Review Article

The Potential of siRNA-Mediated Oncogene Silencing in Cancer Therapy: An Overview of Pharmacogenomics Strategies

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ABSTRACT

siRNA-mediated silencing of oncogenes holds great promise as a potential cancer therapy. By selectively silencing genes involved in cancer progression, siRNA-based therapies have the potential to be highly specific and effective, while minimizing off-target effects and toxicity. However, several challenges need to be addressed before siRNA-based therapies can be widely used in clinical settings. One of the major challenges is the development of efficient and safe delivery systems for siRNAs. Additionally, more clinical trials are needed to evaluate the safety and efficacy of siRNA-based therapies for cancer treatment. Despite these challenges, ongoing research and development in the field of siRNA-based therapies are promising. New delivery systems, personalized medicine approaches, and combination therapies are being explored, which could potentially lead to more effective and personalized cancer treatment. With continued research and development, it is hoped that siRNA-based therapies will eventually become cancer treatments, providing patients with a more targeted and effective treatment option.

Keywords: siRNA, Oncogenes, Cancer Therapy, Gene Silencing, Targeted Therapy, Delivery Systems.

A potent biological mechanism called RNA interference (RNAi) enables the post-transcriptional selective suppression of gene expression. This mechanism has undergone substantial research and has emerged as a potentially useful therapeutic tool for the management of a number of illnesses, including cancer [1]. Small interfering RNAs (siRNAs) are double-stranded RNA molecules that target and degrade particular mRNA regions to silence genes. Oncogenes, which are genes that promote the growth and proliferation of cancer cells, have been discovered as promising targets for siRNA-mediated gene silencing in cancer therapy [2]. An enormous amount of work has gone into creating siRNA-based cancer medicines in recent years. The capacity of siRNAs to specifically target oncogenes offers a promising strategy for the creation of highly effective cancer treatments with little off-target side effects. Moreover, siRNAs have the potential to address the drawbacks of conventional cancer therapies, such as chemotherapy medicines, which frequently exhibit low selectivity and high levels of toxicity [3]. An overview of the present status of siRNA-mediated oncogene silencing for cancer therapy will be given in this thorough review. The review will go over the various siRNA delivery methods, the difficulties faced by siRNA-based therapies, and the development of siRNA-based cancer therapy in the clinic [4]. Future developments in this area as well as the possibilities of siRNA-based cancer therapeutics will be covered. Ultimately, the goal of this study is to provide a thorough grasp of the status and potential applications of siRNA-mediated oncogene silencing for cancer therapy [5].

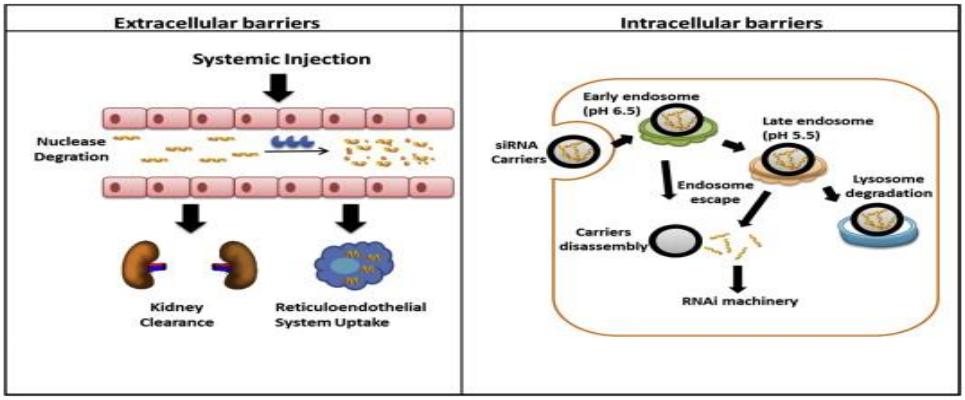

Fig No.1: Delivery systems for siRNA drug development in cancer therapy [6]

