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the dormant ribosome

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Snowdrops are here. The tips of daffodil shoots are pushing through the soil, and soft grey buds are preparing to burst on the magnolias. These are reminders that Winter marks the end of one life cycle while Spring marks the one about to begin. How does a cycle begin, for that matter? In fact, does a cycle ever stop? No, life cycles never truly stop but they can be delayed for certain periods of time. Depending on the organism and the surrounding conditions, quiescence can last for days, weeks, months, years – or even thousands of years. Consider certain bacteria, plant seeds, or even animals that hibernate. In fact, apparently, at least 60% of the planet's microbial biomass spends more time immersed in idleness than in action. In a way, this is not surprising given that any biological activity consumes energy – and some far more than others. Take human egg cells. Stalled for years in ovaries, they patiently await the meagre hope of maturing and the even sparser chance of being fertilized. What causes them to stall? Hosts of protein factors which impede, but also protect, crucial enzymes – such as ribosomes for instance.

Snowdrops, screenprint by Anna Harley

Courtesy of the artist

Ribosomes are large complexes of RNA (rRNA) and proteins that carry out crucial activities in every single living organism and, largely, every single cell. They are small factories whose end product are proteins. In fact, ribosomes synthesize every single protein an organism needs. When you know that one cell hosts about 42 million proteins – which are also recycled – and that the human body accommodates about 30 trillion cells, you realise that an awful lot of ribosomes are working very hard and, usually, without a break. How do ribosomes synthesize proteins? To cut a very long and complex story short, ribosomes read a cell's genes and, much in the way you follow a recipe, they translate them into proteins. With DNA and RNA, ribosomes are therefore at the very heart of life and its continuation.

Infection, lack of food, osmotic stress, temperature shock, gametogenesis are just a few of the circumstances that can trigger off cell dormancy – which is a way of keeping a cell alive with its engine, so to speak, running as low as possible. In dormant cells, ribosomes are stalled because proteins are less in demand. This state of affairs is regulated via protein factors known as dormant factors. Why do cells keep their ribosomes? Why not synthesize new ones when needed? Because the production of new ribosomes costs cells a lot of energy. If existing ribosomes are just shut down for a while, cells only have to trigger them back into action again when necessary.

Dormant ribosomes were what molecular biologists James Watson and Alfred Tissières observed in 1958, although they were unaware of it at the time. Cell biologist George Palade was the first to discover ribosomes in 1953, using electron microscopy. Crick and Tissières wanted to know what ribosomes did, so they prepared *E.coli* cultures – first placing them on ice. This caused a cold shock and the bacteria rapidly shut down their ribosomes. Today, we know that dormant ribosomes tend to aggregate thus forming

very large complexes. This is what Crick and Tissières inadvertently observed: ribosomes that were dormant and larger than their natural state. Years later, in the 1970s, snapshots of lizard cells showed ribosomal aggregates set out periodically forming crystalline sheets. This turned out to be a lizard's way of preserving ribosomes while hibernating. So ribosomal dormancy brings about a shift in function as well as in structure – both of which are regulated by dormant factors.

How do dormant factors actually affect ribosomes? First we need to understand a ribosome's architecture. Briefly, active ribosomes are made up of two main subunits – a small one and a big one. Each subunit is itself composed of rRNA and many ribosomal proteins that are important for ribosome assembly and function, while the roles of others remain unknown. This combination of rRNA and protein provides crucial active sites that will collaborate to synthesize a protein chain, amino acid by amino acid, supported by hosts of other factors among them initiation factors, elongation factors, termination factors and recycling factors.

Protein synthesis is a complex and intricate business. Hence, for the sake of brevity and clarity, a number of (important) steps have been omitted. Ribosomes begin by recognizing and then reading the sequence of a given gene – in the form of messenger RNA (mRNA) which, itself, has been transcribed from the cell's DNA. To do this, the mRNA is held between the ribosome's subunits and shifts to one side as it is read – as well as edited to ensure that the gene is read correctly. Much in the way you would translate Chinese into Arabic, the mRNA sequence is translated into amino acids that are subsequently bound to one another in the order they are read. The nascent protein chain protrudes from a tunnel, known as the polypeptide exit tunnel, situated in the large subunit. Once the ribosome has read the whole gene, the completed protein chain is released.

Dormant factors act on ribosomes to repress protein synthesis but also to ensure their preservation. There are many ways of preventing protein synthesis. You can stop ribosomes from initiating mRNA translation. Or you can stop them from adding amino acids to a nascent protein chain. This is exactly what two key dormant factors were found to do in zebrafish and *Xenopus* eggs: intracellular hyaluronan-binding protein 4 (Habp4) and death-associated protein 1b (Dap1b). Dap1b associates with factors that usually initiate protein synthesis, while Habp4 associates with factors that usually elongate nascent protein chains (and also exists in humans). Both factors act by squatting important active sites. Dap1b inserts its C-terminus into the ribosome's polypeptide exit tunnel placing its fifth-last amino acid exactly where the first amino-acid residue of a nascent protein would lodge – thus blocking the initiation of novel protein synthesis. Habp4, on the other hand, squats the entry of the mRNA tunnel so the ribosome is unable to read and translate mRNA. All in all, Dap1b and Habp4, with the help of initiation and elongation factors, respectively, collaborate to stall protein synthesis while also stabilizing the ribosome for future use.

So, depending on the surroundings, cells are able to shift between dormant and non-dormant states relatively fast thanks to hosts of dormant and "re-cycling" factors, respectively. Myriads of factors form multitudes of connections with the ribosomes, protecting their active sites from degradation while putting protein synthesis on hold. Ribosomes are an obvious choice to promote cell dormancy but many other enzymes are also expected to switch to dormant states. Perhaps sets of ribosomes become dormant while others remain active. Perhaps waves of ribosomes are stalled – or re-activated – in a sequential manner. It is an exciting field of research and an emerging one. A field, too, which will help scientists understand how protein synthesis is regulated both in healthy individuals and in disease.

Cross-references to UniProt

Intracellular hyaluronan-binding protein 4, *Danio rerio* (Zebrafish) (*Brachydanio rerio*): Q6NRY1
Intracellular hyaluronan-binding protein 4, *Xenopus laevis* (African clawed frog): Q5XJA5
Intracellular hyaluronan-binding protein 4, *Homo sapiens* (Human) : Q5JVS0
Death-associated protein-like 1 homolog, *Danio rerio* (Zebrafish) (*Brachydanio rerio*): Q9I9N0
Death-associated protein-like 1.S, *Xenopus laevis* (African clawed frog): A3KMU5

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