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Hybrid Nanoparticles Advance in siRNA Therapeutics

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Abstract

Engineering organic-inorganic nanoparticles play the greatest advantages in regulating efficacy and safety when targeted delivery of the small interference RNA (siRNA). This opinion summarizes the current achievements and looks to the future in this area.

Keywords: siRNA therapeutics; Hybrid nanoparticles; Delivery; Efficacy; Safety

Introduction

Comparing with the traditional treatment modalities, small interference RNA (siRNA) has immense potential for the treatment of various human diseases including cancer, since Fire and co-workers discovered the siRNA in 1998 [1]. Despite the great versatility of RNA interference (RNAi) technology which could down-regulate any protein in targeted cells and tissues, many physiological and biological obstacles still stand in the way of successful, safety and efficient delivery in application for clinical. The major challenge indeed for RNAi-based therapy is the development of delivery system [2]. Up to now, a great number of systems were reported for delivery siRNA including the non-virus-based platforms [3]. According resurgence in clinical trials using RNAi occurred in 2012, more than 20 RNAi-based therapeutic cases are currently in clinical trials, and several of these are Phase III trials [4].

These encourage us to indicate the advantages of such platforms, leading to pave the way for the next generation of the siRNA therapeutics. Particularly, an excited news released from the U.S. Food and Drug Administration (FDA) has approved the first siRNA therapeutics for the treatment of peripheral never disease (polyneuropathy) in the 20th anniversary of siRNA Discovery. This great breakthrough encourages the scientist and industries would be more enthusiastic to develop and design functional vectors for siRNA therapies to fight the human diseases. Here, we summarize the advantages of hybrid nanoparticles including metal/non-metal cores further modification with the organic shells. Additionally, some typical examples are briefly illustrated here to provide translational strategies for the siRNA therapeutics in the near furfure.

Hybrid Nanoparticles in siRNA Therapeutics

Non-viral siRNA delivery hybrid nanoparticles have shown promise and have travelled to clinical trial applications. According with the understanding of characterization for the cell types and targeted tissues to rationally design the efficient vectors for siRNA therapeutics. Importantly, these functional systems have the advantages, such as low/non-toxicity, easy fabrication, biodegradation, biocompatibility, non-immunogenicity, low-price and high efficacy comparing with the commercial agents [5]. Gold and Quantum dots are the typically metal-based nanoparticles for the siRNA delivery [6-7]. Nanoparticles with an organic shell embedding a gold core are used for example in highly efficient, stable, organic light emitting diodes and organic photovoltaics [8]. For this application the dual purpose of the nanoparticle is used: gold core offers a plasmatic effect while a mono-dispersed polystyrene shell gives stability and solvent resistance [9].

An example of photothermal therapy is given by proteinases i.e. biological nanoparticles with a gold core and an organic shell engineered to present specified peptides or proteins [10]. Since biological nanoparticles are synthesized inside living cells, they present a much lower toxicity compared to synthetic nanoparticles when use these gold nanoparticles as siRNA delivery systems. Quantum dots possess particular photochemical properties. For instance, it is possible to use selective fluorescent to tag proteins as is traditionally done in classical immunocytochemistry. In addition, quantum dots present minimal photobleaching and a much higher signal to noise ratio compared to traditional methods [11]. They possess

a broad absorption spectrum while maintaining a very narrow emission spectra, allowing multiplexing of many quantum dots of different colors in the same sample. This is unique and cannot be achieved using traditional fluorophores. These nanoparticles could be used in theragnostic siRNA platforms.

The other serial of the hybrid Nano systems is non-metal-based core with further functional organic shells. Two classical materials like silica/silicon or carbon-based nanoparticles widely used for siRNA delivery in vitro and in vivo [12,13]. Precise nanopore formation and ease of surface modifications are the main factors that brought interest silicon and silica nanoparticles to light. Silica nanoparticles have intrinsic biocompatibility, biodegradability and are efficiently bio-eliminated in vivo. However, metabolic changes and increased toxicity was observed especially in vivo due to active silanol groups used for surface modifications [14]. Some of the modifications applied to silica nanoparticles involve the synthesis of a cationic polymer layer or addition of quaternized dendrimers to the surface to permit electrostatic loading of siRNA, PEG (a protective polymer) addition to protect nanoparticles and to improve cellular uptake and delivery of MSNPs-siRNA conjugates [15,16].

Carbon nanotubes possess interesting physical and chemical properties that allow to easily cross the plasma membrane and translocate into the cytoplasm of cells. This property is due to their particular needle shape that exploits the cell's endocytosis-independent mechanism without inducing cell death [17]. It has been shown successful delivery of siRNA using Carbon Nanotubes by functionalizing the nanotubes with functional groups. Using this functionalization siRNA was expelled from the sidewalls of the nanotube to silence telomerase reverse transcriptase expression inducing tumor growth suppression [18]. It has also been shown that amino- functionalized multiwalled carbon nanotubes (f-MWNT) can effectively deliver in vivo an siRNA sequence while triggering cell apoptosis resulting in human lung xenograft eradication and prolonged survival [19]. These nanotube-based siRNA transfer vectors have shown minimal cytotoxicity and effective delivery and gene-silencing capabilities.

Conclusion and Outlook

A central message of this opinion is that inorganic-organic hybrid functional nanoparticles for the siRNA delivery. Under well understand the properties of such nanoparticles when they serve as siRNA delivery systems, which successively addressing each of these barriers, innovative design features can be rationally incorporated that will create a new generation of nanotherapeutics, realizing a paradigmatic shift in nanoparticle-based siRNA delivery.

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