Additional Paper for “RNA Regulation”

Paper reference

Abstract
Since DNA is double stranded, it is possible that complimentary sequences on both strands can be transcribed. These transcripts would then bind each other with high affinity leading to post-transcriptional gene silencing in most eukaryotes. Thus, transcription of antisense strands represents yet another form of RNA-mediated gene regulation in organisms that have evolved the RNA interference (RNAi) pathway.

Yelin et al. used computational methods to predict 2,667 naturally occurring antisense transcripts in the human genome. They then used an RNA microarray to verify that approximately 1,600 of the predicted pairs bind each other to create double-stranded RNA molecules. Yelin et al. also performed Northern Blots on specific cases to verify that the pairings were the result of transcription at overlapping locations from both DNA strands. This suggests that a minimum of 5-10% of protein coding genes may be regulated by this mechanism, if not more.

Antisense RNA transcripts may influence gene expression through a number of processes including transcription, mRNA processing, splicing, stability, transport and translation. The authors also point out that the transcription of a number of these antisense transcripts is often associated with genomic imprinting, the phenomenon in which the expression of certain genes is determined by whether the gene is inherited from the male or female parent.

The authors point out that antisense transcription mediated gene regulation may be far more common than even their estimates, because their computational method only looks at transcripts that overlap exonic regions of the genome. However, consider the case in which an antisense transcript that overlaps an intronic region binds to an immature RNA transcript before splicing and leads to partial or complete degradation. In the case of partial degradation, the gene may end up being up-regulated, down-regulated or even spliced differently. In the case of complete degradation the gene will be silenced. The algorithm also only recognizes *cis*-antisense transcripts, which are transcripts that are transcribed at the same locus on the opposite strand. However, the existence of *trans*-antisense transcripts at other parts of the transcriptome is both possible and likely. Finally, the database of transcripts that they used frequently under-represents the length of 3’ UTRs, which could lead to more extensive transcriptional overlap.

Discussion
This paper examines yet another form of RNA regulation. The idea of antisense regulation through RNAi seems intuitive and natural, so confirmation of antisense transcription is good evidence of evolution’s ability to take advantage of RNAi. However, I would be interested to see a follow up study on how antisense transcription affects gene expression *in vivo*. For example, if the antisense transcript has a translated region, will it begin translation before encountering its RNA target and, in this case, will ribosomal docking block the enzymes that allow for RNAi, or will RNAi always occur before a transcript is exported from the nucleus? Furthermore, does gene silencing for these pairs occur in the nucleus or the cytoplasm? In addition, computational analysis could be used to determine how frequently antisense transcripts code for proteins. Another question that comes to mind is what types of genes are being regulated in this way. The authors claim that genes involved in genomic imprinting may be regulated in this way and I would love to see some experiments to confirm this claim. RNAi has been shown to play a key role in cell-differentiation, so that is another likely candidate. I would also be interested to see if any of these antisense pairings are in genomic sequences that are of viral descent? More specifically, could this antisense transcription be immunological?

Another computational problem is the number of these sense-antisense transcriptional units that are evolutionarily conserved in lower-level organisms that do not have RNAi. Are these conserved units functionally related or randomly distributed, as one would expect since they would have no prior selective force? In the cases where they are conserved, does conservation imply that the antisense transcript in humans does not modulate expression of the sense sequence? Finally, when the first organisms developed RNAi each of these conserved antisense-paired genes would suddenly fall under different regulation. What are the phenotypic differences caused by this sudden change in gene expression between the first RNAi-enabled organisms and their predecessors?