RNA emerges from DNA's shadow

RNA, the transporter of genetic information within the cell, has emerged from the shadow of DNA to become one of the hottest research areas of molecular biology, with implications for many diseases as well as the understanding of evolution. But the field is complex, requiring access to the latest equipment and techniques of imaging, gene expression analysis and bioinformatics, as well as cross-pollination between multiple scientific disciplines. This has led to a major European push to bring the field together via a network of overlapping multidisciplinary projects, spearheaded by the European Science Foundation (ESF) with its RNA Quality programme.

The great potential of the RNA research field to solve a variety of fundamental problems relevant for understanding of life and predicting cures for diseases was unleashed at the ESF Quality programme's first conference, held in Granada in June 2008. As well as many European groups, the conference was represented by leading pioneers from the US in the field, who welcomed the new initiative as an important collaborative force.

RNA was once considered to be just the faithful messenger taking genetic information from the genome to the ribosome, or protein factory, but that view has been blown away by recent research. It is now known that RNA has additional roles in regulating gene expression and as an important structural component both in the cell nucleus and in the ribosomes. Furthermore, errors in transcribing RNA from DNA are frequent and require a variety of elaborate quality control mechanisms to prevent both the mis-regulation of genes, and the manufacture of aberrant RNA and protein fragments that clog up the workings of the cell, and that if unchecked can cause a variety of disorders, including cancers.

Delegates at the conference also heard how there is great potential for creating new compounds that manipulate the cell's apparatus for transcribing DNA into RNA to overcome a number of serious disorders caused by deleterious mutations in specific genes, as opposed to problems with the RNA itself. Allan Jacobson from the University of Massachusetts Medical School presented one of the most exciting developments, a molecule that overcomes a common deficiency in genes that prevents their being read right up to the end of their sequence during transcription. Jacobson pointed out that there are about 2400 human genetic disorders resulting from mutations that cause genes to be incompletely read, including cystic fibrosis and muscular dystrophy. A drug based on the molecule is now entering trials that could lead to it becoming generally available. Results so far indicate dramatic improvements in both cystic fibrosis and muscular dystrophy sufferers, although it is only suitable for those disorders caused by the presence of a premature stop sign in a gene sequence, as a result of a mutation. It does though highlight the huge therapeutic potential of the research into RNA and its quality control.

Significant progress has been made in different aspects of RNA research over the last decade or more, leading to the current situation where many groups are working on different aspects of the problem. The challenge being met by the ESF's RNA Quality programme is to bring these groups together, and make Europe a much greater force in the field, according to Jim Anderson, from Marquette University's Department of Biological Sciences in the US.

Another important aspect of RNA research lies in the interaction between DNA transcription, and the physical structure both of the membrane-bound cell nucleus and the genome coiled within it. Genes are transcribed within the nucleus and the resulting RNA molecules then

emerge through small holes that are connected to the genome by proteins called nuclear pore complexes. In one of the presentations, Nick Proudfoot from Oxford University in the UK explained how some genes are enhanced by being close to the nuclear pore complex, indicating a close relationship between gene expression and nuclear structure that must have played out through evolutionary history. Another point to emerge from Proudfoot's presentation was how some genes are expressed more efficiently for a different reason, because the section of DNA containing their sequence is coiled locally into a loop, rather than as a branch. Quite simply, this speeds up the transcription process of reading the gene because the enzyme concerned, RNA Polymerase, can just keep on encircling the loop. As Proudfoot explained, this is relevant for quality control as well. "They may afford quality control by "telling" the polymerase it is transcribing a bona fide gene, with a proper beginning and end," said Proudfoot. "Otherwise the polymerase may have initiated erroneously." The existence of a DNA ring makes it easier to identify the sequence corresponding to a gene, and transcribe it correctly.

The RNA Quality programme comes under the ESF's EUROCORES (European Collaborative Research) scheme and will last 3-4 years. It includes national funding with additional money from the ESF (currently through EC FP-6 support) for networking and dissemination of results. The first conference was held in Granada, Spain, during June 2008.

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