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The dark side of RNA

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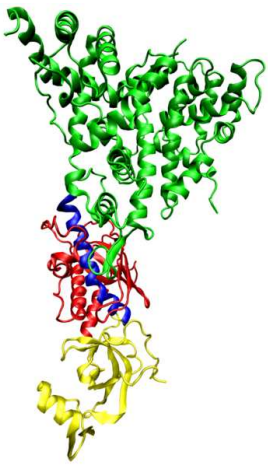
There is more to RNA than meets the eye. In the 1980s, students in biology were told that this molecule's raison d'être was to be a template for the making of a protein. RNA, like DNA, was made out of nucleotides and had no particular function other than that of being a text that was to be read. Today, almost 30 years later, there is growing evidence that little bits of single-stranded RNA are just as crafty as many transcription factors and can regulate the expression of a gene, and hence a protein. However, they cannot do it without the help of enzymes, two of which are known as Drosha and Dicer. Drosha and Dicer are ribonucleases which work in unison to sculpt RNA strands that in turn acquire the ability to bind to specific parts of mRNA, which they subsequently silence. As a result, the mRNA's product is not translated.



3D structure of Dicer

Source : Wikipedia

The expression of a gene is dependent on so many different instances, from the presence of a certain ion to a specific moment in development. However, until recently, it had always been thought that transcription factors had the last word. They were the ones who decided whether a gene would be transcribed and ultimately translated. But it is not so. Tiny strands of RNA – known as microRNAs or miRNA – are beginning to raise their voices and show that they are just as good as any transcription factor. The concept is mind-blowingly simple: miRNAs recognise their complementary sequence encoded in a specific mRNA and bind to it. In so doing, they interfere with the proper translation of the mRNA sequence and no protein product is synthesized. It's a bit like immobilising a locomotive on a railway, thereby hindering the passage of a train.

The knowledge that certain non-coding RNA molecules – the miRNAs – were actually part of protein expression regulation arose in the early 1990s whilst working on *Caenorhabditis elegans*. Since then, many different miRNAs have been discovered in animals and plants – and the viruses that infect them – and it is becoming obvious that their role in protein expression regulation is important. It is thought that the human genome may well house up to 1000 miRNA genes, which could regulate as many as one third of our protein-coding genes…which is not trivial.

Lending the silencing of genes to the sole existence of miRNA is, however, a little short-sighted. In truth, they need a battery of enzymes to meet their ends. Drosha and Dicer are two such enzymes, whose major role is to cleave RNA. The making of mature miRNA – which is the RNA strand that actually recognises its target – is part of a fascinating process. Drosha, like Dicer, carry two domains in their sequence known as ribonuclease III (or RIII) domains. Thanks to protein sequence folding, these two domains meet to form an intramolecular dimer which – in both cases – is the catalytic site for RNA processing.

Drosha is found in the cell's nucleus and specifically recognises primary miRNA (pri-miRNA). Drosha – like Dicer – can only recognise double-stranded RNA so, conveniently, pri-miRNA folds into a hairpin conformation thus producing one double-stranded end. The two RIII domains form a cleft into which the RNA hairpin can lodge. Drosha then cleaves one end to produce what is known as pre-miRNA. Pre-miRNA is then shuttled out of the nucleus where it encounters Dicer. Dicer prepares the other end of the hairpin in much the same way as Drosha and releases the mature miRNA which is then ready to recognise its mRNA target and act upon it.

Plant miRNAs are specific: their sequences match their complementary RNA targets with great precision. Animal miRNAs are far more promiscuous. The match is far less demanding and, as a result, one miRNA will bind to as many as one hundred different target sequences. From Nature's point of view, it may sound economical but it just makes things difficult in the laboratory. It is a relatively easy task to identify a specific miRNA within a specific pathway if the said miRNA only has one target. However, in reality, one particular miRNA regulates many different genes and is thus most probably involved in as many cellular pathways.

The fact that animal miRNAs are so dissolute makes it difficult to use them as diagnostic markers for disease or for exploiting them for therapeutic benefit. Nevertheless, much research is being carried out in this direction to make some sense out of the miRNA jungle. Since miRNA silencing in plants is far more straightforward, a number of applications have already been made. The very first was with on tomatoes where an engineered miRNA was used to prevent the expression of an enzyme which participated in the softening of the cell walls once ripe. Ripe tomatoes could then be harvested without falling apart. Such practises cannot be widely used though because of our whims of genetically modified crops.

An obvious question is why do miRNAs exist? Do they provide some special regulatory property that transcription factors do not? Is the silence Drosha and Dicer create of a different nature to that of the well known transcription factors? Time will tell. Nature continues to show that she has many facets and those she nurtures are usually there for a reason…

Cross-references to Swiss-Prot

Drosha, *Homo sapiens* (Human) : Q9NRR4
Dicer, *Homo sapiens* (Human) : Q9UPY3

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