Abstract of Dissertation

論文の内容の要旨

Polymeric Nanocarriers for Light-directed Gene Transfer After Systemic Delivery

(全身投与による光応答性遺伝子導入のための高分子ナノキャリアの設計)

ARNIDA

Gene therapy promises considerable advances in the treatment of several important diseases. In this regard, a number of elegant molecular strategies have been design. However, the therapeutic usefulness is continually frustrated by inadequate systems for gene delivery. In particular concern is the absence of systems capable of systemic delivery following intravenous injection. On the other hand, it is well known that endosomal escape of DNA complex is a main obstacle in obtaining efficient transfection. Photochemical internalization technology offers a smart solution for endosomal escape by means of endosomal membrane disruption in light-directed manner, while PEgylation is believed to prolong the circulation of the complexes in blood. Hence, integration of these two concepts might solve the above-mentioned problems. Therefore, we developed PEgylated polymeric nanocarriers to deliver pDNA and photosensitizer separately or as one component. The feasibility of this strategy has been studied using PEG-*b*-PLL as vectors and successful result was demonstrated. To further develop this system, we made a synergy between buffering capacity of polymeric carrier bearing ethylene diamine unit and photointernalization concept to enhance the transfection efficiency of the transferred gene. Up to 1,000-fold enhancement of photochemical transfection was achieved with moderate photocytotoxicity when PEG-*b*-polyaspartatamide bearing 3 repeating units of ethylene diamine was used as pDNA vector. The next approach was to incorporate both pDNA and DPc photosensitizer in one component to ensure their simultaneous uptake and the same intracellular localization. In this regard, we constructed a novel ternary complex, which consist of triblock copolymer PEG-PMPA-PLL, pDNA and DPc. The excellent physicochemical properties of this complex and its ability to release DPc at endosomal pH lead to high enhancement of photochemical transfection with reduced photocytotoxicity. Moreover, as addition to PEG steric protection, the slightly negative charge of the complex might help in repelling the serum albumine from binding therefore provide a prolong blood circulation which has been foreseen *in vitro* by dynamic light scattering study.