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Small RNAs hit a new target

Modulation of gene expression by targeting the non-coding sequences downstream from a gene

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The University of Texas researchers have recently discovered that small synthetic RNAs (sRNAs) that are complementary to sequences located 3'-outside of genes can efficiently modulate gene expression. These new findings significantly expand the transcription-regulatory potential of sRNAs, and they also may provide useful leads for other artificial nucleobase oligomers to target sequences beyond the 3' termini of mRNA.

Key words: small RNAs, 3' non-coding transcripts, gene expression modulation, DNA looping, peptide nucleic acid (PNA)

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Commentary to: Yue X, Schwartz JC, Chu Y, Younger ST, Gagnon K, Elbashir S, Janowski BA, Corey DR. Transcriptional regulation by small rnas at sequences downstream from 3'- gene termini. Nat Chem Biol 2010; 6:621–9; PMID: 20581822; DOI: 10.1038/nchembio.400.

Synthetic small RNAs (sRNAs) have become valuable research tools in genomic studies, and they promise to develop into potent drugs, too.[1-3] So far, sRNAs have been targeted to sequences located inside of genes, such as mRNA coding regions,[4] or 5' to gene promoters[5] and promoter-overlapping sequences,[6] by rationally assuming that all major gene-regulatory sites lie within these non-coding regions.

Surprising (but actually anticipated by the scientists) recent findings,[7] convincingly prove that sRNAs can influence gene expression by recognizing sequences located beyond the 3' end of genes, as well. In this thorough study performed by the groups of David Corey and Bethany Janowski at the University of Texas Southwestern Medical Center, the researchers have analyzed the transcription at the chromosomal locus covering the progesterone receptor (PR) gene and identified the presence of non-coding transcripts that overlap the 3' end of the PR gene.

When cells were targeted by sRNAs complementary to sequences beyond the 3' terminus of PR mRNA, the activation or repression of PR expression (depending on the pre-existing level of PR expression) was observed.[7] These breakthrough results uncover additional layers of complexity in gene structure at the PR locus, and suggest the possibility of involvement of 3' non-coding transcripts in gene regulation.

It is worth mentioning that up till now the function of these 3' non-coding transcripts remained essentially unknown, and no investigation has been done on whether some of the 3' non-coding RNAs might be a target for modulating gene expression. For instance, there have been no reports on such kind of gene expression modulation at the latest international conference on gene regulation by sRNAs held in Oxford, UK in March 2010.[3]

Yue et al.[7] proposed a possible mechanism for the unusual effect they observed: sRNA targeted to the PR 3' non-coding transcripts recruits argonaute 2, a key protein involved in RNA interference. Attachment of argonaute 2 to the 3' gene terminus may affect, via gene looping, the protein complex assembled at the promoter region near the 5' terminus of the transcriptionally active PR gene (as shown schematically in Fig. 7 of Yue et al.[7]). Both the recruitment of argonaute protein to non-coding RNAs and the PR gene looping that brings 3' and 5' PR sequences separated by 100 kb into close proximity were confirmed by experiment.[7]

Keeping in mind that chromosomal DNA is a difficult target for sequence-selective recognition by synthetic agents,[8] the new results expand the transcription-regulatory potential of sRNAs

by providing additional sites for gene targeting. Besides, the suggested mechanism may also provide a useful approach for other artificial nucleobase oligomers, such as peptide nucleic acid (PNA), to target sequences beyond the 3' termini of mRNA.

To this end, it is known that: i) PNA is able to target the transcribed region of chromosomes;[8] ii) normally, PNA is appended with cationic oligopeptide to improve the solubility of PNA oligomers, and to strengthen their binding to DNA;[9] iii) the PNA binding generates a sharp bend of duplex DNA, which affects the communication of DNA-bound proteins.[10] These two latter conditions could change the DNA looping-mediated interaction between gene-regulatory proteins bound to 3' and 5' gene termini, thus altering the level of gene expression.

I am positive that the seminal study by Yue et al.[7] will serve as an inspiration for other thoughts in the field of gene targeting by artificial DNA constructs.

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