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Nanocarriers in Gene Therapy: Bridging Nanotechnology and Diseases

Review Article

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ABSTRACT

Nanoparticles have emerged as transformative tools in gene therapy, presenting innovative solutions to address the challenges of gene delivery. These minuscule particles (between 1 and 100nm), often, can be engineered to carry and to protect genetic material such as DNA or RNA with ensuring its stability and functionality until it reaches the target cells. The identical and physicochemical properties of nanoparticles, including their surface charge, size and shape, facilitate their penetration through biological barriers and enhance cellular uptake. One of the significant advantages of using nanocarriers for gene delivery is their capacity to be tailored for specific applications. By modifying the surface of nanoparticles with ligands, peptides, or antibodies, they can achieve targeted delivery to particular cell types, thus increases the precision of gene therapy and minimizes off-target effects. These nanoparticles can be designed to release their genetic payload in response to particular stimuli such as enzymatic activity or pH changes, providing controlled and sustained gene expression. Nanoparticles offer a promising platform for gene delivery, holding the potential to treat a myriad of genetic disorders with precision and efficacy.

Keyword: *Nanocarriers, Gene delivery, Diseases, Efficacy, Conventional treatment*

Introduction

Nanoparticles are utilized as gene carriers because of their versatile properties including rich functionality, wide availability, easy preparation, potential for targeted delivery, storage stability and good biocompatibility (Sun et al. 2008, Yu et al. 2007, Yang et al. 2012). Challenges with nanoparticles use usage include low loading efficiency, potential aggregation and limited in vivo metabolization necessitating ongoing research to

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address these limitations for safe and effective gene delivery (Tian et al. 2013). Gene therapy has attracted more and more attention for treating various human genetic diseases (El-Aneed et al. 2004, Olefsky et al. 2004). The secret to effective, target-specific, and dependable gene therapy with excellent purity, stability, and integrity is gene transfer systems (Jiang et al. 2023). Recently, nonviral vectors have been proposed as safer alternatives for gene therapy to viral vectors (Kim et al. 2003, Mintzer et al. 2009). Additionally, nanoparticles can navigate biological barriers, enhancing cellular uptake and gene expression (Chung et al. 2010). Recent advancements in nanoparticle design have improved biocompatibility and minimized toxicity paving the way for safer and more effective therapeutic applications (Davis et al. 2010, Morille et al. 2010). Among nonviral vectors, nanoparticles are applicable as carriers for the treatments of a wide range of diseases like diabetes, cancer etc (Song et al. 2010). For a therapy to be effective, genetic elements must be delivered specifically and released from their carriers efficiently (Brannon-Peppas et al. 2004). Either "passively" or "actively," specific delivery and targeting might be accomplished. "Active" targeting entails delivering genetic materials with the help of a magnetic gradient, as in the case of magnetic nanoparticles, or internally, through molecular recognition-driven binding between a functional nanocarrier and the receptors on a target cell's membrane (Brigger et al. 2012). Systems that simply use the "passive" targeting approach may encounter issues with non-specific uptake and possible macrophage destruction (Bergen et al. 2006).

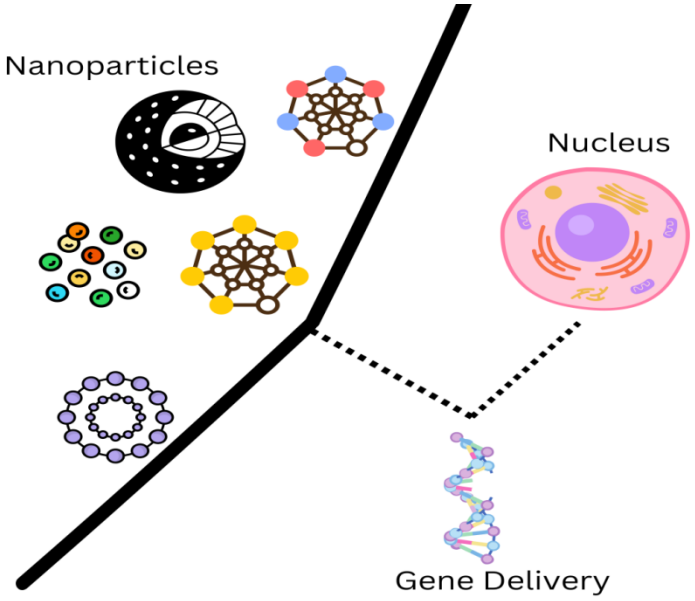

Figure 1: Nanocarriers in Gene Delivery System

Nanoparticles hold great promise as gene delivery systems, offering targeted, efficient, and safe delivery of genetic material. In this review, their continued development could be revolutionized the field of gene therapy, addressing a broad range of genetic disorders and diseases with unprecedented precision and effectiveness.

