NEWS & VIEWS

MOLECULAR BIOLOGY

RNA lost in translation

David Tollervey

In any manufacturing process, quality control is crucial, and gene expression is no exception. A new pathway monitors mRNAs — the intermediaries of gene expression — and destroys faulty molecules.

For most human genes to be usefully expressed they must first be copied into messenger RNAs by the process of transcription. These then program large, RNA–protein complexes called ribosomes to synthesize a specific protein by 'translation'. The fidelity of mRNA translation into protein is vital for the overall accuracy of gene expression, and cells have evolved ways to detect any aberrant mRNAs that have structural defects. Doma and Parker (page 561 of this issue)[1] have discovered an mRNA quality-control system — 'no-go decay' — with some unexpected features.

Cells alter their rates of mRNA transcription to change mRNA levels, and so rates of protein synthesis, in response to many stimuli. To adjust mRNA levels, cells must be able to rapidly get rid of normal mRNAs that were previously synthesized (turnover). In fact, different mRNAs differ radically in their rates of degradation, and this is subject to both metabolic and developmental regulation. In addition, cells must guard against the synthesis of abnormal mRNAs (surveillance), which can produce defective, potentially toxic, protein products.

The normal turnover of mRNAs has been extensively analysed in budding yeast. In this organism, two main pathways have been identified, each of which degrades the mRNA from only one of its ends — either the 5′ or the 3′ end. Two further pathways deal only with quality control, specifically degrading mRNAs with structural defects. 'Nonsense-mediated decay' recognizes mRNAs where the site of translation termination occurs too early in the RNA. By contrast, mRNAs that entirely lack a translation stop site are subject to 'non-stop decay' (reviewed in refs 2, 3).

In each of these four pathways — at least in yeast — the mRNAs are degraded exclusively from their ends. But the no-go decay pathway identified by Doma and Parker[1] is different: this pathway begins its work in the middle of the mRNA (Fig. 1).

The authors engineered an obstruction into mRNAs (a very stable 'stem–loop' structure) to stall the translating ribosome, and showed that this triggered degradation. The no-go decay is initiated by cleavage of the mRNA close to the stall site. This break generates entry sites for enzymes that degrade the remainder of the RNA: the free 5′ end is degraded by Xrn1, and the 3′ end is degraded by a complex termed the exosome (Fig. 1). Both enzymes have similar roles in the other degradation pathways. No-go degradation definitely requires stalling of the ribosome, because the termination of translation before the obstruction prevents cleavage of the mRNA[1].

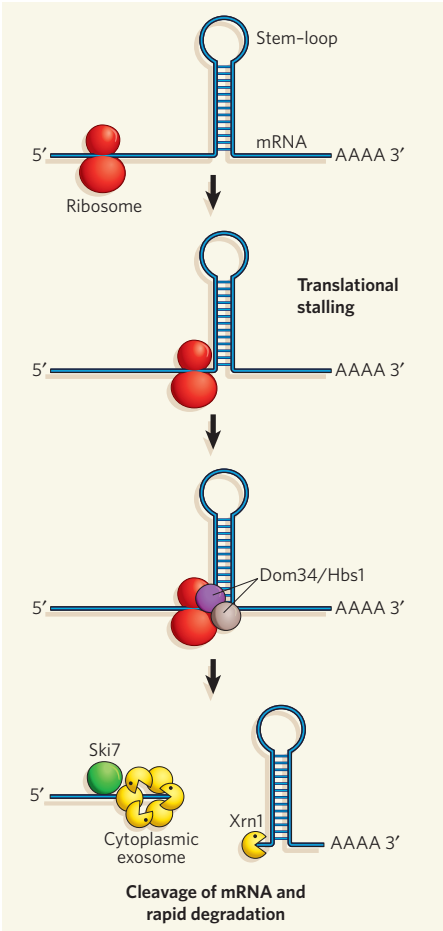

Figure 1 | No-go decay. Doma and Parker[1] show that the no-go decay pathway results in rapid mRNA cleavage and degradation. This pathway is different from other mRNA degradation pathways in yeast, in that stalling of the ribosome by a stem–loop structure leads to cleavage of the mRNA[1], a process that involves the Dom34 and Hbs1 proteins[4]. This cleavage generates free ends that are subject to degradation: the enzyme Xrn1 chews up the mRNA from the 5′ end, whereas the multi-enzyme exosome complex degrades from the 3′ end. Dom34 and Hbs1 might interact directly with the 'A site' of the stalled ribosome, possibly to promote release of the ribosome and allow subsequent mRNA cleavage, or they may directly stimulate cleavage of the mRNA.

