entities on their surfaces were led to increase the plasma protein adsorption followed by improving the pharmacokinetics and evading immune surveillance [20-23].

2.1 AuNPs as Hybrid Multifunctional Tumor Gene Delivery Vehicle

AuNP coupled Ad vectors for hyperthermic tumor cell ablation had been found quite suitable with laser induced hyperthermic tumor cell killing therapy. AuNPs were also fabricated by grafting

various compatible biocompatible polymers and natural or synthetic biomolecules that may needed more suitable nanotechnological advances to realize the exact potential of the multifunctional AuNP-coupled Ad vector system for simultaneous hyperthermia coupled targeting, imaging and tumor gene therapies [24,25].

2.2 AuNPs as Hybrid Nanotheranostic Tool

An advanced nonviral tailored therapeutic strategy had been employed by using gold nanoparticles having high ease of surface modification that reduce the side effects associated with the conventional treatments to improve the safety profile of a given gene therapy to elicit more clear advantageous cell targeting transfection efficiency [26,27]. The process of magnetofection was also carry out to accelerate gene complexes sedimentation to the cell surface to promote the phagocytosis of gene complexes efficiently, to enhance the fast the gene transfection carrying a plasmid DNA harbouring target genes or a synthesized small interference RNAs (siRNA) using charge-reversal functional gold nanoparticles to improve the nucleic acid delivery efficiency [28-30]. Previously, non-toxic gum arabic gold nanocomposite (GA-AuNPs) have also been proposed as nanotheranostic nonviral gene tool used in corneal surgery at the University of Missouri-Columbia [31].

2.3 AuNPs-nanoscaffold as Hybrid Nonviral Gene Delivery

Covalent and noncovalent gold nanoparticle conjugates were found to be safe and effective nucleic acids delivery vehicles along with RNA-interference technologies [32]. Surface modified AuNPs can be easily incorporated into polymeric nanoparticles or liposomes which have been used in various biomedical applications due to having potent amenability of their synthesis and multisystem functionalization [33,34].

2.4 AuNPs-dendrimer as Hybrid Nonviral Gene Delivery

The use of partially acetylated dendrimer-entrapped gold nanoparticles (AuDENPs) were also designed and studied for gene delivery applications that may serve as key nonviral gene delivery nano-bio-vehicle for safe gene delivery applications with desired gene transfection efficiency [35,36]. As well as, cationic gold nanoparticles were synthesized by carrying out possible modification done with 2-aminoethanethiol, 8-amino-1-octanethiol, and 11-amino-1- undecanethiol by $NaBH^4$ reduction of $HAuCl^4$ in the presence of thiols in water or a water/ethanol mixture solvent to promote the gene transfection with high efficacy [37]. Previously, Di-sulfide linked polyethylenimine coated gold nanoparticles (ssPEI-GNPs) were also prepared and used for the transgene delivery capability of the ssPEI-GNPs [38]. Recently, a novel clinical study had been carried out size-dependent gene tranfection potential of ultra-small gold nanoparticles (upto 2 nm in diameter) for potential application of intranucleus delivery nonviral gene delivery vehicle as nanotherapetic tool when compared with free triplex-forming-oligonucleotides (TFO). The nanoparticle-conjugated TFO was found more active at reducing c-myc RNA and c-myc protein that resulted in reduced cell viability [39].

3. AgNPs (SILVER NANOPARTICLES) AS HYBRID NONVIRAL GENE DELIVERY

Silver nanoparticles (AgNPs) were found to exhibit a consistent amount of versatile properties which endorse their vast spectrum of applications in nanomedicine having high antimicrobial efficacy against many pathogenic bacteria such as *Escherichia coli, Neisseria gonorrhea, Chlamydia trachomatis* and other viruses too. In biomedical engineering, silver nanoparticles are found to be considered more potent and ideal gene delivery systems for tissue regeneration and used as safe biosensors for nonviral gene therapeutic tool [40,41].