Different Approaches Used For Sirna Delivery For Cancer Therapy

The development of siRNA-based cancer therapeutics faces significant challenges in the efficient delivery of siRNA to cancer cells. Delivering siRNAs to target cells can be difficult since they are generally big, negatively charged molecules that are prone to nuclease destruction [5]. Biological obstacles like the extracellular matrix, cellular membranes, and endosomal compartments must also be surmounted by the siRNA delivery mechanism. To get over these obstacles and make siRNA distribution to cancer cells easier, a number of strategies have been devised [7]. Lipid-based delivery systems one of the most widely used methods for siRNA distribution is lipid-based delivery systems. A hydrophobic core that can enclose siRNAs is often surrounded by a lipid bilayer in lipid nanoparticles [8]. These nanoparticles can passively gather in tumor tissues due to the improved permeability and retention impact because their size ranges from 20 to 100 nm (EPR). By integrating targeting moieties like antibodies, peptides, or aptamers, lipid-based delivery systems can also be designed to target particular cell types [9]. Polymer-based delivery systems are biodegradable polymers used to encase siRNAs in polymer-based delivery systems. These systems can be made to have different characteristics, such as size, charge, and hydrophobicity, which can influence how they are taken up by cells and transported within them. By adding targeting moieties, polymer-based systems can also be created to target particular cell types [10].

Delivery methods based on inorganic nanoparticles for the transport of siRNA, and inorganic nanoparticles like gold, silica, and iron oxide have been researched. To make these particles easier for cancer cells to absorb, they can be functionalized with siRNAs and/or target molecules [11]. The special physicochemical characteristics of inorganic nanoparticles can be used to promote cellular absorption, endosomal escape, and gene silencing [12]. Viral vectors have been used to distribute siRNA because they are particularly effective in delivering genes to cells. However, because of safety issues such as immunogenicity and mutagenicity, their use is restricted. Usually, viral vectors are altered to lose their pathogenicity and designed to express siRNAs for certain targets [13]. Cell-penetrating peptides (CPPs) are short peptides that can penetrate cell membranes and facilitate the delivery of siRNAs into cells. CPPs can be fused to siRNAs to enhance their cellular uptake and endosomal escape. However, the delivery efficiency of CPPs is often low and is dependent on the type of CPP used [14]. Overall, each delivery system has its advantages and limitations, and the choice of delivery system will depend on the specific application and target. To overcome the challenges associated with siRNA delivery, researchers are continuing to develop new and innovative delivery strategies for siRNA-based cancer therapies.

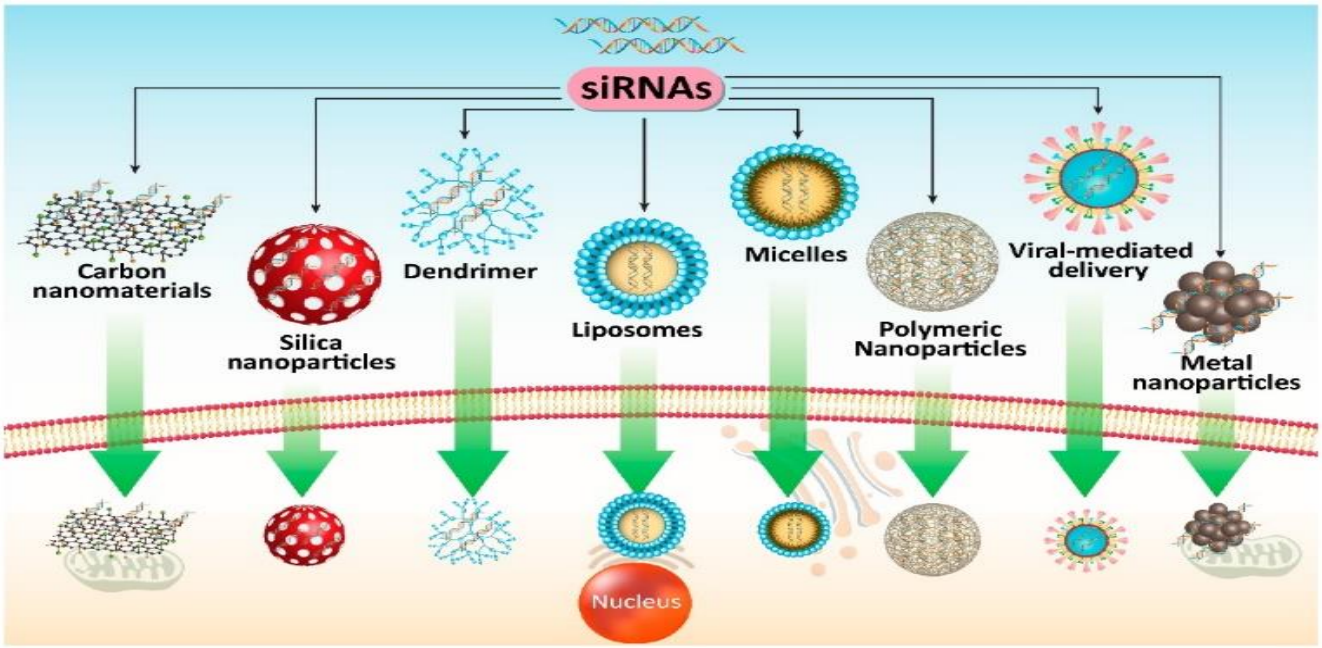

Fig No.2: Different approaches used for siRNA delivery for cancer therapy [15]

