

A Mystery Solved: How Genes Are Selectively Silenced

Cells have to use their resources economically. Therefore, they read only those genes which are needed at a given moment, while the others are chemically labeled and, thus, selectively turned off. Scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now been the first to discover how these labels are placed at exactly the right spot in the genetic material. Important players are regulatory RNA molecules. Their sequence exactly matches the region of a gene which is to be labeled. At this site, RNA and DNA form a plait-like triple helix serving as a signpost for the labels.

Our genetic material is often compared to a book. However, it is not so much like a novel to be read in one piece, but rather like a cookbook. The cell reads only those recipes which are to be cooked at the moment. The recipes are the genes; 'reading' in the book of the cell means creating RNA copies of individual genes, which will then be translated into proteins.

The cell uses highly complex, sophisticated regulatory mechanisms to make sure that not all genes are read at the same time. Particular gene switches need to be activated and, in addition, there are particular chemical labels in the DNA determining which genes are transcribed into RNA and which others will be inaccessible, i.e. where the book literally remains closed. The biological term for this is epigenetic gene regulation.

Among the epigenetic mechanisms which are well studied is the silencing of genes by methyl groups. This is done by specialized enzymes called methyltransferases which attach methyl labels to particular 'letters' of a gene whereby access to the whole gene is blocked. "One of the great mysteries of modern molecular biology is: How do methyltransferases know where to attach their labels in order to selectively inactivate an individual gene?" says Professor Ingrid Grummt of the German Cancer Research Center (DKFZ).

Grummt has now come much closer towards unraveling this mystery. She has focused on studying those text passages in the genetic material which do not contain any recipes. Nevertheless, these texts are transcribed into RNA molecules in a controlled manner. "These so-called noncoding RNAs do not contain recipes for proteins. They are important regulators in the cell which we are just beginning to understand," says Ingrid Grummt.

In her most recent work, Grummt and her co-workers have shown for the first time that epigenetic regulation and regulation by noncoding RNAs interact. The scientists artificially introduced a noncoding RNA molecule called pRNA into cells. As a result, methyl labels are attached to a particular gene switch so that the genes behind it are not read. The trick is that pRNA exactly matches (is complementary to) the DNA sequence of this gene switch. The investigators found out that pRNA forms a kind of plait, or triple helix, with the two DNA strands in the area of this gene switch. Methyltransferases, in turn, are able to specifically dock to this 'plait' and are thus directed exactly to the place where a gene is to be blocked.

More than half of our genetic material is transcribed into noncoding RNA. This prompts Ingrid Grummt to speculate: "It is very well possible that there are exactly matching noncoding RNA molecules for all genes that are temporarily silenced. This would explain how such a large number of genes can be selectively turned on and off."

Kerstin-Maike Schmitz, Christine Mayer, Anna Postepska and Ingrid Grummt: Interaction of noncoding RNA with the rDNA promoter mediates recruitment of DNMT3b and silencing of rRNA genes. *Genes & Development* 2010, DOI: 10.1101/gad.590910

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,200 staff members, including 1,000 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Württemberg (10%).

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