Progress in Polymer Science 64 (2017) 154–181

Contents lists available at ScienceDirect

Progress in Polymer Science

journal homepage: www.elsevier.com/locate/ppolysci

Recent advances in the design, development, and targeting mechanisms of polymeric micelles for delivery of siRNA in cancer therapy

Muhammad Wahab Amjad[a,1], Prashant Kesharwani[b,c,1], Mohd Cairul Iqbal Mohd Amin[a,**], Arun K. Iyer[c,d,*]

[a] *Centre for Drug Delivery Research, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia*

[b] *Department of Pharmaceutical Technology, School of Pharmacy, The International Medical University, Jalan Jalil Perkasa 19, Kuala Lumpur 57000, Malaysia*

[c] *Use-inspired Biomaterials & Integrated Nano Delivery (U-BiND) Systems Laboratory, Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI 48201, USA*

[d] *Molecular Therapeutics Program, Barbara Ann Karmanos Cancer Institute, Wayne State University, School of Medicine, Detroit, MI 48201, USA*

Abbreviations: AFM, atomic force microscopy; AMD, age-related macular degeneration; ANG, Angiopep-2; apoB, apolipoprotein B; ATP, adenosine triphosphate; AURKA, Aurora A kinase; BMA, butylmethacrylate; BPEI, branched PEI; BSA, bovine serum albumin; CCP, charge-conversional polymer; Chol, cholesteryl; Chol-siRNA, cholesterol-modified siRNA; CMC, critical micelle concentration; cRGD, cyclo-Arg-Gly-Asp; DA, 1-octadecylamine; DMAEMA, dimethylaminoethyl methacrylate; DN, dimethoxy nitrobenzyl; DOX, doxorubicin; DP, *N*,*N*-dimethyldipropylenetriamine; DTX, docetaxel; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EPR, enhanced permeability and retention; FITC, fluorescein isothiocyanate; Gal-MNP, *N*-acetylgalactosamine functionalized mixed micellar nanoparticles; Gal-PEG, galactosylated PEG; HDP, low molecular hyaluronic acid-1-octadecylamine-spermine; HLP, low molecular hyaluronic acid-1-laurylamine-spermine; HOP, low molecular hyaluronic acid-1-octanamine-spermine; HSC, hepatic stellate cells; HUVEC, human umbilical vein endothelial cell; 2IT, 2-iminothiolane; IV, intravenous; LA, 1-laurylamine; LCST, lower critical solution temperature; LHRH, luteinizing hormone-releasing hormone; LMHA, low molecular weight hyaluronic acid; mAb-SA, streptavidin-conjugated monoclonal antibody mRNA messenger ribonucleic acid; MAL-PEG-NHS, alpha-maleimide-omega-*N*-hydroxysuccinimide ester polyethylene glycol; MePEG-*b*-PVL, methoxy PEG-*b*-poly(δ-valerolactone); M6P, mannose 6-phosphate; MPEG, methoxy poly(ethylene glycol)MPS mononuclear phagocyte system; mPEG-*b*-PCL-*b*-PPEEA, monomethoxy PEG-*b*-PCL-*b*-poly(2-aminoethyl ethylene phosphate); MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); NB, nanobubble; NGR, Asn-Gly-Arg; NIR, near-infrared; NSC-PLL-PA, *N*-succinyl chitosan-poly-L-lysine-palmitic acid; OA, 1-octanamine; ODN, oligonucleotide; PAA, polyacrylic acid; pDNA, plasmid deoxyribonucleic acid; PEO, poly(ethylene oxide); PEG, poly(ethylene glycol) (PEG); PPO, poly(propylene oxide); Pgp, P-glycoprotein; PAA, poly(L-amino acid); PCL, poly(ε-caprolactone); PDLLA, poly(D,L-lactide); PGA, poly(glycolide); PIC, polyion complex; PEI, polyethylenimine; PHDCA, PEGylated cyanoacrylate-*co*-*n*-hexadecyl cyanoacrylate; PLL, poly(L-lysine); PPA, polyphosphoramidate; PLys, poly(L-lysine); PAsp(DET), poly{*N*-[*N*-(2-aminoethyl)-2-aminoethyl]aspartamide}; PDMA-*b*-PDPA, poly(2-(dimethylamino)ethyl methacrylate)-*block*-poly(2-(diisopropylamino)ethyl methacrylate); PEC, polyelectrolyte complex; polyHPMA-*co*-PDSMA, poly[*N*-(2-hydroxypropyl)methacrylamide-*co*-*N*-(2-(pyridin-2-yldisulfanyl)ethyl)methacrylamide); PEI-C-AuNPs, polyethyleneimine (PEI)-coated gold nanoparticles; PLG*LAG, matrix metalloproteinase 2 (MMP-2)-degradable peptide; PAsp, polyaspartamide derivative; PPEEA, poly(2-aminoethyl ethylene phosphate); PEC*b*D, mPEG-PCL-*b*-PDMAEMA; PECgD, mPEG-PCL-*g*-PDMAEMA; PEC, polyelectrolyte complex; PBS, phosphate buffered saline; PLL, poly(L-leucine); Plk 1, polo-like kinase 1; PIPAAm, poly(*N* isopropylacrylamide); PSpMA, poly(spiropyran-methacrylate); PPyMA, poly(1-pyrenylmethyl methacrylate); PNBMA, poly(2-nitrobenzylmethyl methacrylate); PDT, photodynamic therapy; R-, arginine; R9, cell penetrating peptide; RAFT, reversible addition fragmentation chain transfer; RES, reticuloendothelial system; RHAMM, receptor for hyaluronan-mediated motility; RISC, RNA-induced silencing complex; RNAi, RNA interference; RVG, rabies virus glycoprotein; ScFvs, single chain-fragmented antibodies; siAC, siRNA-loaded anticeramidase; siDNMTs, DNA methyltransferases 1 and/or 3b siRNA; siRNA, small interfering ribonucleic acid; SP, spermine; SP, spiropyran; SS, disulphide linkage; TEP, tetraethylenepentamine; TNF-α, tumor necrosis factor alpha; TP, tetraethylenepentamine; TPP, sodium triphosphate; UCST, upper critical solution temperature; VEGF, vascular endothelial growth factor; V-, valine.

