13IL8

22

Amphipathic peptides-mediated delivery of siRNA for antiviral therapy against influenza

W Liang[1], LLM Poon[2,3], AJ Mason[4] & Jenny KW Lam[1,2]

[1]Department of Pharmacology and Pharmacy, The University of Hong Kong
[2]Centre of Influenza Research, The University of Hong Kong
[3]School of Public Health, The University of Hong Kong
[4]Insitute of Pharmaceutical Science, King's College London, United Kingdom

RNA interference (RNAi) technology has emerged as a novel and potentially effective therapy against respiratory viruses. RNAi is a naturally occurring process that inhibits specific gene expression in a post-transcriptional manner, mediated by small interfering RNA (siRNA). Properly designed siRNAs have already been shown to function as potent inhibitors of viral replication. By delivering exogenous siRNAs to mammalian cells, RNAi could be induced to degrade the viral mRNAs, leading to clearance of infection.

The design of an effective antiviral siRNA sequence is laborious but is not the limiting step. Influenza viral replication could be inhibited by targeting the viral genes encoding nucleocapsid protein (NP) or components of RNA transcriptase (PA and PB1) of the viruses. Delivery is indeed the major bottleneck to siRNA therapy. siRNAs are negatively charged hydrophilic macromolecules which are susceptible to nuclease degradation with poor membrane permeability. Multifunctional delivery vectors are therefore required to serve a number of purposes (i) protect siRNA from enzymatic degradation; (ii) facilitate cellular uptake at target cells; (iii) release siRNA at the site of action in cytoplasm and initiate RNAi mechanism.

Recently our group is investigating a series of novel pH responsive amphipathic peptides containing ionizable histidine (LAH series) or diaminopropionic acid side chains (LADap series) for siRNA delivery. These peptides can form non-covalent complexes with siRNA, effectively protect siRNA from nuclease degradation, facilitate cellular uptake via endocytosis and respond to endosomal acidification by dissociating from the complexes and destabilizing endosomal membranes, resulting in the release of siRNA into cytosol. The pKa of the peptides can be manipulated to tune their functional pH response in order to afford optimal siRNA transfer with negligible toxicity and they are highly effective at delivering siRNA and mediating specific gene silencing on a wide variety of cells even in more challenging environments such as in the presence of lung surfactants. Significant reduction of viral titers (up to 8,000-fold reduction) was observed in vitro after delivering siRNA targeting influenza viral nucleocapsid protein of H1N1 (PR8) virus to the infected mammalian cells using LAH or LADap peptides. The results suggests that the amphipathic peptides are promising delivery vectors against viral infection. Further work will be focused on the formulation of the peptides/siRNA complexes into dosage form and explore its therapeutic potential in animal model.