Construction of siRNA delivery system targeting to angiogenic vessels with peptide modified-liposomes

○Kentaro Hatanaka[1], Saori Matsushita[1], Atsushi Tsuruta[1], Tomohiro Asai[1], Tatsuhiro Ishida[2], Hiroshi Kiwada[2], Takehisa Dewa[3], Mamoru Nango[3] and Naoto Oku[1]
([1]Dep. of Med. Biochem., Grad. Sch. of Pharm. Sci., Univ. of Shizuoka, and [2]Dep. of Pharmacokin. and Biopharm., Inst. of Health Biosci., Univ. of Tokushima, and [3]Dep. of Mater. Sci. and Eng., Nagoya Inst. of Tech.)

Recently expectation has been growing regarding the role of nucleic acids as future therapeutic agents. Small interfering RNA (siRNA) in particular, which induces sequence-dependent gene silencing, has been widely studied. We previously developed liposomes modified with polycation as carriers of siRNA and succeeded in showing their potent gene knockdown efficiency. In addition, we identified a peptide that has an affinity towards angiogenic vessels which are involved in proliferation and metastasis of tumors. And then, we proposed antineovascular therapies that cause lethal damage to angiogenic vessels with peptide-modified liposomes encapsulating cytotoxic agents.

In the present study, we attempted to construct siRNA delivery system targeting to angiogenic vessels in a systemic administration. Synthetic siRNA was incorporated in polycation liposomes modified with polyethyleneglycol (PEG) and the functional peptide on their surface. After lipid composition and preparation method of liposomal siRNA were investigated in detail, specific knockdown efficacies of the liposomal siRNA were obtained *in vitro*. When the liposomal siRNA were injected into mice, it showed an improvement in stability in blood circulation compared with control carriers. Next, we focused on Argonaute2 (Ago2), a main constitution protein of RNA-induced silencing complex, as a therapeutic target molecule. We hypothesized that angiogenesis regulated with certain microRNAs would be disrupted by Ago2 knockdown. As a result, Ago2 knockdown using liposomal siRNA suppressed indispensable processes of angiogenesis such as endothelial cell proliferation and tube formation. In addition, we will present the result of our recent study that focused on the knockdown of mammalian target of rapamycin (mTOR) which is involved in angiogenesis and regulation of immunoresponse.