Unusual protein production found in trypanosome mitochondria

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Scanning electron micrograph picture of a trypanosome. Credit: Dr. Christopher Jackson - IKELOS

Mitochondria, the power plants of the cell, have their own protein factories, although the cell apparatus could easily do the job for them. A

special species of eukaryotes even has all the transfer-RNA it needs for protein assembly promptly delivered. Researchers from the University of Bern have now uncovered how this highly unusual import mechanism works in detail.

There are two reasons why trypanosomes, little unicellular organisms, are of special interest for researchers. For one, trypanosomes cause various diseases, including the fatal human sleeping sickness, for which still no good treatment is known. But maybe even more interesting are the unique biochemical features of trypanosomes. Understanding the deviations in basic mechanisms in these organisms can produce valuable insights into the characteristics of our own cells.

Mysterious effort for a protein machinery

One of these mysteries has proven to be especially intriguing for the research group of André Schneider from the Department of Chemistry and Biochemistry of the University of Bern. It has to do with mitochondria, the power plants of the cell. These organelles are thought to have been independent lifeforms in the early eras of evolution, eventually kidnapped by other cells. That is why they still possess their own gene material and the associated machinery to fabricate proteins. Mitochondria could therefore have a certain autonomy in their function, but they are making only very spare use of it.

In human cells, the mitochondrial genome contains only 13 protein-coding genes, whereas about 1500 other proteins are produced by the normal cell machinery to be imported into the mitochondria later. Why all this effort to run protein machinery if they could just as well obtain all the proteins from an external source? This is even stranger in the case of trypanosomes. Scientific consensus is that this import business works for proteins only – the tRNAs necessary for the fabrication of mitochondrial proteins need to be produced by the the mitochondria

itself. But strangely enough, the trypanosome mitochondria are lacking all the genes for this task – apparently, the factory has to be provided with these components as well.

Hypothesis proven wrong

The researchers from Bern and their colleagues from the Universities Freiburg and Bremen were fascinated by this – and they decided to figure out how these tRNAs find their way into the mitochondria. "By the book, you would expect that on a molecular level, all the processes in mitochondria are very similar across all eukaryotic species – but in this case, there are striking differences," says André Schneider.

This is interesting from an evolutionary point of view, as well: Understanding these differences can reveal the history of evolution in detail. Recently, the group has been able to show that the protein import channels in the membranes of mitochondria are used for the import of tRNA, as well. This has been suggested before, but with the hypothesis that tRNA would be something of a stowaway, smuggled into the mitochondria in complex with a protein. With the help of several experiments, this theorized mechanism in trypanosomes has now been shown to be wrong: tRNA import is independent from imported proteins. How, exactly, the import channel accomplishes this supplementary task will be the subject of future research.

These insights might lead to new paths in pharmaceutical research. The big problem with sleeping sickness therapeutics is that these trypanosome pathogens are eukaryotes as well, just like us humans. So their cell function is closer to that of our cells than that of bacteria, for instance. This makes it much harder to find efficient drugs without too many serious side effects. If researchers can find ways to block this newly discovered import function, it could lead to new drug targets.

On the other hand, André Schneider could imagine a kind of 'upgrade' for human cells, as well: by using experimental tricks, perhaps tRNA import could be switched on in human cells. This would open up new therapeutic options for mitochondrial diseases by the means of gene therapy, which often makes use of RNA. Today, it is not possible to get these therapeutical agents into the mitochondria.

RNA is pivotal for many vital processes and much more complex than initially assumed. For instance, RNA defines the conditions in a cell under which a given gene is or is not activated. If any part of this process of genetic regulation breaks down or does not run smoothly, it can cause heart disease, cancer, brain disease and metabolic disorders.

More information: Moritz Niemann et al. tRNAs and proteins use the same import channel for translocation across the mitochondrial outer membrane of trypanosomes, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1711430114

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