* Corresponding author at: Use-inspired Biomaterials & Integrated Nano Delivery (U-BiND) Systems Laboratory, Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI 48201, USA. Fax: +1 313 577 2033.

** Corresponding author. Fax: +603 2698 3271.

E-mail addresses: mciamin@ukm.edu.my (M.C.I. Mohd Amin), arun.iyer@wayne.edu (A.K. Iyer).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.progpolymsci.2016.09.008

ARTICLE INFO

Article history:
Received 1 November 2015
Received in revised form 13 August 2016
Accepted 9 September 2016
Available online 19 September 2016

Keywords:
Polymeric micelles
siRNA
Active targeting
Passive targeting
Multidrug resistance
Proton sponge effect

ABSTRACT

Small interfering RNA (siRNA) is a relatively novel nucleic acid-based therapy to treat diseases such as cancer. Nevertheless, substantial obstacles to its clinical applications have been reported, such as low cellular uptake, immunogenicity, off-target effects, and instability in physiological environments. The design of appropriate delivery vehicles capable of transporting siRNA to target cells has been pursued. Nanoparticles are extensively studied for the delivery of siRNA. Among the various nanocarriers, polymeric micelles have recently gained strong interest. Polymeric micelles of average nanometer size are straightforward to design and modify. Hydrophilic groups incorporated in the polymeric micelles can extend *in vivo* half-life of siRNA to ensure adequate accumulation in tumors, be exchanged for cations that electrostatically interact with siRNA, and be coupled to various ligands for cell-specific targeting. The polymeric micelle core provides stability and serves as a loading dock for drugs. In this review, the different types of polymers used, the design and characterization of polymeric micelles for siRNA delivery, and the established polymeric micelle targeting mechanisms are discussed.

Contents

1. Introduction

The mechanism of RNA interference (RNAi) was discovered in plants, while the mechanism of gene silencing was later found in *Caenorhabditis elegans*. Gene expression may be inhibited by small interfering RNA (siRNA) *via* the well-controlled enzyme-mediated gene silencing mechanism [1]. RNA–protein interactions are categorized into four main phases: association of the RNA-induced silencing complex (RISC) and siRNA, stimulation of RISC, and recognition and cleavage of the target gene. Intracellularly, siRNA is integrated into the RISC, which separates the RNA duplex strands and removes the sense strand, while activated RISC uses the antisense strand to guide the cleavage of messenger RNA (mRNA) [2,3]. The mRNA cleavage of RNAi is mediated by an endonuclease, Argonaute 2, within the RISC [4,5].

siRNA blocks the expression of target genes in numerous cells. Apart from drug development and biological research, siRNA possesses remarkable therapeutic properties that may be applied to the treatment of, for example, macular degeneration and cancer by inhibiting the overexpression of angiogenic growth factors or oncogenes. The Nobel Prize (medicine) in 2006 reiterated the commitment of global research to RNAi [6].

Ten years after the discovery of RNAi, some therapeutic siRNAs are now undergoing clinical trials [7,8], the majority of which involve local administration of siRNA *via* the intranasal or intravitreal route, for example Refs. [9,10]. The first therapeutic siRNA, bevasiranib, designed to treat wet neovascular age-related macular degeneration (AMD) by targeting vascular endothelial growth factor (VEGF) [11,12], has reached phase III of clinical testing. Another VEGF-targeting therapeutic siRNA, AGN-745, was the sec-