Methodology

We included all articles regarding nanoparticles as gene delivery system. We conducted systematic

search up to august 2024 using three electronic databases including Google Scholar, PubMed, Scopus with the search term: (Gene delivery OR "Evaluation of nanoparticles" OR Nanoparticles OR "Concept of nanoparticles as gene delivery system" OR "Gene therapy") OR "Nanocarriers in treating diseases" OR "Treating formulation" OR with limit to human in Scopus, Google Scholar and PubMed. We performed a manual search in order to find more relevant papers through different means. A total of 200 articles were initially found in the search up to January, 2023. Among this, 100 records were excluded due to reviews, irrelevant studies and animal studies. After applying the exclusion criteria, 70 articles were selected for study. The below flow chart shows how we conducted our literature search. The characteristics of the selected articles were analyzed based on their research design, population, intervention or exposure, comparator or control group, outcome measures and study results. These 70 articles contain precisely detailed on how nanocarriers act in gene delivery system and how it is important for modern nanotechnology. Then finally 70 articles were included.

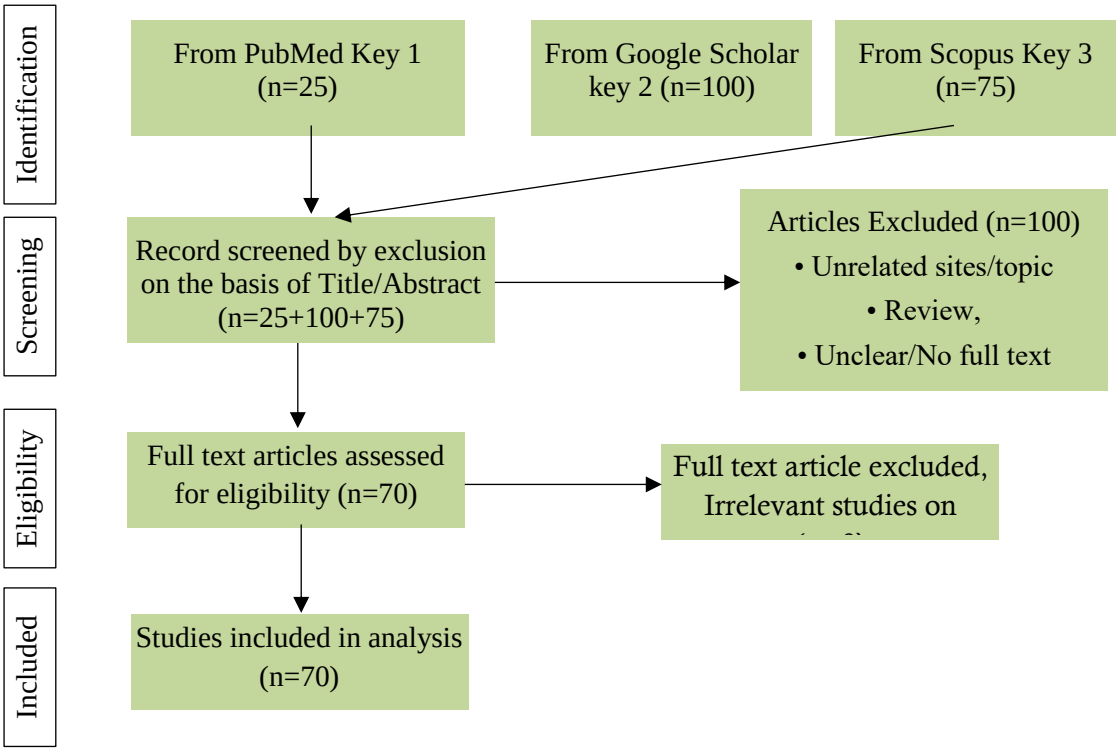

Figure 2: Flow Diagram of Nanocarriers Used in Gene Delivery System

Nanocarriers Used in Treating in Various Diseases

Chitosan respond to particular stimuli like pH, temperature enabling precise delivery and regulated release of genes, offer a promising platform in treating cancer, with their capacity to enhance drug delivery, reduce side effects, and improve treatment outcomes nanoparticles offer a promising platform in treating cancer with their capacity to enhance drug delivery, reduce side effects and improve treatment outcomes. Moreover, chitosan nanoparticles have been explored for their potential

