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Synergistic nanomedicine by combined gene and photothermal therapy☆

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ABSTRACT

To date, various nanomaterials with the ability for gene delivery or photothermal effect have been developed in the field of biomedicine. The therapeutic potential of these nanomaterials has raised considerable interests in their use in potential next-generation strategies for effective anticancer therapy. In particular, the advancement of novel nanomedicines utilizing both therapeutic strategies of gene delivery and photothermal effect has generated much optimism regarding the imminent development of effective and successful cancer treatments. In this review, we discuss current research progress with regard to combined gene and photothermal therapy. This review focuses on synergistic therapeutic systems combining gene regulation and photothermal ablation as well as logically designed nano-carriers aimed at enhancing the delivery efficiency of therapeutic genes using the photothermal effect. The examples detailed in this review provide insight to further our understanding of combinatorial gene and photothermal therapy, thus paving the way for the design of promising nanomedicines.

Contents

Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid; EPR, enhanced permeation and retention; PEI, polyethylenimine; PEG, polyethylenglycol; NIR, near infrared; AuNP, gold nanoparticle; AgNP, silver nanoparticle; CNT, carbon nanotube; TMDC, transition metal dichalcogenide; AuNC, gold nanocluster; pDNA, plasmid DNA; siRNA, small interfering RNA; Bcl-2, B-cell lymphoma 2; AuNR, gold nanorod; PKM2, pyruvate kinase 2; SWNT, single-walled carbon nanotube; hTERT, human telomerase reverse transcriptase; SNA, spherical nucleic acid; PLK1, polo-like kinase 1; PCI, photochemical internalization; GO, graphene oxide; Ce6, chlorine e6; Baf A1, bafilomycin A1; GSH, glutathione; ERBB2, epidermal growth factor 2.

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1. Introduction

The development of nanotechnology has enabled the development of diverse nanomaterials possessing distinct structural features and paves the path for the application of nanomedicines as promising next generation therapeutics [1–6]. By exploiting the distinct structural features of template nanomaterials, various molecules including therapeutic genes [7,8], biomolecules [9,10], and small molecular agents [11–13] have been loaded into diverse nanoparticles and are eventually delivered to the regions targeted for their unique functions. In particular, the use of therapeutic genes in nanomedicine, known as gene therapy, has attracted significant attention owing to its excellent potential for treating the cause of the disease genetically, thus constituting a promising resource for next generation therapeutics [14–16]. Moreover, the option of facile and versatile functionalization of nanomaterials has facilitated the straightforward integration of targeting capabilities [17–19]. That is, the functionalization of nanomaterials with specific ligands that can selectively interact with the surface of target cells enables active targeting of specific tissues. In addition to these characteristics, the enhanced permeation and retention (EPR) feature that enables nanomaterials to selectively penetrate leaky tumor blood vessels further supports the utilization of nanomaterials in the treatment of cancer [1,20–25]. Nanomaterials can provide additional functions aside from delivery such as bioimaging [26–30], photodynamic therapy [31–34], and photothermal therapy [35–39]. Photothermal therapy, in particular, has provided alternative routes for cancer therapy *via* spatio-temporally controlled photothermal effects independent of cell type, resulting in elevated specific therapeutic effects within the light-irradiated region without systemic toxicity.

Although gene therapy and photothermal therapy with nanomaterials have shown great potential for targeted therapy, both strategies have faced complex problems, such as low therapeutic efficiency and difficulty in the treatment of metastasis-related cancers [40–42]. Therefore, in this review, we discuss nanomedicines combining gene and photothermal therapy aimed at maximizing therapeutic effects by utilizing the advantages of both methods. Preceding this discussion, we provide a brief summary of gene and photothermal therapy as background for the subsequent sections.

