免疫回避型高分子による DNA アプタマー修飾の検討

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Study on DNA aptamer modifiers using immune-evading polymers (Graduate School of Engineering, The University of Tokyo[1]) CHO, Seojung[1], IKI, Haruka[1], NAGAI, Yukiko[1], SAITO, Yutaro[1], UEKI, Ryousuke[1], SANDO, Shinsuke[1]

DNA aptamers, single-stranded DNAs with defined structure, bind to their specific biomolecular targets with high affinity, and therefore are considered to be promising therapeutic agents. However, their clinical applications have been hindered by their limitation of short half-lives *in vivo*, mostly owing to their small sizes of 5 to 15 kDa below the molecular weight cutoff of glomerular filtration. Modification with poly(ethylene glycol) (PEG) to increase the molecular size of aptamers has been a common solution for several decades, although activity loss to some extent upon modification with PEG has been often reported (*Nat. Rev. Drug Discov*. **2006**, *5*, 123). Recently, it was reported that the PEGylated products can evoke anti-PEG antibodies, which directly bind to PEGylated aptamers and compromise their efficiency (*Cell Chem. Biol.* **2019**, *26*, 645), in some cases causing systematic allergic reactions to terminate clinical trials. Therefore, PEG alternatives to modify DNA aptamers are in demand.

As promising substitutes for PEG, several synthetic polymers with equivalent or higher levels of hydration are attracting attention in the delivery of drugs including peptides or siRNA. In this research, we examined poly(oligoethylene glycol methacrylate) (POEGMA), poly(methacryloyloxyethyl phosphorylcholine) (PMPC), and poly(sulfobetaine methacrylate) (PSBMA) as potential modifiers for DNA aptamers. POEGMA, a brush polymer with short PEG side chains, has been reported to exhibit reduced immune reaction induced by anti-PEG antibodies and used to modify RNA aptamer (*Adv. Mater.* **2022**, *34*, 2107852). Meanwhile, PMPC and PSBMA, the zwitterionic polymers, another type of hydrophilic synthetic polymers, can be considered as potential PEG alternatives, since they exhibit superior antifouling effects by strong hydration through electrostatic interaction and their chemical structures mimicking biological molecules that contribute to lower susceptibility to immune problems. They have been made use of in the area of biomaterial and delivery of peptides or nanoparticles, while their application is yet to be expanded to modification of DNA aptamers.

In this presentation, we report the selection and evaluation of new potential aptamer modifiers, with particular attention to their pharmacokinetic properties and their ability to evade recognition by the immune system.