

When RNAs retire

What happens when molecules have outlived their usefulness?

DNA creates RNA creates protein, said Francis Crick, and yes, he was right, but they shouldn't keep doing it forever. No one knows how many RNAs a single gene will produce during the lifetime of a cell. If it's a gene that's needed all the time – say, to produce the building

blocks of microtubules – the number could be trillions. And each of the RNAs can be used to create an incredible number of proteins. But sometime it had better stop – if for nothing else, for a service check.

Defective mRNAs get broken down in a process called NMD (see previous story). In fact, all mRNAs – even those in perfect health – retire someday. There's a procedure to be followed: it doesn't involve a final paycheck, or turning in keys. Instead, it starts when a large complex of proteins begins chewing the molecule apart, starting at the tail and working its way upwards.

This process is called *deadenylation*, and it's been one of the interests of Dietrich Suck in Heidelberg for a long time. He began studying proteins that bind to DNA and RNA before he came to EMBL in the 1980s. That makes him one of just a few scientists to escape the normal process of deadenylation at EMBL – which usually takes nine years. But if you were looking to find out something about his own plans for retirement, you've come to the wrong place. His lab is still going strong, and this year he's thinking about other things: like the molecular machines that retire RNAs.

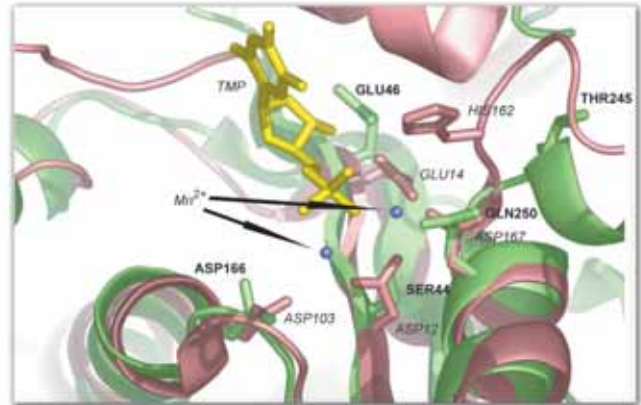
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DNA is made up of subunits called *nucleotides*, so are the RNA molecules that are transcribed from a gene. RNA undergoes some processing and refining in the cell nucleus before it is carried out to the cytoplasm, where it will be translated into proteins. One step is to attach a long tail of *adenosine* nucleotides onto it – the *poly(A)* tail. This can be very long – it may stretch to 250 amino acids for an mRNA in mammals. In yeast it's somewhat shorter – by the time it leaves the nucleus, it usually contains between 50 and 75 As.

The length of the tail is important; it acts like a timer. Out in the cytoplasm, the mRNA will usually be attacked by a *deadenylase* complex that starts eating its way up the poly(A) tail; when that's gone, the protein-producing part of the mRNA will be open to attack.

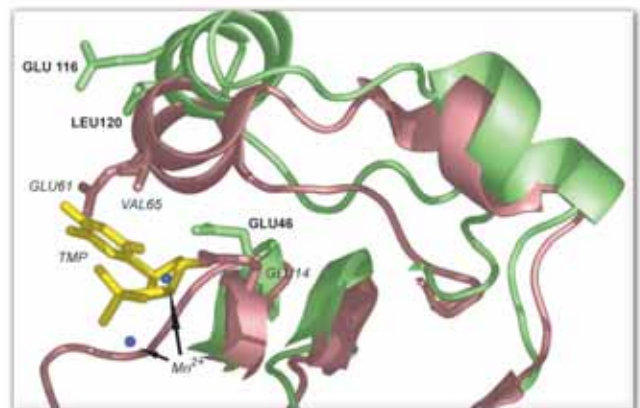
In yeast cells, deadenylation is carried out by a large protein machine called Ccr4-Not. At the heart of the machine is a core of seven proteins. "Two of these are deadenylases, capable of cutting nucleotide chains," Dietrich says. "But we haven't known whether one or both of these are responsible for digesting the poly(A) tail." One, called Ccr4, plays some sort of role, because disrupting its functions dramatically slows the breakdown of the tail.

Stéphane Thore, a PhD student in his group, managed to obtain a crystal of the cutting part of the seventh molecule, the other deadenylase, called *Pop2*. He carried it



Above and below: Two views of very similar structures. Each image shows PolIII-epsilon (salmon color) and Pop2 (green); the arrows show where the chemically-active site lies. The yellow structure is the nucleotide.

Left: Dietrich Suck and Jerome Basquin snip off "A"s and passport photos of Stéphane Thore, who has just finished his PhD and left EMBL.



off to one of the beamlines at the EMBL Outstation in Grenoble to get a look at the details of its building plan.

He found that Pop2's digestive structure is very similar to a molecule called the *PolIII epsilon* subunit. "They both have a cavity where the nucleotide activity takes place. What we see in Ccr4 is the first example of this type of cavity in an RNA-digesting molecule."

Experiments show that in yeast, Ccr4 seems to dominate the process of degrading mRNAs. "But this complex is very old, and very well-maintained across many species including humans," Dietrich says. "Human cells have a very similar complex, which has undergone a number of evolutionary adaptations. It will be interesting to see if the balance is the same in our own cells and in other species."