in photothermal therapy, where they can be used to generate heat upon exposure to specific wavelengths of light, leading to the destruction of cancer cells (Pakunlu et al. 2004, Yin et al. 2012, Cheng et al. 2012, Chen et al. 2009, Meng et al. 2013, Saad et al. 2008, Xu et al. 2010, Sun et al. 2011). Another nanoparticle is solid- lipid nanoparticles (SLNs) can be used in combination with other therapeutic strategies including immunotherapy and gene therapy, to provide a comprehensive approach to HBV curing. One of the key advantages of using SLNs for HBV treatment is their capacity in order to enhance the bioavailability and stability of the encapsulated drugs. This results in improving reduced side effects and therapeutic efficacy compared to conventional treatments. SLNs have shown significant potential in the treatment of Hepatitis B virus (HBV) due to their unique properties and advantages in drug delivery (Singh et al. 2018).

Table 1: Nanocarriers Used in Treating in Various Diseases

Nanocarriers	Disease	Aim	Result	Reference
Chitosan Nanoparticle	Lung Cancer	Aiming to enhance drug delivery efficiency and reduce side effects	Leading to destruction of proliferating cells	Pakunlu et al. 2004, Yin et al. 2012, Cheng et al. 2012, Chen et al. 2009, Meng et al. 2013, Saad et al. 2008, Xu et al. 2010, Sun et al. 2011
Solid lipid Nanoparticle	Hepatitis Virus	To target specific pathogens and enhance drug efficacy makes them valuable in addressing antimicrobial resistance	Improving reduced side effects and therapeutic efficacy compared to conventional treatments	Singh et al. 2018
Polymeric Nanoparticle	Epilepsy	In improving drug penetration and targeting specific brain regions for enhanced therapeutic effects.	Improving patient's condition with other side effects	Musumeci et al. 2019
Chitosan Nanoparticle, Plasmid DNA	Diabetes	respond to particular stimuli like pH,	Keeping illness under control by managing adverse consequences	Jean et al. 2012, Shahriar et

Nanocarriers	Disease	Aim	Result	Reference
Nanoparticle		temperature enabling precise delivery and regulated release of genes, offer a promising platform in treating cancer, with their capacity to enhance drug delivery, reduce side effects, and improve treatment outcomes		al. 2021
PLGA Poly(lactic-co-glycolic acid)	Alzheimer's Disease (AD)	To target specific brain regions for enhanced therapeutic effects.	Improving patient's condition with other side effects	Anand et al. 2022
Gold Nanoparticles	Cardiovascular Disease	To target drug delivery, imaging and therapeutic interventions	Treatment for specific therapeutic interventions	Zhang et al. 2018
Liposome Nanoparticles	Nucleic Acid Therapy	To enhance the delivery and stability of nucleic acid drugs	Protecting them from degradation and enhancing their delivery to target cells or tissues	Gao et al. 2023

One of the key advantages of polymeric nanocarriers is their capacity to cross the blood-brain barrier (BBB), a significant challenge in epilepsy treatment (Musumeci et al. 2019). Chitosan nanoparticles are derived from chitin, a natural biopolymer, and are known for their biocompatibility, biodegradability, and non-toxicity. These nanoparticles can be used to deliver insulin or other antidiabetic drugs directly to target cells, enhancing drug stability and bioavailability (Jean et al. 2012). By encapsulating drugs, chitosan nanoparticles ensure controlled release, decreasing side effects and reducing the frequency of administration (Jean et al. 2012).

Plasmid DNA nanocarriers, on the other hand, are used in gene therapy to address the underlying genetic causes of diabetes. These nanoparticles can deliver therapeutic genes, such as those encoding insulin or other regulatory proteins, directly into target cells. For instance, the delivery of the GLP-1 gene using chitosan/plasmid DNA nanocomplexes has shown significant improvements in levels of blood glucose in animal models of type 2 diabetes (Jean et al. 2012, Shahriar et al. 2021). In cellular

and animal models of AD, many methods shown that FDA-approved biodegradable PLGA nanoparticles, largely used as a drug delivery medium and not conjugated with any agent, can reduce Aβ aggregation/toxicity and AD-related pathology (Anand et al. 2022). Gold nanoparticles (GNPs) are utilized as a new drug delivery system in treating heart diseases, providing hopes for better drug delivery and reducing side-effects of existing drugs. GNPs show size-dependent accumulation in both healthy and diseased hearts, enabling accurate targeting and delivery of drugs to the targeted tissues (Zhang et al. 2018).

