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> ONE MONTH, ONE PROTEIN <

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round in circles

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There will always be more to Nature than meets the eye. During the 1950s and the 1960s, the importance of RNA in protein synthesis gradually emerged. RNA has always been seen as a linear molecule, a bit like a sentence which has a beginning and an end, and is read from one end to the other, letter by letter, word by word. Yet in the 1970s, scientists discovered another kind of RNA molecule: one that was, to their surprise, circular. Circular RNAs were first thought to be biological oddities, something that had gone wrong in the process of transcribing a gene, and which drifted in a cell's cytoplasm the way flotsam would in the sea. But as the years went by and technology evolved, it became all too clear that there was far too much circular RNA swilling around cells for its presence to be purely accidental. Today, not only are researchers discovering that circular RNAs – or circRNAs – seem to be another way of regulating gene expression but some circRNAs can also give rise to proteins. One such circRNA is known as cir-ZNF609.

Rythme no.1 (1938), by Robert Delaunay

Source: wikipedia

During the second half of the 20th century, RNA turned out to be the missing link between genes (DNA) and proteins. The British molecular biologist Francis Crick and his American counterpart James Watson were the first to discover the structure of DNA in 1953. Though they had understood that genes carry all the information cells need to make proteins, they hadn't understood how it occurred on the molecular level. It was the American biochemist and geneticist Marshall Nirenberg who first suggested, in 1961, that RNA was the connection. This gave rise to two exciting years during which scientists raced to "crack the genetic code", in other words: understand how genes are read to produce RNAs (known as messenger RNAs, mRNAs), which are subsequently translated into proteins.

Barely 10 years later, the first circular RNAs appeared. Termed viroids, they were in fact plant pathogens. Then, in the 1990s and quite by chance, researchers identified circular RNAs that were generated from eukaryotic genes. They imagined that the machinery involved in creating them was probably the same used to produce mRNAs, and that circRNAs were the unfortunate result of random errors, when a gene was misread for instance. However, they began to see things in a different light when they observed that most RNAs – up to 90%! – for a mouse gene (known as Sry) turned out to be circular. Surely this meant that circRNAs were not just a form of misinterpretation. In the past few years, technology and computational algorithms have lifted yet another veil: circRNAs can be counted by the thousands. Though the majority are indeed expressed at relatively low levels with respect to their linear mRNA counterparts, many are expressed many times more.

CircRNAs are produced by thousands of different genes – i.e. many genes express a "classical" linear mRNA and, more rarely, a circular counterpart. How, though, are circRNAs translated into proteins

– if and when they are? The machinery involved in translating, i.e. ribosomes, needs to be able to recognise a beginning and an end within the circRNA, much in the way we recognise the beginning of a sentence by a capital letter, and the end by a full stop. mRNAs have "caps" at their beginning to which ribosomes bind, and then proceed to translate. circRNAs are not capped, but scientists have observed regions that can act as entry sites for ribosomes. These particular entry sites are highly methylated and known to promote the initiation of protein translation in human cells.

Are the mRNA and circRNA versions of a protein the same? No, not necessarily. Cir-ZNF609 is translated from the circular form of its RNA. The linear mRNA gives rise to a transcription factor that has two zinc finger domains. The circRNA version does not have the zinc finger domains, so there is a great chance that it doesn't have the same role as its linear counterpart either. Cir-ZNF609 is largely expressed in the brain, as many circRNAs happen to be, but also in muscle tissue where cir-ZNF609 seems to be involved in muscle cell differentiation, proliferation and migration. No one knows, however, how this is achieved on the molecular level. Could cir-ZNF609 act by modulating or controlling the activity of its linear counterpart for instance? An intriguing thought.

Is this the role of circular RNAs? Are the circular transcripts of genes used to regulate the expression of their linear counterpart? Could this be yet another way of regulating gene expression? Circular RNAs seem to have a role in cell proliferation and the progression of diseases such as cancer, Alzheimer's and Parkinson's disease. Some of them may be used to sponge up tiny little bits of RNA known as micro RNA that are also known to have regulatory roles in cells. Others may compete with their linear mRNA, or bind to other RNA-binding proteins, thus sequestering them. What is more, circRNAs are not only more stable than mRNAs – in human cells, they last up to 48 hours while mRNAs only last for about 9 hours – but they are also conserved across species which is reason enough to believe that they exist for a purpose. Only a few of them, however, seem to be translated into proteins.

It is becoming clear that circRNAs – and their products – play important roles in cells. Many questions arise. How do genes "indicate" which version of RNA – mRNA? circRNA? – is to be produced? There must be signals that are recognised by the machinery that transcribes genes into RNA. And how do cells get rid of circRNA? Are they put into vesicles that are secreted? Could this perhaps represent an alternative form of cell to cell communication? Are circRNAs a means of reacting rapidly to environmental stress? Certainly, the corners of the "one gene, one protein" dogma we were taught in the 1980s, are becoming a little blurred. Not only do we know today that a gene produces more than just one protein when you consider the realms of splicing and posttranslational modification, but here is evidence that a gene is able to produce not only one mRNA but also an alternative circRNA. Once largely ignored because they simply could not be seen, circRNAs are now tracing the borders of what is proving to be a big unexplored country.

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