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Bioinformatics in Action

a shrewd tweak

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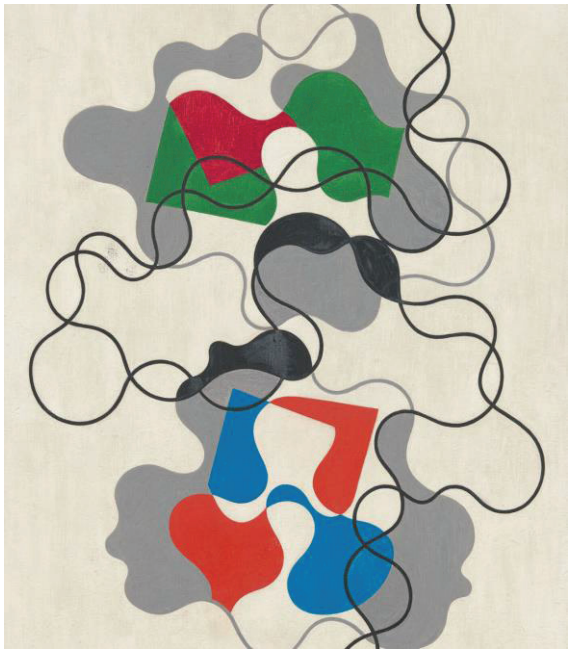
The chairs were rickety. So I rummaged around the kitchen drawer, extracted an old knife and used its tip to drive a few screws back into the wood. The knife kept on losing grip and I kept on swearing. The fastest and least infuriating way to have done the job would have been to go down to the cellar and find a screwdriver. Both utensils can be used to drive in screws, but one has been intentionally manufactured to perform just that, simultaneously reducing the time and energy involved. Nature, too, has its screwdrivers. Given time and chance, it will always take the opportunity to select a commodity which will make things, if not easier, at least more in tune with what is needed. One example: ribosomes are huge molecular complexes whose role is to synthesize proteins in cells. Until recently, it was thought that all ribosomes were alike. A bit like kitchen knives. However, it turns out that some ribosomes differ slightly in their makeup and are found only in certain kinds of cell – presumably because they synthesize proteins particular to these cells. One such ribosome has been discovered in sperm cells, along with a protein known as large ribosomal subunit protein eL39-like*, or RPL39L.



Lines of Summer (detail), 1942
by Sophie Taeuber-Arp

Ribosomes are among the most fundamental molecular complexes to be found in organisms. And with good reason: they are where cells synthesize proteins. Ribosomes are themselves an assemblage of various proteins mingled with RNA, known as ribosomal RNA (rRNA). And yes, ribosomes need ribosomes to synthesize the proteins that are part of their own constitution. From bacteria to fungi, plants, insects and mammals, ribosomes are all built according to the same architectural plan: one large subunit, one small subunit, and a handful of rRNA. Prokaryotic ribosomes are composed of one large subunit, itself a complex of about 30 proteins and two rRNAs, and a small subunit of about 20 proteins and one rRNA. In eukaryotes, the large subunit is characteristically composed of 47 proteins and three rRNAs, and the small subunit of 33 proteins and one rRNA.

Uniting as many as 47 proteins and three rRNAs into one large ribosomal subunit – which does not fall apart and performs the multiple tasks involved in protein synthesis – demands careful assembly. Making a ribosome is like building a factory while also hiring employees to carry out different tasks. In eukaryotes, everything begins in the nucleolus, a region located within the cell nucleus that is dedicated to the first steps of ribosome formation. Here the rRNAs are prepared and added to pre-ribosomal proteins. Both the small and the large subunits then begin, independently, to migrate towards the cell cytoplasm, where they will finally bind to one another, ready to do their job. During their migration, the subunits slowly mature as the parts which make them up are folded, processed, rotated, checked and finally channelled through the nuclear membrane.

In ribosomes, each protein has a different role – as do the rRNAs. Certain proteins are needed to stabilize the overall architecture while others help the large

and small subunits assemble, and of course you have the proteins that are involved in exporting the ribosome from the nucleolus to the cytoplasm in the first place. Then you need the proteins that take an active part in protein synthesis *per se* – a process so incredibly delicate and intricate, it takes any student days, if not weeks, to grasp. Briefly – so much so, it may seem criminal – to synthesize one protein sequence, ribosomes read and translate (into amino acids) genes from their mRNA. The required amino acids are taken from the cell cytoplasm by tRNAs and added, in the correct order, to a growing protein chain which protrudes from a spot on the large subunit of the ribosome. A spot known as the nascent polypeptide exit tunnel, or NPET. When the sequence is complete, the protein slips out of the NPET and is sent to where it is needed in the cell, or outside the cell. What do rRNAs do? Like proteins, certain RNAs also have roles. In particular, rRNAs help ribosomes assemble the amino acids in the correct order – which is of utmost importance. With all the molecules and the many steps involved in protein synthesis, needless to say, it is one of the most costly activities of a cell, lapping up over 70% of its energy!

Around the NPET, ribosomes do an extra bit of quality checking, to make sure that the genes have been correctly read and their sequence properly assembled. If they have not, the faulty nascent chain is directed towards another part of the cell where it is disposed of. Recently, researchers discovered that the very end of NPET in mammalian sperm cells differs from its counterparts and seems to have become specialised. As in other cells, protein sequences are double-checked in sperm NPETs, but sperm NPETs also seem to keep an extra good look out for proteins that are essential for sperm function. This would imply that sperm NPETs do not serve the exact same purpose as NPETs in other ribosomes, which turns out to be the case. A protein known as RPL39 is usually located in NPETs where it forms part of the wall. In mammalian sperm, RPL39 has been replaced by a paralog, termed RPL39L.

RPG39L illustrates well the advantage of heterogenous ribosomes. Though RPL39L and its paralog RPL39 differ by only three amino acids, it is enough to impart to RPL39L roles that are advantageous to sperm. What is more, RPL39L and RPL39 are not interchangeable as is often the case with paralogs, further suggesting that RPL39L is cell-specific. RPL39L seems to have been tweaked to monitor the well-being of sperm in particular. In which way? Sperm motility requires a lot of energy. Few cells need to travel so far – what is more by their own means – to reach their destination. Such a trip requires energy, or ATP, which is produced by a cell's mitochondria. It so happens that RPL39L has a role in mitochondrion formation. In its absence, the organelles are malformed and sperm motility is defective. This could be explained by a role for RPL39L in double-checking the correct formation of mitochondrial proteins in the NPET. Moreover, RPL39L also seems to be involved in the faithful assembly of the large ribosomal subunit which, besides quality checking, is paramount to protein synthesis.

At the very heart of what could be defined as life, ribosomes represent the elemental passage from DNA to protein. The need for protein is unending within any living organism as each of our activities – visible or invisible – requires it. Cell homeostasis, on which life depends, relies on protein homeostasis. So, too, does sperm motility, and hence fertility. If sperm are unable to wriggle and swim because their flagella are not beating properly, they will never reach their destination. Or if they do, they may not have the wherewithal to fight and forage their way through the egg's coat and fertilize it. RPL39L could therefore constitute a therapeutical target to help counter infertility – at least the type of infertility caused by sperm that lack stamina.

** this is the protein's new name which will be used from July 2023; otherwise, it is known as: 60S ribosomal protein L39-like*

Cross-references to UniProt

60S ribosomal protein L39-like / large ribosomal subunit protein eL39-like, *Homo sapiens* (Human) : Q96EH5
60S ribosomal protein L39-like / large ribosomal subunit protein eL39-like, *Mus musculus* (Mouse) : Q9CQD0

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PMID: 34825148

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