Proceedings of the 5th International Conference on Nanotechnology: Fundamentals and Applications
Prague, Czech Republic, August 11-13, 2014
Paper No. 321

Targeted Drug Delivery to Microvascular Endothelial Cells: From Therapeutic Applications to an *In Vivo* Tool for Endothelial Cell Biology Studies

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Extended Abstract

Endothelial cells covering the walls of the microvasculature in the organs are main players in a large number of diseases. They engage in new blood vessel formation during solid tumor growth and in leukocyte recruitment and permeability dysfunction in acute and chronic inflammatory reactions. The cells exert a heterogenic phenotype both in quiescence and in response to disease initiation and continuation, which is depending on their location in the body. Their easy access for systemically administered nanotherapeutics combined with this heterogenic behavior make microvascular endothelium an attractive target for targeted drug delivery.

In our laboratory, we have employed these differences in behavior for immunoliposome-based targeted delivery of anti-inflammatory small chemical drugs. In *in vivo* inflammation models the nanotherapeutics exerted improved performance, consisting of less systemic side effects and pharmacological effects in the target vasculature only. A better understanding of the limited capacity of endothelial cells to metabolically handle the delivery systems led to the development of a new generation of liposomes. These so called SAINT-O-Somes more easily release their cargo in the endocytotic compartments inside the cells by virtue of their novel composition including the cationic lipid SAINT-C18. These SAINT-O-Somes were next applied to formulate small interfering RNA (siRNA), until now mainly used for *in vitro* application to silence dedicated target genes in cell culture. Besides a high encapsulation efficiency and improved intracellular siRNA delivery capacity, targeted SAINT-O-Somes containing an NFκB specific siRNA were able to downregulate NFκB gene expression in the target microvascular segments, upon systemic administration to mice suffering from an inflammatory insult. This was associated with a marked reduction in inflammatory activation of the endothelium and leukocyte recruitment.

This new generation of siRNA delivery devices has been designed to deliver and silence target genes in endothelial cells in specific microvascular segments in the body. They will now be further developed into a tool to study endothelial cell biology *in vivo*, as they enable gene knock down on demand in the microvascular segment of interest.