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Cover Story

Endothelial specific delivery of siRNA

The discovery of RNA interference (RNAi) a little more than a decade ago, and the subsequent introduction of short interfering RNA (siRNA) as a tool to specifically interfere with gene expression has enormously advanced our understanding of gene regulation and function. In addition, it paved the way for the development of a whole new class of, siRNA-based, therapeutics. The time-line from siRNA discovery and development to the translation of this technology into clinical trials is unprecedented. Some important hurdles, however, have to be overcome to have siRNAs meet their expectations and fulfill their potential as effective therapeutic agents in clinical applications. First of all, siRNAs, which are relatively large hydrophilic charged molecules, are rapidly cleared from the blood, degraded by serum RNases, and unable to enter the target cells easily. Thus, it is prerequisite to formulate siRNA into a suitable delivery system for improvement of the pharmacokinetic behavior of siRNA, reduced off-target effects and efficient uptake, and intracellular release in target cells.

About 5 years ago the group of Kamps and Molema developed a novel lipid based carrier referred to as SAINT-O-Somes because of the presence of the cationic lipid SAINT-C18 in the formulation [1]. SAINT-O-Somes have a pharmacokinetic profile that is comparable to that of long circulating PEGylated liposomes, and have been shown to perform better than conventional liposomes in terms of the siRNA loading capacity and intracellular release property. The latter feature is of utmost importance for delivery to cells, e.g., endothelial cells, which do not have the machinery to efficiently process a siRNA carrier. Endothelial cells, forming the inner lining of blood vessels, are able to internalize lipid based carriers but do not efficiently process them. The poor release of carrier content results in a limited pharmacological effect. Moreover, endothelial cells are actively engaged in inflammatory processes and angiogenesis, and play a pivotal role in the pathophysiology of widespread chronic diseases e.g., atherosclerosis, diabetes, sepsis and cancer. Thus, targeted pharmacological interference in endothelial cells is important, and siRNA can offer a relevant approach allowing for specific inhibition of endothelial activation in inflammation. Recent *in vitro* studies revealed that SAINT-O-Somes, which are targeted to adhesion molecules, delivered siRNA and effectively inhibited the expression of the target gene in endothelial cells [2].

The paper by Kowalski et al. in this issue demonstrates endothelial specific delivery of siRNAs by SAINT-O-Somes and subsequent down-regulation of inflammatory genes in activated endothelium in vivo [3]. To create specificity for inflamed endothelial cells, these SAINT-O-Somes were harnessed with antibodies against vascular cell adhesion protein 1 (VCAM-1). Mice of a simple inflammation model were challenged with TNFα, followed by intravenous administration of anti-VCAM-1 SAINT-O-Somes. These anti-VCAM-1 SAINT-O-Somes exerted long circulation times and targeted to VCAM-1 expressing endothelial cells in inflamed organs. No liver and kidney toxicities were observed in the SAINT-O-Some treated mice. Anti-VCAM-1 SAINT-O-Somes containing siRNA to knock down VE-cadherin mRNA were successfully delivered in inflamed renal microvasculature, as demonstrated by laser microdissection of different vascular beds prior to analysis of gene expression. Applying this strategy, the authors also demonstrated attenuation of endothelial inflammatory responses towards lipopolysaccharide in kidneys of diseased mice treated with anti-VCAM-1 SAINT-O-Somes containing NFκB p65 (RelA) specific siRNA. They conclude that this is the first demonstration of an endothelial specific lipid-based carrier that is capable of selectively delivering siRNAs into inflamed vascular segments in vivo and to interfere with disease associated endothelial activation.

There are a few issues and observations in this study that are of particular interest. First, the down-regulation of NFκB was not complete, but a ~50% down-regulation of pro-inflammatory genes was found, and this had an impact on one of the key processes in inflammation, namely the recruitment of leukocytes. Clearly, further studies in more clinically relevant animal models are necessary to prove the real impact of the siRNA delivery approaches presented. Second, targeting cells that are under-represented in mass of the tissue requires advanced approaches to address the difficulty in finding the intended target cells and exerting pharmacological effects in vivo. The difficulties in delivery of siRNA to target cells are not isolated from delivery of other drugs. The same difficulties exist for targeted delivery of anticancer agents to target tumors. Showing the efficacy of any drug delivery system using in vitro cell culture models and, in many cases, in small animal in vivo models has not been translated into clinical applications. It is time for the drug delivery scientists to focus on the weaknesses and limitations of the small animal models and try to understand the differences between humans and small animal models that prevent successful translation of the drug delivery technologies to clinical applications.

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