化学修飾による機能性人工核酸医薬の開発

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Development of Functional Nucleic Acid Therapeutics by Chemical Modification (*Graduate School of Engineering, The University of Tokyo*) ○Kunihiko Morihiro

Nucleic acid molecules, such as DNA and RNA, have been the focus of much-applied research around the world. They have attracted great attention not only as imaging tools and delivery carriers but also as pharmaceutical materials because of their ability to form sequence-selective duplexes with complementary strands and to interact with a variety of nucleic acid-binding proteins. However, natural DNA and RNA often have an insufficient affinity for complementary strands, resistance to nucleases, and selectivity for target tissues and cells, so chemically modified "artificial nucleic acids" are generally used to enhance their functionality in and outside the body. Although many artificial nucleic acids have been developed so far, only a few of them have been put into practical use, and it is necessary to devise an organic link between molecular design and functionality.

I have designed and synthesized artificial nucleic acids with chemical modifications on the nucleobase of nucleic acids, which have been used for the control of biological functions including pharmaceutical applications. Nucleobases are not only important substructures that form hydrogen bonds with the complementary strand in the duplex but also can significantly affect the interaction with nucleic acid recognition proteins, including enzymes. In this presentation, we will discuss (1) artificial nucleobases that selectively function in cancer cells by imparting hypoxia responsiveness (Figure A)[1)], (2) unnatural base pairs that enable DNA self-assembly orthogonal to natural bases (Figure B)[2)], and (3) the development of artificial nucleobases that can significantly reduce hepatotoxicity of nucleic acid drugs (Figure C)[3)].

Keywords : Nucleic Acid Therapeutics; Chemical Modification; Antitumor Drugs; Unnatural Base Pairs; DNA Nanotechnology

DNA や RNA などの核酸分子を材料とした応用研究が世界中で盛んに進められている。核酸は相補鎖との配列選択的な二重鎖形成が可能であることや、様々な核酸結合タンパク質と相互作用できることから、イメージングツールやデリバリー担体などの利用にとどまらず、医薬品の素材としても大いに注目を集めている。しかし、天然の DNA や RNA は相補鎖に対する親和性やヌクレアーゼに対する抵抗性、標的組織や細胞に対する選択性が不十分である場合が多く、生体内外での機能性を高める目的で化学修飾を施した「人工核酸」が用いられることが一般的である。これまでに数多くの人工核酸が開発されてきたが、実用化されているものはわずかであり、分子設計と機能性を有機的に結びつける工夫が必要である。

申請者はこれまで特に核酸の塩基部に化学修飾を搭載した人工核酸を設計、合成することで医薬応用をはじめ生命機能の制御に用いてきた。核酸塩基は二重鎖中で相補鎖と水素結合を形成する重要な部分構造であるだけでなく、酵素を含む核酸認識タンパク質との相互作用などにも大きく影響を与え得る。本発表では①低酸素環境応答性

を付与することでがん細胞で選択的に機能する人工核酸医薬 (Figure A)[1] ②天然塩基と直交した DNA 自己集合を可能にする非天然塩基対 (Figure B)[2] ③核酸医薬の肝毒性を大幅に低減できる人工核酸塩基 (Figure C)[3] の開発について講演する。

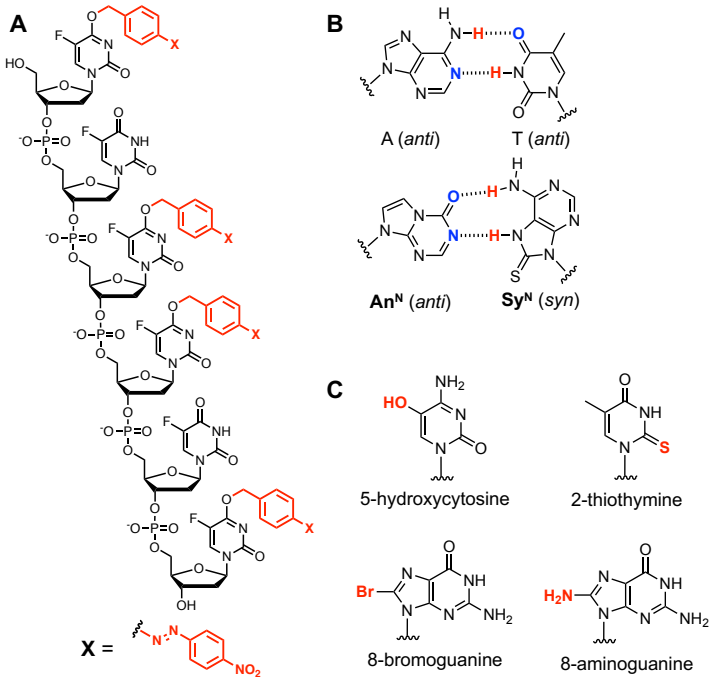

Figure. (A) Hypoxia-responsive nucleic acid anticancer drug. (B) Unnatural Base pair with *anti-syn* glycosidic conformation. (C) Nucleobase analogs to reduce hepatotoxicity of gapmer antisense oligonucleotides.

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