1.1. Gene therapy

Gene therapy aims to treat diseases using therapeutic nucleic acids [43–45]. In contrast to chemotherapy, which consists of small-molecule drug-based therapy, gene therapy attempts to treat the cause of the disease by altering the expression of dysregulated genes rather than simply alleviating disease symptoms. Although gene therapy has attracted much attention as a potential next generation therapeutic method, its clinical applications have been limited because of the susceptibility and undesirable characteristics of nucleic acids [46–48]. Naked nucleic acids can be degraded by various biomolecules including nucleases in the blood stream. In addition, the direct delivery of genetic material such as plasmid DNA (pDNA) into cells is hindered by its large size (~μm). Furthermore, nucleic acids must escape from the endosome prior to the fusion with the lysosome that contains diverse enzymes that inactivate or degrade foreign molecules. Consequently, many gene delivery systems, including viral vectors and non-viral carriers, have been developed [49–53]. Viral vectors generally enable the facile integration of therapeutic genes into host cells with long-term expression and high transfection efficacy [54–61]. However, critical concerns regarding immune responses or mutagenesis of host cell genes have been raised. Therefore, several studies have focused on developing non-viral carriers for efficient and safe gene therapy [62–64].

Various non-viral gene delivery carriers have been reported including lipid-based, polymer-based, and inorganic nanoparticle-based systems [65–72]. The majority of systems are based on the electrostatic interaction between cationic materials and the negatively charged nucleic acids, which makes nano-sized complexes possible. Polyethylenimine (PEI) is one of the cationic materials most widely used in the gene delivery since it facilitates the formation of nano-sized complexes with genes, subsequently enhancing cellular uptake by interacting with the negatively charged cell membrane as well as endosomal escape *via* the proton sponge effect [73–76]. However, the use of cationic carriers has raised serious concerns such as phagocytic elimination, hemotoxicity, and low transfection efficiency. Therefore, several alternatives to the common non-viral gene delivery system have been suggested [77–86]. For example, polyethylene glycol (PEG) and stimuli-responsive materials have been commonly employed to improve stability, biocompatibility, and gene delivery efficacy [81–83]. In addition, several reports have proposed well-defined nanostructures as novel nanomedicines for the delivery of gene contents without the aid of cationic vehicles [84–86].

Moreover, many efforts are being made to increase the therapeutic effects of gene therapy *via* combination strategies. Inorganic nanoparticle-based gene delivery systems, in particular, have enabled additional or synergistic performance by means of their own multifunctional properties [87–89]. Almost importantly, the photothermal effects of various inorganic materials have attracted significant attention as a tool for synergistic anticancer therapy due to the photothermal ablation effect and ability for enhancing the delivery efficacy of cargo.

1.2. Photothermal therapy

Photothermal therapy refers to the use of photo-induced heat for the treatment of cancer. This therapeutic method has been considered as a promising anti-cancer treatment since it can be controlled spatio-temporally, thus avoiding damage to non-targeted regions [35–40,90–93]. As most photothermal-inducing materials are nanoscaled, photothermal therapy constitutes a category of nanomedicine.

Several fundamental prerequisites are required for effective photothermal therapy. First, template nanomaterials to be used for therapy should possess a photothermal effect that converts light energy into heat energy, *i.e.*, they should have high photothermal conversion efficiency. Second, the photothermal effects should occur in response to near infrared (NIR) light to ensure deep tissue penetration. Finally, the surface of the nanomaterials should be easily modified to enable the efficient photothermal therapy. Previous studies have demonstrated that these conditions can be met using nanoparticles decorated with targeting ligands that aid in selective internalization followed by laser irradiation to induce the photothermal effects within the target cell [90–93].

Many nanomaterials that fulfill the aforementioned criteria have been developed. Plasmonic nanoparticles such as gold nanoparticles (AuNPs) [94–96] and silver nanoparticles (AgNPs) [97], or sp^2 domain rich carbon nanoparticles such as carbon nanotubes (CNTs) [98–100] and graphene [100–102] are well known as photothermal converting nanoparticles. In addition, single layered transition metal dichalcogenides (TMDCs) [103–106] and melanin structures [107–109] have recently shown great potential for application as photothermal therapeutic agents.

Photothermal therapy has recently been applied with other therapeutic methodologies. Since the primary purpose of photothermal therapy is eradication of the target cells only at the light-subjected region, various treatment strategies like chemotherapy or gene therapy have been combined with photothermal ablation for the synergistic therapeutic effects [110]. In particular, many of recent studies have focused on the combination of photothermal therapy and chemotherapy. Hydrophobic interactions between drug and photothermal nanomaterials are commonly employed to load small-molecular anticancer drug such as doxorubicin or paclitaxel, allowing the chemotherapy and hyperthermia therapy simultaneously [111–114]. Although the combination of photothermal therapy and chemotherapy has shown the successful synergistic anticancer effects at preclinical level [110–114], clinical