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> ONE MONTH, ONE PROTEIN <

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wrong place

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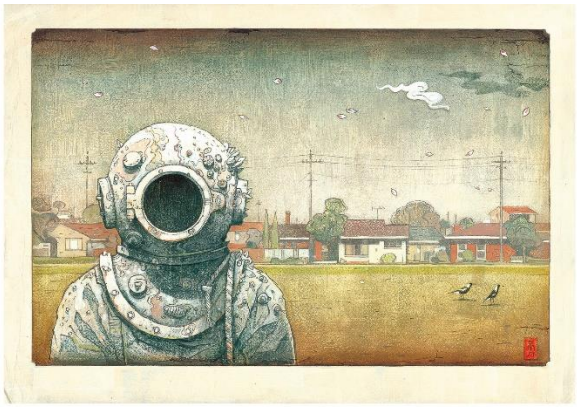
When you reach a certain age, one question arises on a painfully regular basis. It begins with a "Where are my…?" or a "Where is my…" Reading glasses are a constant. Frequently, they are not where they ought to be. Having relocated them, you may well remark that they are not where you put them. But they are. The thing is, in a moment of distraction, you left them where you would not normally: on the garden wall, in your coat pocket, on the clothes washing machine, perhaps even in the fridge. All in all, they were inadvertently mislocated. On a far smaller scale, the same kind of thing can happen to proteins. There are times when proteins end up where they should not be – which is a source of stress both for their unusual environment and the one they have not reached. Over time, cells have developed various quality control systems to correct all sorts of mistakes – one of them being mislocation. As an illustration, lodged in the endoplasmic reticulum membrane, the enzyme P5A-ATPase is able to spot mislocated transmembrane mitochondrial proteins, grab hold of them and fling them back into the cellular cytosol.



'The Visitor' by Shaun Tan

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Every cell is a metropolis in itself – with motorways running from one end to the other, bodies travelling along them, buildings going up and some coming down, and scaffolds being erected while myriads of entities get on with the business of breaking down, assembling, inhibiting, stimulating, folding, transporting, denaturing, translating, binning, sorting, orchestrating… Proteins constitute, without a doubt, one of the cell's most precious components in that they do most, if not all, of the work. However, every single protein must go to the right place to get on with what it has been programmed to do. There would be little advantage in sending a cobbler to work in a bank. So how do proteins end up in the right place? It all has to do with 'protein signaling' or 'protein targeting'.

For many years, scientists wondered whether the ribosomes sent the newly synthesized proteins to their destinations, or whether the proteins themselves knew the address. It was an issue of great biological importance, which was clarified in the 1970s following studies undertaken by the German-American biologist Günter Blobel. Targeted proteins know themselves where to go thanks to a 15 to 30 amino-acid sequence they carry and which forms what has been dubbed a 'signal peptide' or 'transit peptide'. In essence, a signal/transit peptide is a tag on which is written the protein's destination. It turns out that there are three kinds of tags. The first – and the most frequent – is situated on the N-terminal or the C-terminal end of a nascent protein. The second kind of tag requires additional specifications because the address held within it is not sufficient – there lacks a postal code, or the street number. This occurs by way of protein modifications, such as glycosylation for instance. The third type of peptide signal is formed thanks to an assembly of 'signal patches'. In this case, a number of incomplete, so to speak, signal peptides are scattered within the protein. The address is completed once the protein folds into its 3D conformation and the patches join, as in a puzzle, to complete the tag.

Though the destination they must reach is written on them one way or another, proteins need other molecules – sometimes many others – with whose help they are finally delivered to the correct port of call. Like our own mail, the chances of a protein ending up at the wrong address are bound to occur from time to time, and if there is no kind of quality control, things will gradually go wrong: parts of a cell will begin to stutter, and perhaps even end up failing completely. So how do cells correct mistakes? In a variety of ways; one illustration is the transmembrane helix dislocase P5A-ATPase.

P5A-ATPase is lodged in the endoplasmic reticulum (ER) membrane and belongs to the P-type ATPases family of active transporters whose primordial function is to drive ions or lipids across membranes. P5A-ATPase, however, does not seem to transport ions or lipids, and has a particularly large substrate-binding pocket suggesting that it transports something else. Like other members of the family, the pocket has an opening towards the ER lumen or to the cytosol depending on its dynamic state, but it also has a lateral opening onto the ER lipid bilayer. This suggests that its role may be to transfer molecules located within the actual membrane to the cytosol. Mitochondria and the ER interact closely with each other, which is why mitochondrial proteins may sometimes end up at the wrong address. As ER proteins may too. In particular, P5A-ATPases seem to be able to spot, specifically, tail-anchored transmembrane mitochondrial proteins which have, despite their natural fate, managed to slip into the ER membrane.

Like all P-type ATPases, our dislocase is rather a bulky protein which crosses the ER membrane a dozen times, from which protrudes a characteristic arm-like domain. During ATP-driven ion and lipid transfer, P-type ATPase substrate pockets undergo an important conformational change alternating between a V-shape and a U-shape. Such a change also occurs in our dislocase but the lateral opening is not affected and swings between the cytosol and the ER membrane. This swing is interpreted as the mechanism P5A-ATPase uses to transfer mislocated proteins in the ER's lipid bilayer out into the cytosol. How exactly? By grabbing hold of a short segment of the mislocated protein that dangles in the ER lumen, and literally pulling on it to fling the protein back into the cytosol, much in the way you would sling a ball to the other side of a street by the end of a short rope attached to it. It is a very elegant way of dealing with unwanted material, and it may be that the mislocated protein is actually re-targeted to its correct destination, i.e. the mitochondrion itself.

Cells have a variety of much-needed quality control systems which have developed over time and throughout all kingdoms of life. Take protein synthesis, for instance, which makes use of such systems at every single step to ensure that a gene is correctly transcribed and then translated, and that the product is not only processed the way it should be but also targeted to the right place. A cell's organelles – its nucleus, the mitochondria, the endoplasmic reticulum, the Golgi apparatus to name but four – each require myriads of different proteins to function properly, both within their membranes and in their lumens. It is not difficult to understand, then, that not only must these proteins function properly but that they need to be in the right place. It is a question of organ and cell homeostasis. And, in the end, life itself.

Cross-references to UniProt

Endoplasmic reticulum transmembrane helix translocase, *Homo sapiens* (Human) : Q9HD20
Endoplasmic reticulum transmembrane helix translocase, *Saccharomyces cerevisiae* (Baker's yeast) : P39986

References

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