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Perspective

Nanoparticles for cancer gene therapy: Recent advances, challenges, and strategies

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ABSTRACT

Compared to conventional treatments, gene therapy offers a variety of advantages for cancer treatment including high potency and specificity, low off-target toxicity, and delivery of multiple genes that concurrently target cancer tumorigenesis, recurrence, and drug resistance. In the past decades, gene therapy has undergone remarkable progress, and is now poised to become a first line therapy for cancer. Among various gene delivery systems, nanoparticles have attracted much attention because of their desirable characteristics including low toxicity profiles, well-controlled and high gene delivery efficiency, and multi-functionalities. This review provides an overview on gene therapeutics and gene delivery technologies, and highlight recent advances, challenges and insights into the design and the utility of nanoparticles in gene therapy for cancer treatment.

1. Introduction of cancer gene therapy

Despite the advances in treatment of a number of hematologic and solid tumors, many current cancer therapies fail to produce durable remissions in an appreciable fraction of patients [1]. For pancreatic, lung, liver, and brain tumors, five-year survival rates remain abysmally low. Even tumors that are highly responsive to initial treatment (*e.g.*, prostate and breast cancer) frequently display lethal treatment resistance upon recurrence [2]. In 2016, nearly 1,685,210 new cases of cancer are diagnosed in the U.S. and 595,690 people will die from the disease as projected by National Cancer Institute. The new cancer cases are expected to rise to 22 million worldwide within the next two decades [1]. While conventional treatments can produce lasting remissions, survival following aggressive surgical intervention followed by chemo- and radio- therapy is often accompanied by deleterious physical and/or cognitive consequences that degrade quality of life [3]. Although better controlled than in the past, the systemic toxicity of chemotherapy still results in acute and delayed nausea, mouth ulcerations, and mild cognitive impairments [4]. The long-term side effects can also increase the risk of developing other types of cancers. Similarly, radiation therapy can cause a host of additional side effects, including diarrhea, mucositis, skin toxicity, and xerostomia [5]. As a result, considerable research efforts have been devoted to the development of novel therapies that provide enhanced efficacy and minimize off- target toxicity.

Gene therapy holds unique promise in meeting these goals by offering a means of specific targeting of tumor genes that promote malignant behavior and treatment resistance [6]. The first gene therapy study approved by the U.S. Food and Drug Administration (FDA) in 1990 was for a four-year old girl having adenosine deaminase deficiency, an autosomal recessive metabolic disorder that causes severe combined immunodeficiency [7]. Since then the majority of gene therapy trials worldwide are aiming at the treatment of solid and hematological malignancies [8]. To date, successful trials have been reported in patients with chronic lymphocytic leukemia, acute lymphocytic leukemia, brain tumors, and others. However, only a few gene therapy products are available for clinical use such as ONYX-015 (Onyx Pharmaceuticals) and Gendicine (Shenzhen SiBiono GeneTech) for refractory head and neck cancer [9]. Although these successes indicate the utility of gene therapy in cancer treatment, their clinical application remains largely limited primarily due to the poor potency and pharmacokinetics, uncertain target specificity, and unacceptable levels of systemic toxicity of the delivery strategies [10]. The dearth of clinically approved cancer gene therapies indicates the significant need for development of new delivery approaches.

Nanotechnology has shown great potential to improve gene therapy by improving the pharmacokinetics of gene therapeu-

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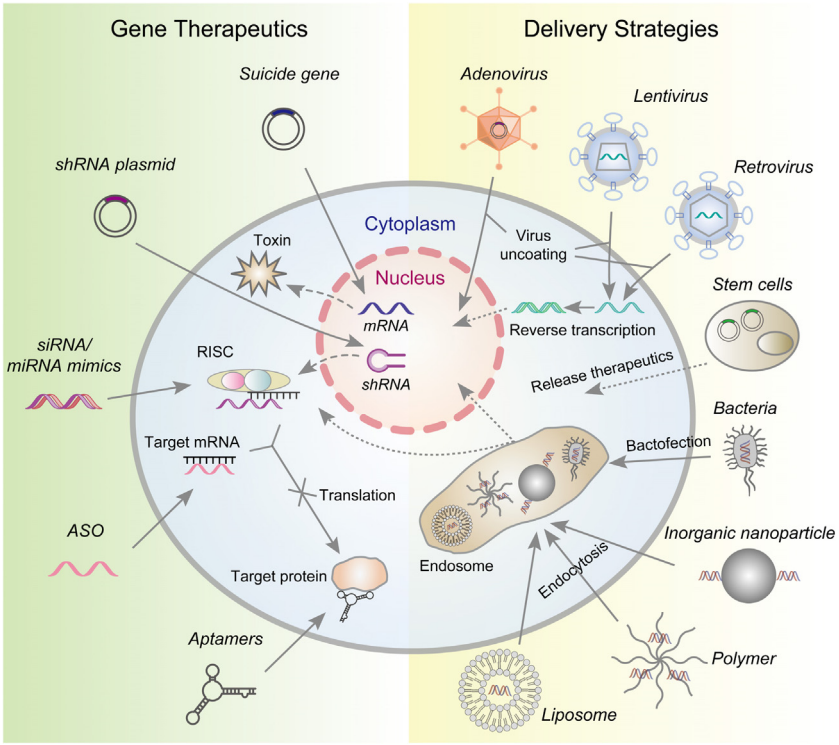

