Exploring a Nuclear-Selective Radioisotope Delivery System for Efficient Targeted Alpha Therapy

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Targeted alpha therapy (TAT) has attracted significant attention as an innovative cancer treatment method. Alpha rays have high energy and short range, so selective accumulation in target tumor cells is important to achieve high efficacy without side effects. Therefore, we have produced an innovative radiolabeled antibody designed to selectively deliver ^{211}At (alpha particle emitter) to the nucleus of cancer cells. In this study, we produced a novel radiolabeled antibody designed to selectively deliver ^{211}At to the nucleus of target cells for efficient TAT. For this purpose, we utilized a nuclear localization signal (NLS) that serves as a tag for protein transport to the nucleus. We further hypothesized that nuclear transport of the drug could be achieved by binding the antibody to the NLS-drug complex via a valine-citrulline sequence (Val-Cit) that is degraded by the lysosomal enzyme cathepsin B. Such high-resolution targeting of radioisotope was expected to improve selectivity and be highly effective, especially in TAT based on the high energy and short range of α-rays.

This molecular design was validated by fluorescence imaging. Val-Cit-NLS-fluorescent complexes with fluorescent groups at the drug moiety were synthesized and their intracellular dynamics were evaluated by fluorescence imaging. Three fluorescent groups with different properties (AlexaFluor 488, TAMRA, and BODIPY) were used to investigate the applicability of the payload. The complex with AlexaFluor 488, which is less membrane-permeable, was taken up slowly and remained in endosomes/lysosomes after uptake, while the complexes with TAMRA and BODIPY were rapidly taken up from the cell membrane and accumulated in the nucleus and nuclear membrane, respectively. This is due to the high membrane permeability of both fluorescent groups, but BODIPY is particularly liposoluble and is thought to be trapped in the nuclear membrane after nuclear translocation. Based on this finding, we devised a design that facilitates this step by exploiting the dual function of decaborane ($[B]_{10}$) as a carrier for ^{211}At and as a membrane-permeating agent. As a result, the developed nucleus-targeted ^{211}At-labeled antibodies showed excellent efficacy in cytotoxic activity[1)]. Thus, this study proposes high-resolution DDS with remarkable potency and selectivity as a new trend in drug development.

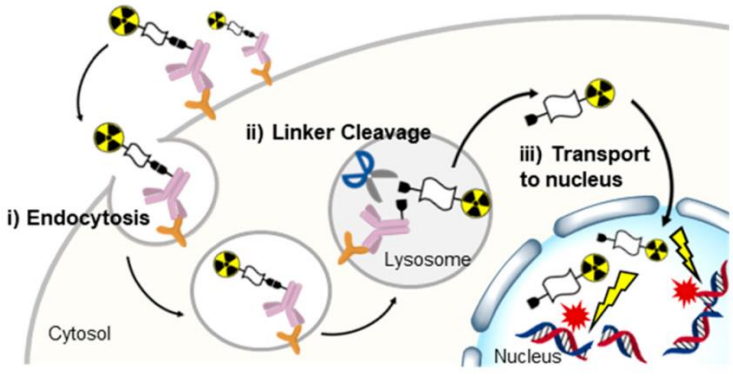

Figure 1. Possible mechanisms for nucleus-selective RI delivery

Reference

[1)] Iizuka, Y.; Manabe, Y.; Ooe, K.; Toyoshima, A.; Yin, X.; Haba, H.; Kabayama, K.; Fukase, K.; *Int. J. Mol. Sci.* **2023**, *24*, 9593.