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Stimuli-responsive polymers and nanomaterials for gene delivery and imaging applications ☆

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ABSTRACT

Multiple extra- and intracellular obstacles, including low stability in blood, poor cellular uptake, and inefficient endosomal escape and disassembly in the cytoplasm, have to be overcome in order to deliver nucleic acids for gene therapy. This review introduces the recent advances in tackling the key challenges in achieving efficient, targeted, and safe nonviral gene delivery using various nucleic acid-containing nanomaterials that are designed to respond to various extra- and intracellular biological stimuli (e.g., pH, redox potential, and enzyme) as well as external artificial triggers (e.g., light and ultrasound). Gene delivery in combination with molecular imaging and targeting enables diagnostic assessment, treatment monitoring and quantification of efficiency, and confirmation of cure, thus fulfilling the great promise of efficient and personalized medicine. Nanomaterials platform for combined imaging and gene therapy, nanotheragnostics, using stimuli-responsive materials is also highlighted in this review. It is clear that developing novel multifunctional nonviral vectors, which transform their physico-chemical properties in response to various stimuli in a timely and spatially controlled manner, is highly desired to translate the promise of gene therapy for the clinical success.

Contents

Abbreviations: Au NPs, gold nanoparticles; azoTAB, azobenzene trimethylammonium bromide surfactant; CAT, chloramphenicol acetyltransferase; CDs, cyclodextrins; Chk- α, choline kinase-α; COX-2, cyclooxygenase-2; CPP, cell penetrating peptide; DODAC, dioleoyldimethylammonium chloride; DOPE, dioleoylphosphatidyl ethanolamine; DSPC, 1,2-distearoyl-*sn*-glycero-phosphatidylcholine; DSPE, 1,2-distearoyl-*sn*-glycero-3-phosphatidyl-ethanolamine; DTT, dithiothreitol; EAA, ethyl acrylic acid; EPPT, uMUC-1-specific peptide; GAGs, glycosaminoglycans; HBV, hepatitis B virus; HMA, hexyl methacrylate; i.a., intra-arterial; i.v., intravenous; LCST, lower critical solution temperature; MEND, multifunctional envelope-type nano device; MMP, matrix metalloproteinase; MPAP, Myr-Ala-$(Arg)_7$-Cys-$CONH_2$; MR, magnetic resonance; NIPAM, *N*-isopropylacryamide; NIR, near-infrared; NLS, nuclear localization signals; OCT, optical coherence tomography; ODNs, oliogodeoxynucleotides; PAMAM, polyamidoamine; P(Asp), poly(aspartic acid); PBAA, poly(butylacrylic acid); PDMAEMA, poly(2-(dimethyl amino)ethyl methacrylate); PDPA, poly(2-(diisopropylamino)ethyl methacrylate); PEAA, poly(ethylacrylic acid); PEG, polyethylene glycol; PEI, polyethylenimine (PEI); PET, positron emission tomography; PHPMA, poly[*N*-(2-hydroxypropyl)methacrylamide]; PIC, polyion complex; plk 1, polo-like kinase 1; PLL, poly-L-lysine; PMPC, poly(2-(methacryloyloxy)ethyl phosphorylcholine); POrn, poly(L-ornithine); PPAA, poly(propylacrylic acid); PSD, poly(methacryloyl sulfadimethoxine); RES, reticuloendothelial system; RGD, Arg-Gly-Asp peptide; RNAi, RNA interference; SDBS, sodium dodecylbenzenesulfonate; SDS, sodium dodecylsulfate; SPION, superparamagnetic iron oxide nanoparticle; TMAEMA, trimethyl aminoethyl methacrylate; US, ultrasound.

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1. Introduction

Achieving multiple key milestones in gene delivery, including high gene transfer efficiency, cell targeting specificity, facile regulation of gene expression, and acceptable vector safety is indispensible for realizing the promise of gene therapy [1]. The safety concerns (e.g., immunogenicity and mutagenesis) of engineered viruses, which were the first type of gene carriers to meet these challenges, have motivated the exploration for safer nonviral alternatives utilizing lipids and polymers [2,3]. Nonviral gene delivery systems offer molecular tunability of their physico-chemical properties, stability for long-term storage and reconstitution, and unlimited capacity of delivered gene sizes [4,5]. As a result, clinical attempts to treat inherited and acquired human diseases using nonviral vectors have been increasing [4].