Fig. 1. Schematic representation of major types of gene therapeutics and delivery strategies for cancer gene therapy. Suicide gene is delivered into tumor cells as plasmid DNA, which expresses prodrug-converting enzymes or toxic proteins intracellularly. RNAi constructs can be introduced to tumor cells in forms of short hairpin RNA (shRNA) encoding plasmids DNA, small interfering RNA (siRNA), micro RNA (miRNA) mimics, or antisense oligonucleotide (ASO), which can be further processed by host endonucleases, or directly incorporate into RNA-induced silencing complex (RISC), or hybridize with the complementary mRNA to initiate gene suppression. Aptamers can directly bind to the target proteins to modulate downstream signaling. Gene therapeutics can be transduced into tumor cells using viral vectors. Adenovirus is capable of transducing its DNA into nucleus, which is further processed to cancer therapeutics. Lentivirus and retrovirus can integrate into host genome of tumor cells in a stable fashion after reverse transcription of the viral genome. Genetically modified stem cells can release their therapeutic payload locally after migrating to and incorporating within the tumor microenvironment. Other non-viral based delivery vectors, including bacteria and nano-constructs (inorganic nanoparticles, polymers, and liposomes) loaded with nucleic acids can enter tumor cells and release therapeutics via endocytosis.

tics, facilitating targeted delivery to tumors and across complex biological barriers, and offering multi-functionality when carrying multiple diagnostic/therapeutic payloads [11]. Nanoparticles, typically with sizes ranging from 1 to 1000 nm, have attracted significant interest because they can be made using a variety of materials, tailored to be multi-functional, and designed to offer high gene delivery efficiency in a tumor-targeted fashion [12–14]. Here, we provide an overview on gene therapeutics and delivery strategies, and discuss recent advances and challenges in preclinical and clinical uses of nanoparticles in gene delivery. We also present some strategies on improving their gene-delivery efficacy, tumor specificity, and their evaluation methods and large-scale production.

2. Approaches of cancer gene therapy

2.1. Suicide gene therapy

Suicide gene therapy is based on the use of transgenes that produce therapeutic proteins or conversion of a non-toxic compound into a lethal drug after being introduced into tumor cells (Fig. 1). Among the suicide systems that have been reported, herpes simplex virus type-1 thymidine kinase with ganciclovir (HSV-tk/GCV), cytosine deaminase (CD), BCL-2-like protein 4 (BAX), and human tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL), are the most extensively studied because of their cytotoxicity in tumor cells.

HSV-tk/GCV is one of the most thoroughly studied suicide gene therapy systems. The HSV-tk gene can produce viral thymidine kinase that metabolizes the non-toxic prodrug, GCV, to ganciclovir monophosphate and further convert into ganciclovir triphosphate by host kinases. The ganciclovir triphosphate inhibits DNA polymerization, leading to tumor cell apoptosis. This approach has shown promising preclinical and clinical efficacy in a number of cancers [15–17]. Using a similar strategy, CD is used to catalyze the non-toxic prodrug 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU) that is subsequently converted by endogenous enzymes into potent pyrimidine antimetabolites (5-FdUMP, 5-FdUTP, 5-FUTP) that induce apoptosis. The efficacy of the CD/5-FC system has been demonstrated in gliomas, nerve sheath tumor, and breast cancer [18–20]. BAX is the first identified pro-apoptotic member of the BCL-2 protein family. It relays pro-apoptotic signals within cells by activating the caspase pathway and inducing release of apoptotic molecules such as cytochrome c from the mitochondria to the cytosol. By this mechanism, over-expression of BAX induces cells to undergo apoptosis. It has been proved to induce apoptosis in a wide variety of cell lines including those derived from prostate, cervical, and brain cancers [21–23]. TRAIL is a TNF cytokine superfamily member, which forms a homotrimer that crosslinks death receptors on the cell surface leading to downstream signaling of apoptosis. It is an attractive anticancer agent due to its ability to induce apoptosis in various types of tumors without significant cytotoxicity towards normal cells [13,24].

Other suicide genes, such as truncated Bid [25], carboxyl esterase/Irinotecan [26], nitroreductase NfsB/5-(aziridin-1-Yl)-2 4-dinitrobenzamide [27], and carboxypeptidase G2/4-[(2-chloroethyl) (2-mesyloxyethyl) amino] benzoyl-L-glutamic acid [28] have also been investigated in different types of tumors. At