Séminaire de l'axe Formulation et analyse du médicament

Designing Lipopolymers to Deliver Gene-Based Medicines

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à l'invitation du professeur Davide Brambilla

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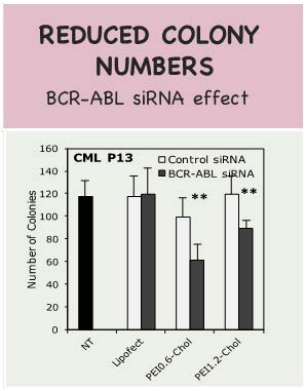
Treating human diseases with gene-based agents is providing exciting opportunities to fulfill unmet medical needs. It is becoming possible to augment missing or defective genes using various expression systems to introduce the correct copy of the protein to patients. It is also becoming possible to delete specific gene products that are the cause of abnormal physiology. Gene medicines are implemented by synthetic nucleic acids that can interface with the flow of genetic information inside cells. The unique features of nucleic acids, however, make them difficult to deliver in a clinical setting. While viral vectors are being explored in gene therapy trials, the unpredictable safety and immune responses are worrying the clinicians.

As an alternative, synthetic biomaterials are being designed to undertake effective delivery of nucleic acids in a safe manner. One such class of biomaterials, namely lipid-incorporating cationic polymers (lipopolymers), are extensively explored in Uludag Lab. The polymers can effectively assemble nucleic acids (both RNA and DNA) into nano-sized particles suitable for cellular uptake. Incorporating lipids in cationic polymers reduced the binding capability to nucleic acids, which needs to be compensated during nanoparticle assembly, but the lipids enhanced the delivery efficiency of nucleic acids into cells significantly. An inverse correlation between the ability of nanoparticles to dissociate and delivery into cells was noted, indicating the need for stable assembly for membrane crossing. We found the same amphiphilic materials to be functional for delivery of both siRNA and plasmid DNA into human cells.

It was possible to express therapeutic proteins, as well as silencing aberrant genes with lipopolymers and co-pDNA/ siRNA delivery. Delivery of siRNA into patient derived cells was also effectively implemented with the right choice of the lipopolymer. Our studies indicate a close relationship between the molecular details of lipid-substitution and physicochemical properties of nanoparticles, and ultimately their physiological performance in biological systems.

This presentation will emphasize the therapeutic potential and operational basis of lipophilic polymers in delivery of nucleic acids. We will focus on the delivery of siRNA to silence oncogenic genes in leukemic cells that cause uncontrolled proliferation of such blood borne cells [1-4]. We show that different lipopolymers had to be tailored for different types of leukemic cells and no universal carrier readily emerged to tackle the delivery to different cell types. While being effective in patient derived leukemic cells, the performance of the polymers was variable in different patient derived cells; some patient cells readily displayed enhanced uptake of designed nanoparticles, while other patient cells did not display any uptake. While targeting oncogenic transformers of cells with siRNA alone led to reduction in cell proliferation (Figure), it was possible to combine the siRNA therapy with clinical drugs to better control cellular proliferation. Our results are providing exciting possibilities for clinical use of gene medicines to combat deadly cancer in a more comprehensive manner.



References.
[1] Remant Bahadur et al. Cationic lipopolymers from cholesterol-substitution on low molecular weight polyethylenimines: selective siRNA carriers for chronic myeloid leukemia therapy. JBMR (2019) in press.
[2] Valencia-Serna et al. siRNA-mediated BCR-ABL silencing in primary chronic myeloid leukemia cells with lipopolymers. J. Controlled Release (2019) 310: 141-154.
[3] Remant Bahadur et al. BCR-Abl silencing by siRNA: a potent approach to sensitize chronic myeloid leukemia cells to TKI therapy. Stem Cells Develop (2019) 28: 734-744.
[4] Valencia-Serna et al. siRNA/Polymer nanoparticles to arrest growth of chronic myeloid leukemia cells in vitro and in vivo. European J. Pharmaceutics and Biopharmaceutics (2018) 130: 66-70.