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Far-Red Light-Mediated Programmable Anti-Cancer Gene Delivery in Cooperation with Photodynamic Therapy

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ABSTRACT: Effective anti-cancer therapy is hurdled by the complicated extracellular and intracellular barriers, and thus a smart gene vector that can enable programmable gene delivery is highly demanded. Photo-manipulation of gene delivery processes features spatial and temporal precision, while majority of current strategies utilizes short-wavelength UV/visible light with poor tissue penetration or high-power-density near-infrared (NIR) light that would cause undesired heat damage. Herein, a ROS-degradable polycation was designed and co-delivered with a photosensitizer (PS), thus realizing photo-programmable gene delivery using far-red light (661 nm) at low optical power density (down to 5 mW cm^{-2}). Thioketal-crosslinked polyethyleneimine (TK-PEI) was synthesized to condense p53 gene to form nanocomplexes (NCs), and hyaluronic acid (HA) modified with pheophytin a (Pha) was coated onto NCs to enhance their colloidal stability and enable cancer cell targeting. Short-time (8-min) light irradiation produced non-lethal amount of ROS to disrupt the endosomal membranes and facilitate p53 gene release via degradation of TK-PEI, which collectively enhanced p53 expression levels toward anti-cancer gene therapy. Long-time (30-min) light irradiation at the post-transfection state generated lethal amount of ROS, which cooperatively killed cancer cells to strengthen p53 gene therapy. To the best of our knowledge, this study represents the first example of a “one stone, three birds” approach to realize cooperative anti-cancer gene therapy using low-power-density, long-wavelength visible light as a single stimulus.

1. Introduction

Gene therapy that rectifies genetic defects and disorders is regarded as a promising modality for cancer treatment, and the success of anti-cancer gene delivery mainly relies on effective and safe delivery vectors.[1-6] Cationic polymers are widely used non-viral materials for gene delivery, because they can condense genes into nanocomplexes (NCs) to promote transfection.[7-9] However, controlling the efficiency and specificity of polycation-mediated gene delivery still remains as a considerable challenge against their full potential, mainly because of the complicated extracellular and intracellular barriers that pose multiple and conflicting requirements for material properties.[10-12] During effective transfection, the NCs need to efficiently enter cells, escape from endosomes, and then release genes in the cytoplasm.[13, 14] Polycations with high molecular weight (MW) normally feature better gene condensation efficiency and higher cellular internalization level, while at the meantime, lead to poor stability in serum, retarded intracellular gene release, and appreciable material toxicity at the post-transfection state.[15-17] Additionally, insufficient endosomal escape of gene cargoes stands as another