Cancer-Specific RNAi System by Using PNA-Peptide Conjugates

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論 文 名　：Cancer-Specific RNAi System by Using PNA-Peptide Conjugates
（PNA-Peptide コンジュゲートを用いたがん特異的な RNAi システムの開発）

区　　分　：甲

論　文　内　容　の　要　旨

Small interfering RNA (siRNA) received much attention for treatment of intractable disease including cancer. The advantage of siRNA-based cancer therapy is its versatility to target a large number of different genes that are related to distinct cell signaling pathway of cancer cell. However, there are remaining several hurdles to overcome, such as unstable nature, off-target effect, and non-specific delivery. Among these issues, non-specific delivery of siRNA is one of the major causes of adverse effects.

To access the issue, here I designed a new siRNA system which turns on RNAi responding to a cancer cell-specific protease, cathepsin B. The system uses a peptide nucleic acid (PNA)-peptide conjugates to provide a protease-responsive activation. The PNA-peptides were found to form hybrids with double-stranded RNAs with complementary protruding regions, which then affected the susceptibility of dsRNA to Dicer. The dsRNA/PNA-peptide hybrids were activated in cancer cells with a high cathepsin B activity to show RNAi.

Then, I proposed the apoptosis-inducing siRNA system which inhibits the expression of bcl-2 protein for cancer therapy. The dsRNA/PNA-peptide hybrid showed apoptosis induction of cancer cell in response to cathepsin B activity.