4’-THIODNA: UNEXPECTED BEHAVIOUR

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ABSTRACT
This viewpoint briefly discusses the impact of 4’-thiosubstitution on oligonucleotides behaviour. The study in the reviewed articles has shown unexpected A-form formation, and unexpected RNA-like behaviour of the 4’-thioDNA. This has been confirmed by the unexpected interaction of 4’-thioDNA with Lividomycin A, a RNA major groove binder, and by resistance to cleavage by DNase I, which is a DNA-specific endonuclease. 4’-ThioDNA was also recognized by RNase V1 which is a RNA-specific endonuclease. These all findings will trigger the main focus of this viewpoint.

Key Words: Nucleic acids, ThioDNAs, 4’-ThioDNAs Structure and Properties

INTRODUCTION
Irrational unpredictable changes may lead to dramatic effect on people, nature and the world. Changes can be political, environmental, personal or chemical. What chemical changes can do to the behaviour of certain molecules? This leads me to ask the following questions: What a dramatic change will the replacement of oxygen atom by sulphur have on oligonucleotide structure and properties? Shall it really change the structural behaviour of those thio-oligonucleotides (thioONs)? Will they really exhibit any resistance to enzymatic cleavage? In this viewpoint, I will try briefly to answer the above mentioned questions through the discussion of the findings of the two papers on 4’-thioDNAs that were published by both Matsuda [1] and Katahira [2] groups.

DISCUSSION
Matsuda group researchers were working on developing 4’-thionucleic acids as functional oligonucleotides. These oligonucleotides consist of 4’-thionucleosides, a sugar-modified nucleoside analogue, as building blocks (Figure 1) [1, 3, 4]. Although there have been investigations by Walker and his co-workers on the synthesis and properties of 4’-thioDNA (Figure 2) [5], the ONs prepared on those studies were only partially modified with 2’-deoxy-4’-thiopyrimidine nucleosides [6-9]. However, the preliminary results have shown high hybridization to the complementary RNA and promising endonuclease (nuclease S1) resistance [8]. Matsuda group carried out more investigations on 4’-thioDNAs, oligonucleotides batch 1, ONs1 (DNA1, thioDNA1 and RNA1) followed by a series of the complementary oligonucleotides batch 2, ONs2 (DNA2, thioDNA2 and RNA2) (Figure 3) [1].

Ultraviolet melting experiments were used to measure the thermal stabilities of the complementary duplexes. The homo duplex of thioDNA1:thioDNA2 showed a higher $T_m$ value (65.2 ± 0.2 °C) than that of DNA1:DNA2 and it was similar to that of RNA1:RNA2. The hetero duplex RNA1:DNA2 ($T_m$ = 51.6 ± 0.2 °C) was less thermally stable than the corresponding homo duplexes (DNA1:DNA2 and RNA1:RNA2). When RNA1 was changed to thioDNA1, the corresponding $T_m$ value was nearly the same (thioDNA1:DNA2 = 48.3 ± 0.2 °C) as that of the RNA1:DNA2 hetero duplex. In contrast, thioDNA1 formed a thermally stable duplex with RNA2 (thioDNA1:RNA2) to give a $T_m$ value of 64.6 ± 0.2 °C, which is similar to that of RNA1:RNA2. These results made us to believe that 4’-thioDNA may behave as an RNA-like molecule despite the absence of the 2’-hydroxyl groups in the sugar moiety.

To further confirm this speculation, CD spectra of each duplex were measured. The duplex DNA1:DNA2 showed a typical B-form spectrum (having a positive band near 280 nm), while that of RNA1:RNA2 showed a typical A-form spectrum (having a positive band near 260 nm). The CD spectrum of thioDNA1:thioDNA2 had a positive band near 260 nm though a small shoulder was observed near 280 nm, and thus A-form of the duplex was suggested. Additional confirmation of the RNA-like behaviour of 4’-thioDNA...
CONCLUSION

On the basis of the defined structure, I can say that the remarkable properties reported for the fully modified 4’-thioDNA is supported by the following findings:

• ThioDNA exhibits a CD spectrum characteristic of the A-form [14] although DNA usually gives a CD spectrum characteristic of the B-form.

• The fully modified 4’-thioDNA unexpectedly interacts with lividomycin-A, resulting in an increase in thermal stability [1]. Lividomycin A is known to be an RNA major groove binder. In general, RNA usually takes on the A-form, and 4’-thioDNA was shown to take on the A-form.

• The fully modified 4’-thioDNA has shown resistance to cleavage by DNase I, which is a DNA-specific endonuclease [1]. This result is consistent with the earlier report by Walker and collaborators [6, 8].

• The fully modified 4’-thioDNA is recognized by RNase V1 [1], which is an RNA-specific endonuclease [14].

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ABBREVIATIONS

RNA= ribonucleic acid/ DNA= deoxyribonucleic acid/ ONs= oligonucleotides/ SVPD= snake venom phosphodiesterase/ CD= Circular dichroism/ PAGE= Polyacrylamide gel electrophoresis

REFERENCES


Figure 1: Structure of 2'-deoxy-4'thionucleosides.

Figure 2: Comparison of the structures of DNA, RNA, and 4'-ThioDNA.

Figure 3: Sequences of DNA, 4'-thioDNA and RNA.