Nucleic acid drugs play dual roles in modifying genetic structures and regulating gene expression. Genetic abnormalities linked to many diseases, making nucleic acid drugs promising for treatment enhancing their delivery target cells and tissues (Gao et al. 2023). The condensing method has many basic limitations that restrict its use in gene delivery, despite the fact that it appears to be a great option. The internalization of nanocarriers through various endocytic routes has been the subject of extensive research. These include a cationic polymer or lipid's toxicity, the reticuloendothelial (RES) system's quick clearance, the inability to break free from the cell's endosome/lysosome compartments, and the inability to intracellularly unpack the nucleic acid from the electrostatic complex (Ma et al. 2013, Vercauteren et al. 2012). Here chitosan nanoparticles are used in various cancer treatment. gene delivery mediated by non-viral vectors is a promising approach for cancer therapy, offering safe and efficient gene therapy methods for various types of cancers. Prostate cancer is the fourth most common cancer in males, leading to significant mortality rates. Different treatment options include prostatectomy, radiotherapy, hormone therapy, chemotherapy, gene therapy, or a combination of these (Rozanova et al. 2013, Guo et al. 2019, Freytag et al. 2007). Recent PLGA

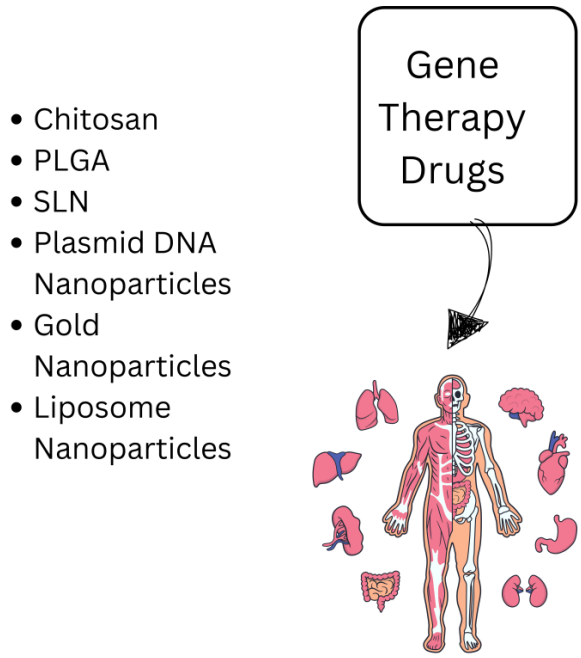

Figure 3 : Nanocarriers in Treating Diseases

Advancements focus on designing novel carriers for breast cancer gene therapy (Tewari et al. 2013, Rabiee et al. 2019). Again, solid lipid nanoparticles (SLN) and RNA interference (RNAi) inhibits the internal ribosome entry site (IRES) mechanism of the hepatitis C virus (HCV). SLNs can effectively deliver short-hairpin RNA (shRNA) targeted at the HCV internal ribosome entry site (IRES), which is crucial for viral replication. This suggests a novel method for inhibiting HCV replication, potentially leading to new therapeutic strategies for patients who do not respond to standard treatments. Gene therapy approach holds the potential to address a wide range of genetic disorders by either correcting or replacing faulty genes, or by introducing new genes to help fight diseases (Tavakol et al. 2017).

Conclusion

Nanocarriers are intended to transport and preserve genetic material (such as plasmid DNA, messenger RNA, or tiny interfering RNA) and deliver it to specified cells. There is little question that a coordinated, multidisciplinary effort will be necessary for the successful clinical application of nanoparticles. Nanocarriers for gene delivery have been globally utilized in all strategies of gene therapy, such as gene complementation, gene correction, suicide gene therapy, and gene inactivation. Research on nanoparticles focuses on improving targeting capabilities to specific tissues, reducing side effects, and enhancing therapeutic outcomes, indicating a bright future for nanoparticle-based therapies.

In conclusion, nanocarriers exhibit great efficacy for use as safe and potent gene delivery systems in a variety of clinical applications. Additionally efforts should be made to highlight the challenges faced by nanocarriers in gene therapy. These should specifically emphasize on the enhancement of transfection efficiency, improvement of targeting specificity ,reduction of toxicity and minimization of tissue damage.

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