DEPARTMENT OF MOLECULAR SCIENCE AND NANOSYSTEMS

Seminars of the PhD Programme in Chemistry

Peptide nucleic acid-based targeting of microRNAs: diagnostic and therapeutic applications

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Abstract
Peptide Nucleic Acids (PNAs) are DNA analogues in which the sugar-phosphate backbone has been replaced by N-(2-aminoethyl)glycine units. These very interesting molecules have been described for the first time by Nielsen et al. [Science. 1991;254:1497-1500] and, despite a radical structural change with respect to DNA and RNA, they are capable of sequence-specific and efficient hybridization with complementary DNA and RNA, forming Watson-Crick double helices. In addition, they are able to generate triple helix formation with double stranded DNA and perform strand invasion. Accordingly, they have been used as very efficient tools for pharmacologically-mediated alteration of gene expression, both in vitro and in vivo. PNA and PNA-based analogues were proposed as antisense molecules targeting mRNAs, triple-helix forming molecules targeting eukaryotic gene promoters, artificial promoters, decoy molecules targeting transcription factors.
For these reasons, PNAs are excellent probes in diagnostic procedures, such are liquid biopsy in tumor diagnosis, including microRNA analysis as a tool for prediction of outcome of therapeutic interventions. Recently, PNAs have been shown to be able of altering biological functions of microRNAs, both in vitro and in vivo. We have recently designed and studied a peptide nucleic acid targeting miR-221-3p (R8-PNA-a221-3p), bearing a oligoarginine peptide (R8) to facilitate uptake by glioma cells. The effects of the R8-PNA-a221-3p were analyzed in U251, U373 and T98G glioma cells and found to strongly inhibit miR-221-3p. In addition, the effects of R8-PNA-a221-3p on p27Kip1 (a target of miR-221-3p) were analyzed in U251 and T98G cells by RT-qPCR and by Western blotting. We found an increase of p27Kip1 mRNA and of p27Kip1 protein in cells treated with R8-PNA-a221-3p. In a further study the biological activity of a combined treatment of glioma cell lines with two PNAs, directed against miR-155 and miR-221-3p was analyzed. Apoptosis was analyzed demonstrating that co-administration of the two PNAs is important to obtain the highest effects. These effects were assessed in the temozolomide-resistant T98G glioma cell line, in order to determine whether combined treatments of glioma cells lead to a reversion of drug-resistance phenotype. In conclusion, microRNA network can be targeted by PNAs to obtain excellent performance in diagnosis and therapeutic interventions.

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