LS-BK SEMINAR

"Development of RNA therapeutics and lipid nanoparticle (LNP) formulation for in vivo delivery"

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- **Inquiry: Prof. Sung Key Jang(279-2298)/Seung-Woo Lee(279-2355)**
- **Abstract:**

In recent years, RNA therapeutics have received tremendous attention as a tool to regulate gene expression in patients. These approaches include the regulation of abnormal gene expression by short interfering RNA (siRNA) and messenger RNA (mRNA). There have been two US FDA approved siRNA therapeutics (Patisiran and Givosiran) for rare disease treatments. These drugs target the selective degradation of mRNA to reduce the expression of disease associated proteins in polyneuropathy and acute hepatic porphyria. In addition, synthetic mRNA can produce insufficient proteins (e.g. Factor IX, VEGF) in patients to treat various diseases such as hemophilia A and ischemic heart disease. To fully realize the potential of RNA therapeutics, an efficient in vivo delivery system is of the utmost importance. Ionizable lipid nanoparticles (LNPs) have been widely utilized for the systemic delivery of RNA therapeutics. LNPs are mainly composed of ionizable lipid or lipid like materials with helper lipid, cholesterol, and polyethylene glycol (PEG)-lipid. Although LNPs are particularly advantageous for in vivo delivery, systemic delivery of RNA therapeutics other than liver hepatocytes remains highly challenging. Ionizable lipid nanoparticles (LNPs) have been widely utilized for in vivo delivery of RNA therapeutics into the liver. However, a main challenge remains to develop LNP formulations for selective delivery of RNA into certain types of liver cells, such as hepatocytes and liver sinusoidal endothelial cells (LSECs). Here we report the engineered LNPs for the targeted delivery of RNA into hepatocytes and LSECs. The effects of particle size and polyethylene glycol (PEG)-lipid content in the LNPs were evaluated for the hepatocyte-specific delivery of mRNA by ApoE mediated cellular uptake through LDL receptors. Targeted delivery of RNA to LSECs was further investigated using active ligands. Incorporation of mannose allowed the selective delivery of RNA to LSECs, while minimizing the unwanted cellular uptake by hepatocytes. These results demonstrate that engineered LNPs have great potential for the cell type specific delivery of RNA into the liver and other tissues.