Challenges Associated With siRNA-Based Therapies

While siRNA-based therapies have shown great promise in preclinical studies and have advanced to clinical trials, there are still several challenges that need to be overcome to ensure their clinical success. As was already indicated, one of the main difficulties with siRNA-based therapeutics is getting siRNAs into the target cells. It is difficult to deliver siRNAs because they are big, negatively charged molecules that are vulnerable to nuclease destruction. A delivery mechanism that can shield siRNAs from deterioration, promote their cellular uptake, and guarantee their intracellular trafficking is necessary for effective siRNA delivery [16]. Although siRNAs are made to target particular genes, they can potentially have unwanted side effects. When siRNAs bind to undesired mRNA targets that

have partial sequence complementarity to the siRNA, off-target effects may result. Unwanted side effects may happen if undesired genes are silenced as a result of this [17]. siRNAs have the ability to elicit an immune response, which can result in the release of cytokines and chemokines that can cause cytotoxicity and inflammation. Although the immune system might become adapted to the siRNA delivery mechanism, this immune response can be particularly problematic for repeated siRNA treatment [18].

Because of their vulnerability to nuclease-mediated degradation, siRNAs have a short half-life in the bloodstream. Moreover, siRNAs' bioavailability can be decreased by the kidneys' quick clearance of the molecules. To enable the optimal distribution of siRNAs to target cells, the pharmacokinetics of these molecules must be adjusted [19]. Tumors are diverse, and various tumor cells may exhibit unique patterns of gene expression. Because of this, achieving uniform and efficient gene silencing across all tumor cells may be challenging. Because of the intricacy of siRNA production and delivery systems, siRNA-based medicines can be expensive to produce. The cost of production may restrict the accessibility of siRNA-based medicines and the scope of their extensive clinical use [20]. Overall, while siRNA-based therapies have great potential, there are still several challenges that need to be overcome to ensure their clinical success. Researchers are continuing to develop and refine siRNA delivery systems and optimize the pharmacokinetics of siRNAs to address these challenges and advance siRNA-based therapies to clinical practice.

Clinical Progress of siRNA-Based Cancer Therapeutics

siRNA-based cancer therapeutics have shown great promise in preclinical studies, but their translation to clinical practice has been challenging. Despite these challenges, several siRNA-based cancer therapeutics have advanced to clinical trials [21]. Several siRNA-based therapies are currently being tested in humans for a range of cancer types, including ovarian, pancreatic, and liver cancer [21]. Patisiran can be used for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR), a rare genetic condition that affects the heart and nervous system, patisiran is a siRNA-based therapy. In clinical trials, the drug patisiran—which inhibits the transthyretin gene—promisingly improved patient quality of life and nerve function [22]. A siRNA-based therapy called inclisiran is used to treat hypercholesterolemia. PCSK9, a protein that controls blood levels of LDL cholesterol, is the target of Inclisiran. Clinical trials on Inclisiran have yielded positive outcomes, with notable drops in LDL cholesterol levels [23].

A siRNA-based therapy called ALN-TTRsc02 is being developed to treat ATTR amyloidosis. In clinical studies, the transthyretin gene-targeting drug ALN-TTRsc02 demonstrated encouraging outcomes with notable improvements in patient quality of life and nerve function [24]. QPI-1002 is used to avoid acute kidney injury, QPI-1002 is a siRNA-based therapy. In clinical studies, the p53 gene-targeting drug QPI-1002 had encouraging outcomes, significantly lowering the risk of acute renal damage in patients having heart surgery [25]. Although siRNA-based cancer treatments are currently in the early phases of clinical research, they have the potential to completely change the way cancer is treated. It is hoped that siRNA-based cancer treatments would advance and eventually become a standard component of cancer treatment with continued research and clinical studies [5].