The initial cleavage of the mRNA involves two proteins called Dom34 and Hbs1. These proteins are related to translation factors[4], which regulate translation through direct contact with the ribosome. So it looks as though Dom34 and Hbs1 might interact with the stalled ribosome. Hbs1 is also related to a protein called Ski7 that is an accessory to the exosome[5]. During non-stop decay, Ski7 is proposed to release ribosomes stalled at the ends of mRNAs that lack a translation-termination site[6]. Ski7 is also needed when the exosome degrades the cleaved no-go mRNAs[1].

How the mRNA cleavage occurs in no-go decay has yet to be worked out. Obvious possibilities are that Hbs1 or Dom34 catalyse it themselves, although their sequences do not suggest this, or they could recruit a specific nuclease enzyme to the site. In either case, it would presumably be necessary to first remove the stalled ribosome, because inspection of the end points of the cleaved RNA does not show an obvious 'footprint' — an area protected from cleavage by the bound ribosome.

Alternatively, interaction with Hbs1 or Dom34 might allow the ribosome itself to cleave the mRNA. In support of this, in the bacterium *Escherichia coli* pausing of translation can cause mRNA cleavage by the ribosome (at the 'A site' of the ribosome)[7,8]. The cleavage converts the mRNA into a non-stop transcript. This can then be dealt with by the bacterium's non-stop decay pathway, which releases the stalled ribosome and degrades the problematic mRNA.

It is attractive to think that a similar mechanism might operate in yeast. However, the ends of the fragments that Doma and Parker[1]

detected following no-go cleavage were quite heterogeneous — more so than might be predicted by cleavage within the stalled ribosome. But in other contexts, mRNA fragments stabilized by the absence of Xrn1 or the exosome are also heterogeneous[9,10]. So it could be that the free ends are nibbled away by other nucleases after the mRNAs have been cleaved by the ribosome.

It is not clear how widespread no-go decay is in yeast, or whether it is conserved in other animals. In fruitflies, recognition of mRNAs by the nonsense-mediated decay system also leads to their cleavage in the vicinity of the translation stop site[11]. This triggers rapid degradation by Xrn1 and the exosome, hinting that a mechanism similar to no-go decay might operate in the flies.

Notably, Doma and Parker report substantial cleavage of mRNAs containing an artificial stem–loop structure that should create an almost impassable block for the ribosome. But other, perhaps more physiologically relevant, mRNAs with translational pause sites were much less subject to no-go decay. It may be that the main targets for no-go decay in the cell are chemically damaged mRNAs, which can cause a complete translation block[12].

In all organisms, the amount of each mRNA is very tightly controlled — a crucial step in the regulation of gene expression. In Doma and Parker's experiments, the no-go pathway is apparently acting specifically as a quality-control system. However, it seems likely that in other contexts this pathway will have been co-opted to regulate the abundance of specific mRNAs. Consistent with this possibility, in mice and fruitflies a mutation of a close relative of Dom34 called Pelota leads to specific defects in development and cell-cycle progression[13,14].

The integrity and functionality of mRNAs are monitored by surveillance activities that act at many steps during the molecules' nuclear maturation and cytoplasmic lifetime. Such continuous surveillance to maintain high fidelity is metabolically expensive but, as elsewhere in life, infidelity is surely still more costly. ■

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BIOGEOCHEMISTRY

Gas with an ancient history

Don E. Canfield

Researchers persist in tackling our ignorance of what life was like way back in Earth's history. Evidence of methane production in ancient microbial ecosystems now emerges from 3.5-billion-year-old rocks.

