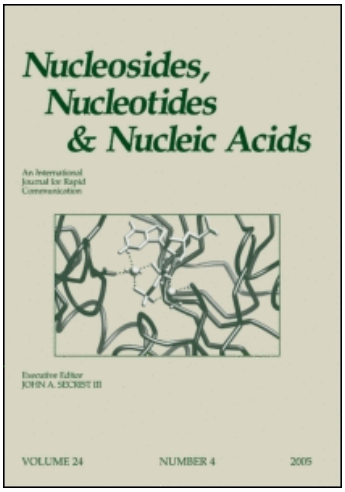

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Comb-Type Copolymers for Controlled DNA Delivery

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COMB-TYPE COPOLYMERS FOR CONTROLLED DNA DELIVERY

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ABSTRACT: Various comb-type copolymer containing a polycation as a main chain was design to construct delivery systems of DNAs. The comb-type copolymers having cell-specific polysaccharides were proved to be useful to deliver DNA to the target cells *in vivo*. Of interest, the copolymers with abundant side chains of hydrophilic polymers are capable of stabilizing DNA triplex. Further, injectable nanoparticles for controlled releases of DNAs were fabricated from the copolymer and a biodegradable polymer.

Regulation of self-assembling structures of DNA complex is the most vital issue for designing DNA vectors based on artificial polymers. We have focused on a series of the comb-type copolymers consisting of a polycation backbone, like poly(L-lysine) (PLL), and hydrophilic graft chains of polysaccharides or other polymers (1–4). The comb-type copolymer formed two types of soluble complexes with DNA depending on the grafting degrees of the hydrophilic chains. The comb-type copolymers having lower grafting degree effectively induced coil-globule transition of DNA and forms soluble complex with compacted DNA. On the other hand, the comb-type copolymers having higher grafting degrees also formed soluble complexes with DNA but without affecting its native secondary and highly-ordered structures. On the basis of these findings, we prepared several types of comb-type copolymers for controlled DNA delivery, namely, targeting (4–6), stabilization and control release of DNA.

The comb-type copolymers with cell-specific polysaccharide were studied to deliver DNA to target cells (4–6). Such as, PLL-g-HA, a comb-type copolymer having hyaluronic acid (HA) graft chains, was used for successful delivery to and expression of a reporter gene in the sinusoidal endothelial cells (SECs) of rat liver from its tail vein. The synergy of the molecular exclusion effect of HA chains to suppress nonspecific

interaction, such as RES uptake, and its specific interaction with the receptors on SEC are supposed to play an important role in the effective targeting.

Of interest, the higher-grafting copolymers were found to promote DNA triplex formation which is involved in "Antigene strategy" (1, 7, 8). The copolymers completely abolished K^+–induced destabilization of triplex formation with the reverse Hoogsteen hydrogen bonding. Furthermore, the copolymer significantly increased stability of the Hoogsteen-type triplex which is very unstable at physiological pH. Restriction enzyme-resistance assays and physicochemical characterizations demonstrated the usefulness of the copolymers as triplex stabilizer.

Multilayered biodegradable nanoparticles were prepared by employing the ionic interaction between the comb-type copolymer and poly(lactic acid) (PLA) in the absence of emulsifier (9, 10). The nanoparticles, consist of PLA as core, polylysine-rich intermediate and polysaccharide-rich as outer most shell, respectively, were easily loaded with DNA without inducing self aggregation. The specific interaction of polysaccharide on the nanoparticles and lectins was also confirmed. *In vivo* study revealed that the particles are capable of reserving oligonucleotides in mouse derma where oligonucleotides alone were rapidly diffused out.

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