siRNA-Based Therapies For Cancer Treatment. The potential of siRNA-based therapies for cancer treatment is significant, and these therapies hold great promise for improving the effectiveness of cancer treatment. Targeted gene silencing is a very specific and exact siRNA-based therapeutics can be created to target particular genes that contribute to the development of cancer. This method of targeted gene silencing may help to lessen the toxicity and side effects of conventional cancer therapies like chemotherapy [26]. Potentially synergistic with other therapies where siRNA-based cancer therapies may be used in conjunction with other cancer therapies, such as chemotherapy or immunotherapy, to increase the efficacy of both. For example, siRNA-based therapeutics could be used to target genes that give resistance to chemotherapy, thus enhancing the efficacy of the chemotherapy [27].

siRNA-based therapies can be designed to target a wide range of genes that play a role in cancer progression, including oncogenes, tumor genes, and genes involved in angiogenesis and metastasis. siRNA-based therapies can be customized for individual patients based on their genetic profile , which could potentially lead to more effective and personalized cancer treatment. siRNA-based therapies can be customized for individual patients based on their genetic profile, which could potentially lead to more effective and personalized cancer treatment [28]. siRNA-based therapies can be customized for individual patients based on their genetic profile, which could potentially lead to more effective and personalized cancer treatment [27]. siRNA-based therapies are highly specific, which means that they have the potential to be less toxic than traditional cancer treatments, which can have significant side effects [5].

Despite these potential benefits, there are still several challenges associated with siRNA-based therapies, as discussed earlier. The delivery of siRNAs to target cells is one of the major challenges associated with siRNA-based therapies. Additionally, the high cost of manufacturing and the potential for off-target effects are also significant challenges that need to be addressed. Overall, siRNA-based therapies have the potential to significantly improve cancer treatment, but further research and development are needed to optimize their efficacy and safety. With ongoing research and clinical trials, it is hoped that siRNA-based therapies will continue to advance and eventually become a routine part of cancer treatment.

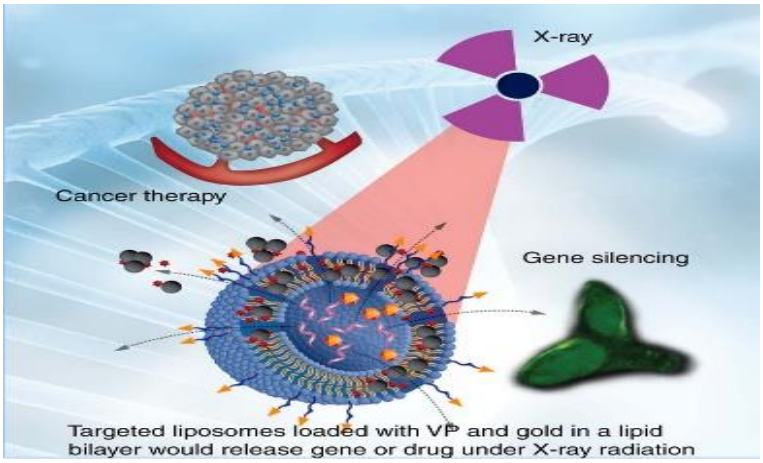

Fig No.3: Targeted gene silencing [29]

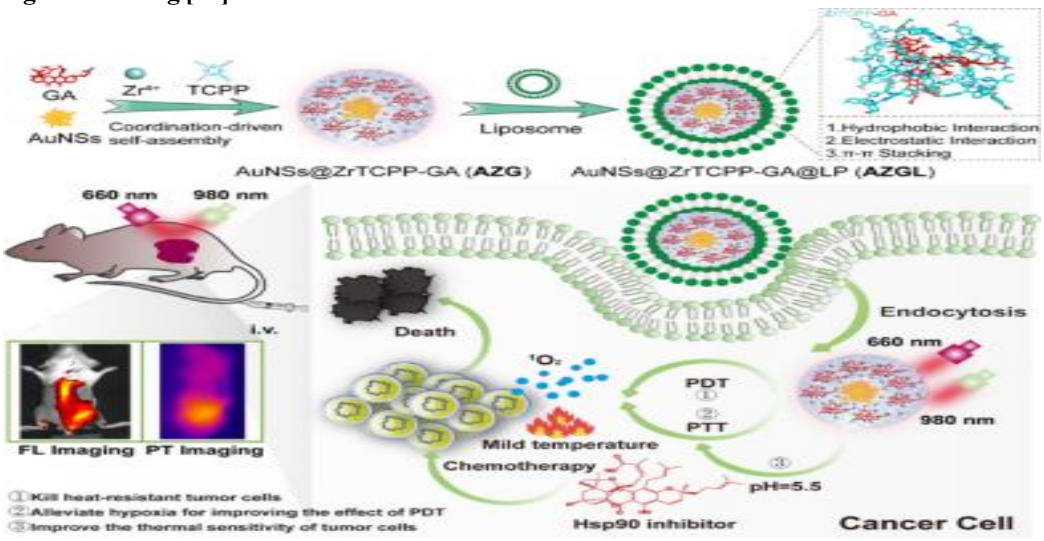

Fig No.4: Synergistic chemotherapy towards breast cancer [30]

