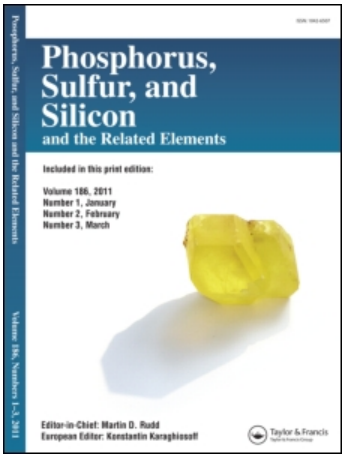

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Molecular Interactions of Oligonucleotides in Organism - A Source of Broad Spectrum of Biological Activities

Valentin Vlassov[a]; Leonid Yakubov[a]; Marina Nechaeva[a]; Ludmila Pautova[a]; Elena Rykova[a]; Pavel Laktionov[a]; Inna Vlassova[a]; Larissa Balakireva[a]

[a] Institute of Bioorganic Chemistry, Novosibirsk, Russia

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MOLECULAR INTERACTIONS OF OLIGONUCLEOTIDES IN ORGANISM- A SOURCE OF BROAD SPECTRUM OF BIOLOGICAL ACTIVITIES

VALENTIN VLASSOV, LEONID YAKUBOV, MARINA NECHAEVA, LUDMILA PAUTOVA, ELENA RYKOVA, PAVEL LAKTIONOV, INNA VLASSOVA and LARISSA BALAKIREVA

Institute of Bioorganic Chemistry, Novosibirsk 630090 Russia.

Abstract Oligodeoxynucleotides interact with a few proteins at the cell surface and in the bloodstream. These interactions determine cellular uptake, biodistribution and some nonspecific antiviral and immunomodulating effects of oligonucleotides.

Key Words oligonucleotides, nucleic acid -protein interaction

Perspective therapeutics, derivatives of oligonucleotides, affect functions of the complementary target nucleic acids and can cause some sequence independent effects, including nonspecific antiviral effects, inhibition of cell proliferation and activation of immune system. The sequence independent effects may be explained by interaction of oligonucleotides with some nucleic acid- related proteins. We investigated nucleic acid binding proteins in the blood plasma and at the cell surface. The method was affinity modification with radiolabeled oligodeoxynucleotides bearing an alkylating group, 4-[(N-2-chloroethyl-N-methyl)amino]benzylphosphamide residue at the terminal phosphate.

We have found that at the surface of eucaryotic cells, oligonucleotides bind to a specific nucleic acid binding receptor and to receptor CD4. Binding of oligonucleotides to cells stimulates incorporation of phosphorus into phosphatidic acid and increases production of diacylglycerol suggesting that the oligonucleotide binding receptor functions as a typical receptor coupled to cellular signaling system. Binding to specific receptors plays an important role in cellular uptake and transcytosis of oligonucleotides through biological barriers. We have found that oligonucleotides can enter organism through mucosa and skin. Using electron microscopy we have observed spontaneous cellular uptake of oligonucleotides and fast transportation of the compounds to the cell nucleus. Interaction of oligonucleotides with receptor CD4 explains sequence-independent anti-HIV effects of the compounds.

In the serum, oligonucleotides were found to bind to epidermal growth factor, immunoglobulins M and G and serum albumin. It was shown, that specific antigens interfere with the oligonucleotide- immunoglobulin interaction. Covalent attachment of oligonucleotides to immunoglobulins yields crosslinked complexes similar to the antigen-antibody complexes in the ability of binding to the Fcγ receptor at the lymphocyte surface. Binding of oligonucleotides to proteins should affect the fate and bioavailability of the compounds in organism. The interaction with immunoglobulins may affect polyclonal activation of immune system. Further investigation of the proteins interacting with oligonucleotides may result in identification of the targets of therapeutic value.