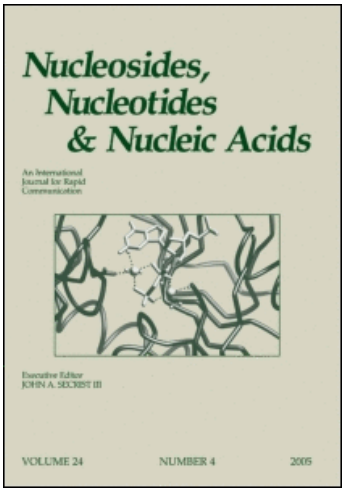

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Suppression of Transcription and Translation of the Influenza Virus RNAs by Oligonucleotide Derivatives

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SUPPRESSION OF TRANSCRIPTION AND TRANSLATION OF THE INFLUENZA VIRUS RNAs BY OLIGONUCLEOTIDE DERIVATIVES

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ABSTRACT. Various derivatives of oligonucleotides have been found to be effective inhibitors of the enzymes of the influenza virus replicative complex.

Biosynthesis of the influenza virus (Fowl plague virus, Weybridge) mRNAs includes an unusual mechanism, incorporation of the 5'-terminal oligonucleotides cleaved from the cellular mRNAs to the viral messengers. This specific process may be suppressed by some oligonucleotide derivatives which may represent a new type of inhibitors of the virus multiplication. We have investigated the effect of various modified oligonucleotide derivatives on the synthesis of the virus specific proteins in infected cells. The oligonucleotides bore different residues at the 5'- or 3'-terminal phosphates: ethidium (Et), quinone (Qn), cholesterol (Chs), hemin (Hem), 5-α-hydroxy-testosterone (Hts), estrone (EsS), derivative of dimethyl ester 2,4-di[α-(2-hydroxyethyl)oxyethyl]deuteroporphyrin IX (DDP) and a complex of Fe(III) with DDP (DDP(Fe)). The above derivatives were synthesized as described earlier (1-3). The compounds do not affect the synthesis of the cellular proteins and they, in contrast to nonmodified oligos, suppress the synthesis of the viral proteins at concentrations of about 0.1-10 μM (see TABLE).

TABLE. Suppression of the influenza virus (Fowl plague, Weybridge) proteins in infected chicken fibroblasts by oligonucleotide derivatives

Oligonucleotides and their derivatives	Suppression of viral proteins accumulation, %		
	10 μM	1 μM	0.1 μM
d(CCAAACA)	23	0	0
$d(pT)_8$	40	10	0
$d(pT)_{10}$	30	5	0
DDP(Fe)	30	10	0
Cholesterol	21	0	0
Quinone	3	0	0
TGACCCTCpDDP(Fe)	60	39	17
DDP(Fe)-pTTCCCATT	59	50	45
$(pT)_{10}$-Hem	24	15	10
DDP-pTGACCCTCTTTCCCATT	63	50	12
DDP(Fe)-pTGACCCTCTTCCCATT	37	12	0
$d(pT)_{10}$-Chs	75	38	25
CCAAACA-Chs	81	20	8
Hts-$(pT)_8$	46	31	29
EsS-$(pT)_8$	57	16	0
$(pT)_8$p-Qn	61	10	0
Et-$(pT)_8$p-Et	54	43	39
Et-$(pT)_4$p-Et	53	10	0
$(Tp)_4$-Et	48	0	0
Et-$(pT)_3$p-Et	48	0	0
$(Tp)_3$-Et	35	0	0
Et-$(pT)_3$	23	0	0

All the derivatives are not complementary to the virus RNA genome and inhibit the protein synthesis due to the interaction with the enzymes of the viral replicative complex. We suggest that the same oligomer derivatives will be efficient inhibitors of different mutant influenza viruses.

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