Application of positron-labeling to cholesterol-modified siRNA and non-invasive pharmacokinetic analysis by PET imaging

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Small interfering RNA (siRNA) is a short double-stranded nucleic acid molecule which induces sequence-dependent gene silencing. Gene therapy using siRNA is expected to be a novel treatment strategy. A delivery system bringing siRNA molecules to the targeted tissue is indispensable for establishing siRNA therapy. Many studies on the *in vivo* applications of siRNA using chemically-modified siRNA have been reported.

The pharmacokinetic study of siRNA is an important stage in the development of siRNAs for use as medicine. For this purpose, we have been established novel technique for labeling siRNA with the positron emitter, ^{18}F, in which double-stranded siRNA was labeled to gain conformational accuracy in examining the pharmacokinetics of siRNA. *N*-succinimidyl 4-[fluorine-18] fluorobenzoate ([^{18}F]SFB) was used as ^{18}F labeling reagent, and the real-time analysis of siRNA trafficking was performed using positron emission tomography (PET). In present study, this method was applied to a labeling of cholesterol modified-siRNA (chol-siRNA), which is one of the chemically modified-siRNA. To examine a behavior of chol-siRNA, they were injected to C57BL/6 mice by tail vein, and then PET scanning was performed for 1 h. The ^{18}F radioactivity of unmodified-siRNA was rapidly detected in bladder, as oppose to that of chol-siRNA accumulated in liver, and were observed retained in blood circulation on the basis of whole-body signal. Therefore, the ^{18}F transfer to bladder of chol-siRNA was slower than that of unmodified-siRNA. Our study provides precise pharmacokinetic information on developing chol-siRNA and gene delivery systems. Our results indicate that the PET imaging of chemically modified-siRNA provides important information for the development of siRNA medicines.

In conclusion, our labeling method was able to be applied to the analysis of various siRNA distributions. It is clarified that the alteration of behavior with chemical modification or not. Since, PET technology can be applied to human; this study might be useful for the development of siRNA medicines.