Future Directions In the Field of Sirna-Mediated Silencing of Oncogenes for Cancer Therapy

The field of siRNA-mediated oncogene silencing for cancer therapy is quickly developing, and it is moving in fascinating directions. Combining siRNA-based therapies with other cancer treatments, such as chemotherapy or immunotherapy, is one of the most promising areas of research. It might be possible to improve therapeutic outcomes by combining siRNA-based medicines with other cancer medications [31]. A key area of research focuses on delivering siRNAs to cancer cells in certain tissues. To deliver siRNAs to cancer cells in certain organs while limiting toxicity and off-target effects, researchers are creating innovative delivery mechanisms [32]. siRNA-based therapies can be customized for individual patients based on their genetic profiles. Developing methods to identify patient-specific targets and designing siRNAs that specifically target these genes is an area of active research [33].

Combating drug resistance is one of the main obstacles in the fight against cancer. To increase the efficiency of chemotherapy and other cancer treatments, researchers are investigating the potential of siRNA-based therapeutics to target genes that are involved in drug resistance [34]. The development of innovative delivery technologies that might increase the effectiveness of siRNA distribution is a key area of scientific interest. To improve the transport of siRNAs to target cells, researchers are experimenting with the use of nanoparticles, liposomes, and other technologies [35]. Further clinical trials are required to assess the security and effectiveness of siRNA-based treatments for the treatment of cancer. To maximize the clinical translation of siRNA-based therapeutics, ongoing research, and development are required [36]. Overall, the field of siRNA-mediated silencing of oncogenes for cancer therapy is rapidly advancing, and there is great potential for these therapies to significantly improve cancer treatment. With continued research and development, it is hoped that siRNA-based therapies eventually become integral to cancer treatment.

Advantages of siRNA-Based Therapies for Cancer Treatment

Very targeted and precise siRNA-based therapeutics can be created to target particular genes that contribute to the development of cancer [2]. SiRNA-based therapies have the potential to be utilized in conjunction with other cancer treatments like chemotherapy or immunotherapy to increase the efficacy of both [37]. siRNA-based cancer therapies can be created to target a multitude of genes, including oncogenes,

tumor suppressors, and genes involved in angiogenesis and metastasis, that are implicated in the development of cancer [38]. siRNA-based therapies have the potential to advance personalized medicine since they can be tailored for specific patients based on their genetic profiles, which may result in more efficient and specialized cancer treatment [39]. siRNA-based therapies are highly specific, which means that they have the potential to be less toxic than traditional cancer treatments, which can have significant side effects [40].

Limitations of Sirna-Based Therapies for Cancer Treatment Include

siRNAs are substantial, negatively charged molecules that are difficult to get through cell membranes. The creation of effective and secure siRNA delivery methods is a difficult task [41]. Possibility for harmful off-target effects: siRNA-mediated gene silencing may have unintended consequences on genes that are not intended targets [42]. siRNA-based medicines still have a high production cost, and patients have less access to them [43]. siRNAs have a short bloodstream half-life; regular dosing may be required [44]. Only a small number of siRNA-based cancer medicines have moved to clinical trials, and none have received approval for use in humans despite extensive preclinical research [4]. Overall, while siRNA-based therapies hold great potential for improving cancer treatment, several challenges still need to be addressed before they become widely used in clinical settings. Ongoing research and development are necessary to optimize the efficacy, safety, and delivery of siRNA-based therapies.

CONCLUSION

siRNA-mediated cancer therapy has great potential for highly specific and effective treatment. However, efficient and safe delivery systems need to be developed, and more clinical trials are required for the evaluation of safety and efficacy. Researchers are working on developing new delivery systems, personalized medicine approaches, and combination therapies to overcome these challenges. Continued development of siRNA-based therapies could revolutionize cancer treatment, providing patients with targeted and effective options.

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