3.1 AgNPs as Hybrid Nanotheranostic Tool

AgNPs tagged photolabile nucleic acid conjugates were used for targeted delivery and controlled release of oligonucleotide therapeutics in vivo to perform the inducible gene silencing [42]. Biofunctionalized stable chitosan-g-polyacrylamide AgNPs complex with good DNA binding ability were also studied for effective transfection of the Arg–Gly–Asp–Ser (RGDS) peptide into host genome and minimal toxicity in wound healing and cancer gene therapy [43,44]. Montmorillonite was conjugated with silver nanoparticles and further stabilized with starch, citrate, polylysine and multiwalled carbon nanotubes that used for further binding of plasmid pcDNA-GFP to carry out effective gene

delivery [45]. The synergistic effect of AgNPs had also been experimented on the uracil phosphoribosyltransferase expression system to sensitized the cells towards the proposed treatment with the drug 5-fluorouracil to induce the apoptotic pathway in the host disease cell [46].

3.2 Oiligonucleotide-thiol Conjugated AgNPs as Hybrid Nonviral Gene Delivery Vehicle

Recently, possible nonspecific interactions of thiol–ssDNA and dsDNA macromolecules with gold nanoparticles were proposed along with dynamic light scattering and cryogenic transmission electron microscopy to measure the nano-visualization and functionalization of gold nanoparticles with thiol–ssDNA and nonthiolated dsDNA [47]. As well as, poly adenine (polyA) DNA functionalized gold nanoparticles (AuNPs) were also fabricated with high density of DNA attachment having high hybridization ability similar to those of thiolated counterparts as an anchoring block for binding with the AuNPs surface. This proposed system was led to facilitate the appended recognition block as a better upright conformation for hybridization that demonstrate its great potential to be a tunable plasmonic biosensor named, polyA DNA–AuNPs nanoconjugates [48,49].

3.3 AgNPs as Photoactivated Antisense Mediated Hybrid Nonviral Gene Delivery Vehicle

The unique photophysical properties of silver nanoparticles were also characterized for their clinical contribution as potential photoactivated non-viral drug delivery vectors. These potential multicomponent delivery agents were studied for oligonucleotide therapeutics through regulation of ICAM-1 (Intracellular Adhesion Molecule-1) silencing for better achieving light-triggered and spatiotemporally controlled gene silencing via nontoxic silver nanocarriers. These tailorable strategy of nanomedicine was found to provide noticeable gene expression observations and effective genetic therapies [42].

Multifunctional nanocomposites of poly(L-lactide) (PLA) and polyethylene glycol (PEG)-grafted graphene quantum dots (GQDs) were also proposed for simultaneous intracellular microRNAs (miRNAs) imaging analysis as combined gene delivery for enhancing therapeutic efficiency. The functionalization of photoluminescent (PL) graphene quantum dots (GQDs) with PEG and PLA was found to be imparted the nanocomposite with super physiological stability and stable photoluminescence having broad pH range which may prove vital for cell imaging with excellent biocompatibility, lower cytotoxicity and protective properties in HeLa cell line. Hence, effective delivery of the desired miRNA probe was carried out by using GQDs for intracellular miRNA imaging analysis and regulation that may highlighted the key role of the highly flexible multifunctional nanocomposite in biomedical applications [50].

4. CONCLUSION

The purpose of this mini review is to provide an update and concise report on hybrid gold and silver nanoparticles (AuNPs and AgNPs) mediated nonviral delivery of gene/drug/nucleic acid/ loaded biological or chemical components. These hybrid nanobiomaterials may be further used for cancer therapy, genetic vaccines and stem cell engineering with various employed possible clinical and pharmaceutical efforts. However, new and advanced strategies are needed to overcome the limitations of their exhibited advantages, especially their ease of production and potential for repeat administrations which are responsible to carry out the effective and safe clinical and pharmaceutical applications. As well as, further improvements in adopted conjugation strategies will also be required for the development of safe, cost effective and more potent hybrid AuNPs and AgNPs nonviral gene delivery vehicles by performing number of experimental trials in-vivo and in-vitro system to carry out effective long lasting and site-specific targeted delivery.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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