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Delivering nucleic acids to CD44-expressing cancer cells: From hyaluronic acid to aptamer-decorated nanocarriers

Downregulation of genes involved in cancer progression using therapeutic nucleic acids remains a promising alternative to conventional chemotherapy. This approach however necessitates an appropriate delivery system allowing not only intracellular delivery but also the targeting of cells involved in cancer progression. To this end, CD44 has been characterized a major biomarker, being overexpressed by many tumors including lung, breast, colon, pancreatic, head, and neck cancers.

Our group has developed over the past years hyaluronic acid (HA)-decorated nanocarriers able to deliver small interfering RNA (siRNA) and DNA plasmids [1] to CD44-expressing lung cancer cells. In particular, HA-decorated lipoplexes exhibited a lamellar structure able to deliver nucleic acids *in vitro* to the CD44-expressing A549 lung cancer cells through CD44-mediated endocytosis, and inhibited the expression of the luciferase (luc) reporter gene [2]. *In vivo*, these lipoplexes significantly inhibited luc after intravenous administration to mice bearing an A459-based lung cancer [3].

In order to increase the specificity of this delivery, we investigated the use of aptamers to functionalize the surface of nanocarriers. Aptamers are nucleic acid-based ligands that can bind their targets with a high affinity and specificity, with virtually no toxicity and immunogenicity. A $2'$-F-pyrimidine RNA aptamer was successfully selected against the CD44 protein by the SELEX method and named Apt1 [4]. Apt1 was conjugated to the surface of liposomes by a thiol-maleimide coupling. Such liposomes exhibited a strong affinity to various CD44-expressing cells, even higher than Apt1 alone [5]. SiRNA-loaded, Apt1-decorated aptamers successfully inhibited luc in the CD44-expressing breast cancer MDA-MB-231 cells *in vitro*. After intravenous administration to mice bearing an orthotopic model of MDA-MB-231-based breast cancer, Apt1-targeted liposomes successfully inhibited luc in the tumor cells, in a specific and targeted manner [6]. These results show the potential of aptamers to selectively target oncogenes to CD44-expressing cancer cells *in vivo*.

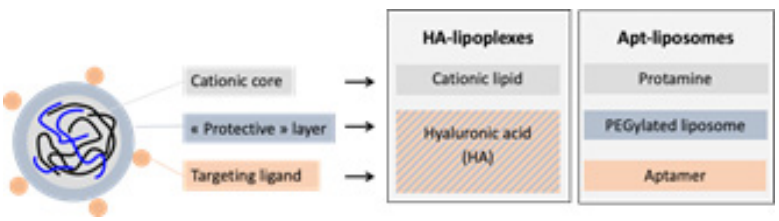

Figure: General architecture of CD44-targeting nanocarriers for anticancer gene delivery developed in our group: (i) HA-decorated, siRNA-loaded lipoplexes and (ii) aptamer-decorated, siRNA-loaded, PEGylated liposomes.

Recent Publications

1. Wojcicki, A. et al. (2012). Hyaluronic acid-bearing lipoplexes: Physico-chemical characterization and *in vitro* targeting of the CD44 receptor. J Control Release, 162(3), 545–552.
2. Nascimento, TL. et al. (2015). Supramolecular Organization and siRNA Binding of Hyaluronic Acid-Coated Lipoplexes for Targeted Delivery to the CD44 Receptor. Langmuir, 31(41):11186-94.
3. Nascimento, TL. et al. (2016). Hyaluronic acid-conjugated lipoplexes for targeted delivery of siRNA in a murine metastatic lung cancer model. Int J Pharm, 514(1), 103-111.
4. Alshaer, W. et al. (2018). Aptamer-guided nanomedicines for anticancer drug delivery. Adv Drug Deliv Rev, 134, 122-137.
5. Alshaer, W., et al. (2015). Functionalizing Liposomes with anti-CD44 Aptamer for Selective Targeting of Cancer Cells. Bioconjugate Chemistry, 26(7), 1307–1313.
6. Alshaer, W., et al. (2018). Aptamer-guided siRNA-loaded nanomedicines for systemic gene silencing in CD-44 expressing murine triple-negative breast cancer model. J Control Release, 271, 98-106.

Biography

Hervé Hillaireau is Associate Professor of Pharmaceutical Technology at the School of Pharmacy of Université Paris-Sud since 2009. His research at Institut Galien Paris-Sud relates to the design and the toxicological evaluation of biodegradable nanoparticles as drug nanocarriers, with a focus on: (i) nanocarrier design for nucleoside/nucleotide analogues and nucleic acids delivery in anticancer and antiviral therapies; (ii) nanocarrier surface functionalization for molecular targeting; (iii) toxicological evaluation of biodegradable nanoparticles. He has been supervising or co-supervising 10 PhD theses. He is the author of 4 book chapters and 38 peer-reviewed international research articles, and has recently co-edited a special issue of Advanced Drug Delivery Reviews on Aptamers in therapeutics and drug delivery.

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