**BPA Delivery System Utilizing Sugar-Modified Polymers Forming Stable Boronate Esters**

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*p*-Boronophenylalanine (BPA) is one of boron-containing drugs used in boron neutron capture therapy. Because of its structure, BPA is recognized as a substrate of an amino acid transporter LAT1 overexpressed on various cancer cells and selectively accumulates in tumors. However, while BPA is effectively taken up to cancer cells, BPA is easily exported due to an antiport mechanism of LAT1, which exchanges extracellular amino acids with intracellular ones. Thus, BPA concentration in cancer cells decreases continuously during the irradiation of thermal neutron and it may lead to decrease of therapeutic effect in BNCT. To overcome the problem of low retention of BPA in tumors, we developed a polymer-based BPA delivery system, termed as poly[lysine(gluconate)]-BPA. BPA is linked to a gluconamide moiety of the polymer via formation of a boronate ester between a boronic acid of BPA and hydroxy groups of the gluconamide, and the phenylalanine moiety of BPA remains on the polymer. Thus, BPA linked to the polymer is expected to function as a ligand for LAT1, and poly[lysine(gluconate)]-BPA may actively target LAT1. Moreover, it is assumed that poly[lysine(gluconate)]-BPA is taken up via LAT1-mediated endocytosis, and localized in endosomes and lysosomes in cancer cells, while free BPA is taken up via transportation by LAT1 and distributes throughout the cytosol. Because of this, the aforementioned export of BPA by LAT1 may be circumvented, permitting prolonged retention of BPA in cancer cells. Indeed, localization of poly[lysine(gluconate)]-BPA in endosomes and lysosomes was observed in cultured BxPC-3 cells. In addition, poly[lysine(gluconate)]-BPA showed effective accumulation in subcutaneous BxPC-3 tumors in mice. Consistent with the efficient tumor accumulation, treatment of poly[lysine(gluconate)]-BPA with the irradiation of thermal/epi-thermal neutrons significantly suppressed growth of tumors. These results indicate the strategy of polymer-based BPA delivery system is a promising approach to potentiate therapeutic outcome of BPA by circumventing the exocytic discharge of BPA by LAT1.

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