Nanoparticles *In Vivo* and the Biomedical Applications

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Efficient delivery of the nanoparticles (NPs) and NPs-based formulation agents to the target organ as well as their optimal retention period inside of the cells plays critical roles of their biomedical efficacy. Although the tissue- and cell-specific targeting of the NS have been intensively studied, there has been no efficient method developed to control the fate of NPs once they enter into the cells. Most of the existing approaches to manipulate the intracellular retention of NPs are mostly “passive” and particle size-dependent. Different sized particles hold distinct cellular responses. The adverse effect of particle size may limit the utility of nanodelivery systems. Therefore, the development of tunable “active” NP intracellular retention systems with fixed particle sizes remains a considerable challenge. By replacing the synergistic anions of transferrin (Tf) immobilized on quantum dots (Tf-QDs, ca. 25 nm), we have examined the feasibility of this concept. Substitution of synergistic anions of Tf from carbonate (holo-Tf) to oxalate (oxa-Tf) significantly increased the intracellular accumulation of the oxa-Tf-QDs as a result of (i) a delay in cellular removal triggered by oxalate (oxa-Tf)-induced endosomal Tf iron-release retardation and (ii) enhanced recycling of Tf-QD/TfR (Tf receptor) complexes from early endosomes to the plasma membrane. This accumulation extended the intracellular NP retention interval. The half-maximum fluorescence intensity of the oxa-Tf-QDs *in vivo* was 4 times higher than that of the holo-Tf-QDs. Programming of the intracellular NP retention time was accomplished through manipulation of the ratio of holo- and oxa-Tfs on the surfaces of the QDs. The preferential residence and accumulation of the oxa-Tf-QDs in animals bearing tumors was also observed. Using this simple and efficient approach, it was possible to readily achieve a desirable intracellular retention interval for the NPs, which may serve as one of the efficient ways for therapeutic nanoparticles to be delivered and accumulated in target tissues.