Pharmacokinetic properties (e.g., distribution, circulation, and clearance) and gene transfer conditions (e.g., nucleic acid concentration, presence of serum, transfection time, and post-transfection time for gene expression) concomitantly affect the gene delivery efficiency of both viral and nonviral vectors [6,7]. Viruses have evolved to obtain optimized receptor-mediated internalization, efficient cytosolic release, directed and fast intracellular transport toward target compartments, and readily disassembly. In contrast, nonviral vectors must overcome multiple extracellular and intracellular barriers: 1) adhesion on the cell surface, 2) cellular entry (internalization), 3) escape from the endosome (cytosolic release), and 4) release of the nucleic acids into their intracellular target sites, mainly mimicking viruses [8,9]. According to the studies over last few decades, it is clear that a number of design factors for nonviral vectors, including size, surface charge and chemistry, chemical components, degradability, and, most notably, stimuli-responsiveness, comprehensively affect cellular uptake pathways and intracellular trafficking of nucleic acids, hence, determine gene delivery efficiency [10,11]. Nonviral vectors transforming their physico-chemical properties in response to various extra- and intracellular stimuli can achieve increased gene delivery efficiency by stimuli-triggered cellular uptake, endosomal escape and cytosolic release, and release of their payloads at the target intracellular locations (Fig. 1). Examples of the most widely utilized extra- and intracellular stimuli in nonviral gene delivery include pH, redox potential, temperature, and enzyme [12–14]. In addition to intrinsically occurring biological stimuli, artificial stimuli (e.g., light, ultrasound, and magnetic field) have also been employed to externally trigger key nonviral gene delivery pathways

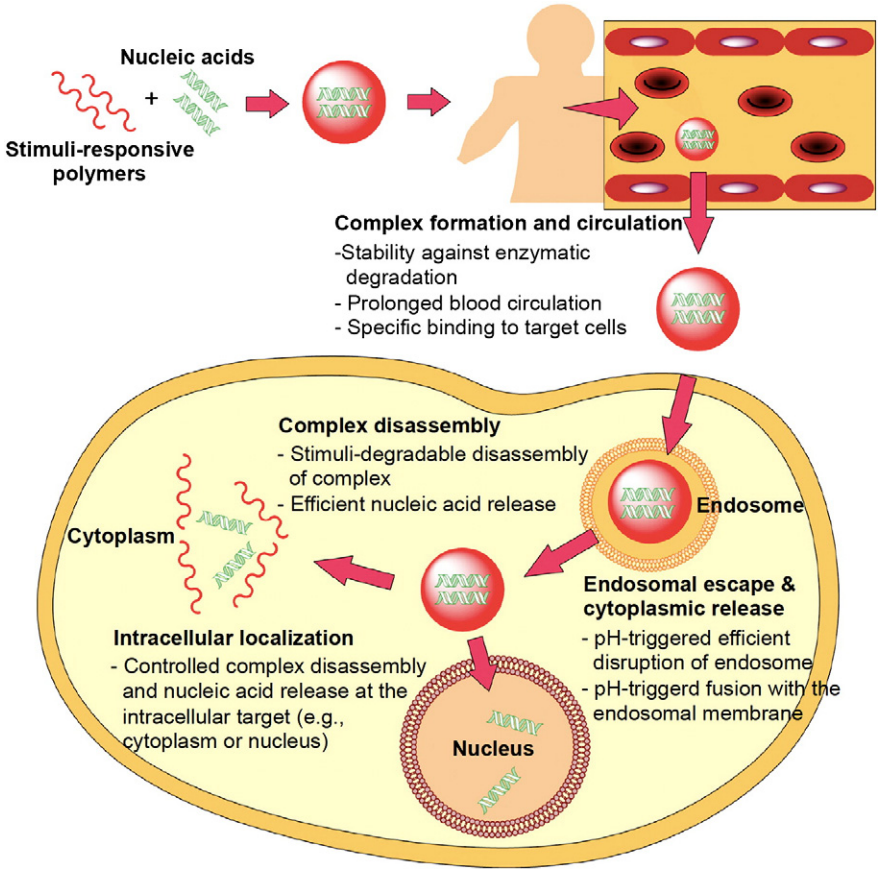

Fig. 1. Various stimuli-responsive approaches to overcoming multi-dimensional (extra- and intracellular) barriers in nonviral gene delivery.