Piecing together the early history of life from the geological record is like putting together an incomplete jigsaw puzzle. A few of the pieces connect, but many of them don't, and most are missing. We know — or at least we think we know — that life evolved by 3.8 billion years ago. The evidence, found in the isotopic composition of organic carbon[1], is rather scarce, but it is compelling. Carbon isotopes of this type, however, cannot tell us which organisms were present.

For further insights into early Earth ecosystems, we zoom forward around 300 million years to the Dresser Formation in Western Australia. It is from here that Ueno *et al.* (page 516 of this issue)[2] report evidence for the existence of an ancient population of methane-producing microbes, commonly known as methanogens. This represents one of the earliest specific microbial processes to have been identified in the geological record: it adds an extra piece to the emerging picture of the structure and complexity of ancient microbial ecosystems.

The story is this. Between 3.5 billion and 3.45 billion years ago, a series of lavas known as pillow basalts, and sedimentary rocks, were deposited in what is now the Dresser Formation. The basalts were intruded by numerous silica dykes, some of which terminate in the sedimentary layers (see Fig. 1 of the paper on page 517). This means that the dykes are ancient and were formed during the deposition of the sediments. Small bubbles (fluid inclusions) are found within quartz minerals in the dykes, and these bubbles contain mainly carbon dioxide and water, but also some methane (CH_4). Many of the bubbles align along the growth margins of the quartz, and so are believed to have formed as the quartz was precipitated: they are viewed as primary inclusions. Other bubbles are scattered randomly within the quartz (and are probably primary), while still others are concentrated where the quartz was fractured and resealed. These are viewed as secondary inclusions.

In their investigations, Ueno *et al.*[2] crushed samples of quartz (Fig. 1) and measured the concentrations of the extracted gases and the isotopic composition of the methane carbon. The primary and secondary inclusions contained methane with distinct isotopic compositions. The secondary inclusions had a composition consistent with (but not proof of) a non-biological, thermal source of methane that was probably introduced some time after

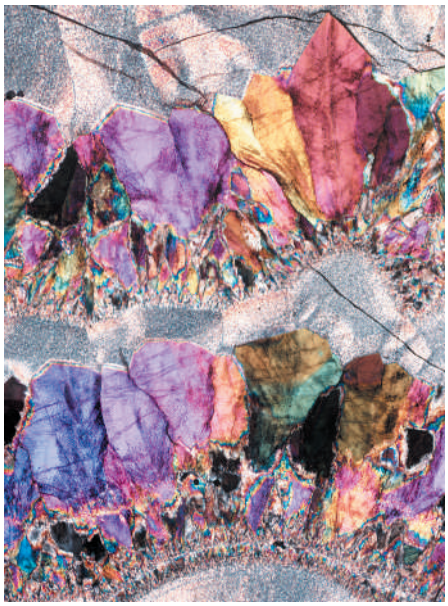

Figure 1 | Inclusive evidence. This optical photomicrograph shows quartz from the Dresser Formation in cross-polarized light. The coloured crystals are coarse-grained quartz, which contain the tiny fluid inclusions analysed by Ueno *et al.*[2]. (Image courtesy of Yuichiro Ueno; width is about 3 mm.)

the silica dykes were first in place. By contrast, the methane from the primary inclusions was much more strongly depleted in ^{13}C, and is consistent with a microbial origin.

Still, the isotopic composition of the methane from the primary inclusions is not very different from that of the most ^{13}C-depleted, thermally formed methane. Might all of the methane have a non-biological source? The authors anticipate this argument and note that their primary fluid inclusions lack the higher (C_{2+}) hydrocarbons that are normally associated with the most strongly ^{13}C-depleted thermogenic methane. All in all, I take the data at face value, and accept that the authors have probably uncovered the oldest-known samples of biologically produced gas.

With this backdrop, let us enquire more broadly into the nature of life 3.5 billion years ago. Evidence for the activities of sulphate-reducing bacteria, which use sulphate rather than oxygen in energy production, has been reported from the Dresser Formation[3]. Fossil structures known as stromatolites, which are probably of biological origin, have been found in slightly younger rocks from the same stratigraphic sequence[4]. The organisms