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GENE EXPRESSION

Common sense and antisense

The common perception is that unidirectional transcription occurs from the majority of promoters to generate sense RNA and that bidirectional transcription occurs from just a subset of promoters. However, the publication of four new studies provides compelling evidence that bidirectional transcription is more common than previously thought and has implications for understanding the complexity of gene regulation.

Preker and colleagues used RNA interference to deplete the exonucleolytic RNA exosome in human cells, preventing the degradation of unstable low-abundance transcripts. They identified a class of short, polyadenylated unstable sense and antisense RNAs transcribed from sequences 0.5–2.5 kilobases upstream of active transcription start sites (TSSs). Bidirectional transcription correlated with active promoter regions.

In another study, He and colleagues describe a new technique, asymmetric strand-specific analysis of gene expression (ASSAGE), that uses bisulphite treatment to identify which DNA strand a transcript originates from and allows the quantification of sense and antisense transcripts. They categorized genes into three classes according to the ratio of sense to antisense transcripts that they produce. The genes in each class varied between different human cell lines, suggesting that the expression of antisense transcripts could be regulated in a cell- or tissue-specific manner.

In a third paper Core *et al.* present an assay, global run-on sequencing (GRO-seq), to map and quantify the density of RNA polymerase II (RNAPII) molecules that are actively engaged in transcription across the genome. They found that ~30% of all human genes have a higher density of RNAPII at the 5′ end relative to the downstream region. This indicated that RNAPII pausing limits the rate of transcription at many genes in the genome. RNAPII was orientated in both the sense and antisense directions at many promoters, and although antisense transcription could be initiated, RNAPII failed to elongate the antisense transcripts beyond promoters.

Seila *et al.* studied short, low-abundance RNAs in mouse cDNA libraries and identified many short TSS-associated sense and antisense transcripts. Using chromatin immunoprecipitation coupled with DNA sequencing (ChIP-seq), they found that hallmarks of transcription initiation, such as promoter-associated RNAPII and trimethylation of Lys 9 of histone H3 (H3K9me3), were present both upstream and downstream of TSSs. However, dimethylation of Lys 79 of histone H3 (H3K79me2), characteristic of RNAPII elongation, was only found downstream of TSSs, again suggesting that antisense transcripts are not elongated.

Many common themes have emerged from these complementary studies. The production of short antisense and sense RNAs seems to be widespread, but these transcripts cluster at TSSs rather than being randomly distributed across the genome. Although transcripts in both orientations are associated with chromatin marks that are characteristic of transcription initiation, only the sense transcripts are associated with markers of transcription elongation, indicating that productive elongation can only occur in the sense direction.

Is initiation of antisense transcription important for gene regulation? One possibility is that antisense transcription might allow transcription factors to access the DNA elements that are upstream of core promoters. Seila *et al.* proposed that RNAPII might induce negative supercoiling upstream of transcription, which initiates antisense transcription. These events could then poise chromatin and the nascent RNA at the TSS in a conformation that is necessary for transcriptional regulation. Dissecting the role of this novel process in gene regulation is the next challenge.

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ORIGINAL RESEARCH PAPERS Preker, P. *et al.* RNA exosome depletion reveals transcription upstream of active human promoters. *Science* 4 Dec 2008 (doi:10.1126/science.1164096) | He, Y. *et al.* The antisense transcriptomes of human cells. *Science* 4 Dec 2008 (doi:10.1126/science.1163853) | Core, L. J. *et al.* Nascent RNA sequencing reveals widespread pausing and divergent initiation at human promoters. *Science* 4 Dec 2008 (doi:10.1126/science.1162228) | Seila, A. C. *et al.* Divergent transcription from active promoters. *Science* 4 Dec 2008 (doi:10.1126/science.1162253)