Making sense of antisense

We all need a bit of peace and quiet from time to time. Now we can get our desired silence wherever we like thanks to noise-cancelling headphones, which work by sampling the ambient sound entering the headphones (the annoying hum of a fridge, say), and then generating an 'anti-noise' soundwave that interferes with, and cancels out, the incoming sound.

Nature has hit on an analogous mechanism for regulating gene expression. Ordinarily, genes are read by transcription factors that scan along the 'sense' strand of DNA, producing sense RNA molecules that guide the construction of the protein encoded by the gene. During the past 15 years, however, biologists have discovered that genes can also be read from the opposite 'antisense' strand. This generates an antisense RNA molecule that can selectively interfere with the expression of the same gene, just as 'antisound' cancels out ambient noise.

Yet the precise function of these antisense mechanisms, how they work, and how widespread they are in the genome remain unclear. "These issues are not really understood," says Lars Steinmetz, a geneticist in the Genome Biology Unit at EMBL Heidelberg. So Lars, working with six other members of the Genome Biology Unit, set about finding out.

To do so, the team carried out a genome-wide screen of antisense transcripts in the yeast *Saccharomyces cerevisiae* under a variety of environmental conditions to see how the repertoire of expressed antisense molecules changed.

This screen produced two key findings. First, genes that need to be switched off under some circumstances but switched on under others — such as those encoding proteins that metabolise certain nutrients whose availability fluctuates — tend to show more antisense expression. This suggests that in addition to being under the control of transcription factors these genes also regulate their expression through antisense mechanisms, which Lars says allows for the fine-tuning of gene expression.

The second finding is that genes that express antisense RNAs also tend to have their activity linked to that of other genes. In earlier work, Lars and colleagues found that in the densely packed genome of yeast, a promoter that regulates the expression of a downstream gene often sits immediately after the protein-coding region of an upstream gene. Producing antisense RNA from the downstream gene's promoter means reading the DNA in an upstream direction, and so can interfere with the expression of the upstream gene. "So you get an interlinking of regulation between neighbouring genes through non-coding antisense RNAs," says Lars.

Although the underlying mechanisms for these two findings remain unclear, the work of Lars and colleagues underscores the widespread importance of antisense-based regulation of gene expression. A better understanding of these processes could shed light on how evolutionary changes in animal design are generated, which largely occur through altering patterns of gene expression during development. The results of Lars's study also point to the need to rethink the classical gene concept, which usually denotes the protein-coding region and the upstream promoter while ignoring downstream elements. "The importance of downstream elements that affect the expression of upstream genes means that these should be part of an expanded concept of the gene," says Lars.

Zhenyu X, Wei W, Gagneur J, Clauder-Münster S, Smolik M, Huber W, Steinmetz LM (2011) Antisense expression increases gene expression variability and locus interdependency. *Mol Syst Biol* **7**: 468