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Messages from intergenic space

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Although it's becoming more apparent that the intergenic space between protein-coding genes - often referred to as "junk" - is actively transcribed and often produces non-protein-coding RNAs, the role of these RNAs and their transcription is largely unknown. In the June 3 Nature, Joseph Martens, Lisa Laprade, and Fred Winston report a previously unknown form of gene regulation involving a non-protein-coding RNA, SRG1, which can regulate a neighboring gene by simply being transcribed.

"I was very pleased to see another role for intergenic transcription which primarily implicates the process of transcription itself rather than the non-coding RNA, which in this case, may be just a by-product," said Peter Fraser, from the Babraham Institute, Cambridge, UK, who was not involved in the study.

The work began with a *Saccharomyces cerevisiae* gene called SER3, which catalyzes a step in serine biosynthesis and was previously found to be tightly repressed by the yeast switch-sniff complex. This was unusual, since the switch-sniff complex is normally associated with activation, not repression, said senior author Fred Winston, from Harvard Medical School, Boston.

When the researchers performed chromatin immunoprecipitation experiments to analyze the SER3 promoter, they found significant levels of the TATA-binding protein and RNA polymerase II bound to the upstream intergenic region of the *SER3* gene. "It was surprising that all the factors necessary for transcription appeared to be there, even though the gene was not on," Winston told us.

However, by examining the intergenic region upstream of SER3 and comparing it to the same region in four closely related yeast species, the team found a second TATA box. The region also contained other promoter regulatory sites, but did not contain an open reading frame, suggesting it potentially encoded a non-protein-coding RNA.

"The first experiment we performed on this region, surprisingly, said there was very active transcription going on across the region," Winston said. When the authors mutated this region - termed SER3 regulatory gene 1 or *SRG1* - and eliminated its transcription, *SER3* was transcribed at high levels. This suggested that *SRG1* was involved in *SER3* repression.

Further investigation, using a *SER3* gene that had been constructed to contain binding sites for the Gal4 transcription factor, showed that *SRG1* transcription blocked the binding of Gal4. This suggested a novel form of regulation, in which turning the *SRG1* gene "on" resulted in transcriptional interference, and thus the repression of the *SER3* gene.

There are lots of intriguing questions that arise out of the work, said Susan Gottesman, from the National Cancer Institute, Bethesda, Md., who was not involved in the study. For example, how widespread is this sort of regulation in yeast and in higher organisms like *Drosophila* and humans?

"Certainly, [the findings] suggest that measurements of transcription in intergenic regions may turn up even more of this sort of regulatory process," Gottesman told us.

"There is an order of magnitude more transcription going on than can be accounted for by what we traditionally call genes (for example, protein-coding transcription units)," said Fraser. "Some of this transcription may be producing functional non-coding RNAs, but there is also clear potential for much of this being the byproduct of the transcriptional machinery doing things other than making mRNA."

Thomas Gingeras, vice president for biological sciences at Santa Clara, Calif.-based Affymetrix, said the results are quite exciting. "This is the start of a number of studies that are beginning to look at these non-coding transcripts and their potential functions. This is a relatively unexplored area that is going to be very abundant," Gingeras, who was not involved in the study, told us.

Fraser agreed that the results will have a large impact. "This regulatory system will undoubtedly produce some very interesting science in the future, partly because it clearly identifies a novel role for intergenic transcription in gene regulation, but also because it creates defined categories," Fraser told us.

The exact mechanism of how *SRG1* regulates *SER3*is still not known, but the interesting thing will be to try to find additional examples of this type of gene regulation, and examine how it might vary, Winston said. "Our guess is that more examples will be found, and this will be really illuminating," he said.

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