Degradable Protein Linkers for pH-Selective Delivery of Protein Drugs

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Degradable bonds are widely used as key components in smart materials. For example, chemical bonds that can degrade in response to biologically tolerable stimuli are applied in drug delivery systems for introducing target selectivity. However, the introduction of stimuli-responsive chemical bonds often involves complex protection-deprotection-purification steps, denaturation, or loss-of-function of biopharmaceuticals in organic solvents, and low conjugation yields. Therefore, it is very attractive to incorporate such stimuli-responsive bonds during biopharmaceutical production without additional modification steps. In this presentation, a pH-responsive linker based on natural amino acids, which can be incorporated into proteins without additional chemical modification, for selective delivery of protein pharmaceuticals is introduced.

My group has recently developed a self-cleaving protein, pH intein$_{N150}$, by mutation of key amino acids in the original pH intein. The pH intein$_{N150}$ linker can be incorporated into protein pharmaceuticals during expression. As a proof-of-concept, we designed fusion proteins with a pH intein$_{N150}$ near cell-penetrating peptide sequences at weakly acidic pH. The intracellular penetration of protein cargos can be selectively turned on or off by cleaving the protein linker at weakly acidic pH. Furthermore, we prepared a recombinant protein in which human necrosis factor-related death-inducing ligand (hTRAIL) was fused with albumin binding domain (ABD) via the pH intein$_{N150}$ linker. The apoptosis-inducing activity of hTRAIL can be selectively activated by cleaving the linker at weakly acidic pH in tumors of a xenograft mouse model.

We expect that this new protein linker can be used for actively controlling various protein-based pharmaceuticals responding to delicate pH variations around inflammatory or cancerous tissues.

References

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[Field of research] Signal-responsive materials; Membrane-active peptides; Biocompatible materials; Drug delivery; Biopigments