proteinspotlight
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Issue 205, July 2018
www.proteinspotlight.org

life, a subtle balance

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Life is a continuous balance between what needs to remain, and what must disappear. We are not aware of it but our bodies unceasingly shed cells that have received orders to die, which is a necessary process if tissues are to be renewed or to stay healthy. It does seem an odd paradox, but this surprising phenomenon is an integral part of every living being and known as regulated cell death. There are different ways of dying, and cells are imaginative. One of the more select ways has been coined ferroptosis. Ferroptosis occurs when the level of iron-dependent lipid hydroperoxides has become toxic for a cell, which is then left to perish. But before this occurs, cells have to be equipped with the necessary means to prevent precocious poisoning, or they will never be able to get on with what they are expected to. This regulation of the level of toxins is ensured by a special version of an enzyme known as glutathione peroxidase 4, or GPX4, that carries a very rare amino acid in its active site: selenocysteine.

"Le Funambule"

engraving, by Claude Weisbuch

Just like humans, cells have many ways of drawing their last breath. They can be hindered by accumulated toxins in their cytoplasm, or any part of their replication machinery and vital metabolic pathways can be impeded one way or another. Characteristically, a cell that has died shrinks in size, large blebs sprout from its membrane, its nucleus falls apart, or its DNA fragments into many parts. There is much talk among researchers about the peculiar, yet essential, necessity for cells to know how and when it is time to go, and the way they ultimately choose to die has been classified into several categories: apoptosis, autophagy, necroptosis, eryptosis, aponecrosis, NETosis… and ferroptosis. Ferroptosis involves the concentration of iron-dependent lipid peroxides in a cell's cytoplasm. When their concentration increases and becomes detrimental, the cell's membrane is damaged or other toxic products can be generated – unless it is checked in time.

GPX4-Sec blocks ferroptosis by way of a rare selenocysteine (Sec) residue lodged in the enzyme's active site. Selenocysteine is similar to the amino acid cysteine, differing only by the insertion of a selenium (Se) atom where you would normally find a sulfur (S) atom. Selenium is therefore responsible for adding another amino acid to the canonic twenty, which is why Sec is referred to as the 21st amino acid.

This sounds straightforward enough, but if you have spent hours understanding how a gene is transcribed and then translated into a protein, you may be wondering how and what pops Sec onto the nascent amino-acid sequence. What, for instance, is its genetic code? The answer: UGA. But UGA is usually a stop codon. So how does this work? For Sec to be part of a protein, UGA is tricked into not

being read as a stop codon. The codon, itself, is not modified but a special Sec insertion sequence (SECIS) is slipped into the gene immediately after the UGA stop codon. A SECIS has a stem-loop like structure that acts like a set of traffic lights which, instead of turning red, shift to green and whisper to the ribosome: "Keep going, ignore UGA, don't end protein synthesis here but grab a Sec residue instead, and move on."

The biological role of selenium had been extensively documented since the 1930s. It gradually became apparent, however, that Se was also incorporated into certain proteins – coined selenoproteins – but it was only in the 1970s that the American biochemist Thressa Stadtman described exactly how, when she uncovered the existence of Nature's 21st amino acid: selenocysteine. Though a rare occurrence, and not present in every organism, selenoproteins are spread across all three kingdoms and about 50 have been identified to date. Their very existence remained a conundrum for years since selenoproteins all seem to have a "normal" cysteine homolog which, apparently, carry out the same job and just as efficiently. Until several scientists unveiled the unique and essential role of selenocysteine in a particular Sec-containing glutathione peroxidase 4: GPX4-Sec.

GPX4-Sec is a medium-sized protein, barely 200 amino acids long. It belongs to what has been dubbed the selenoenzymes because the Sec residue is part of the enzyme's active site and has therefore an essential role in its activity. The presence of GPX4 in a cell helps to reduce the concentration of lipid peroxides that are harmful to a cell. GPX4-Sec specifically prevents ferroptosis, i.e. cell poisoning caused by an over-accumulation of iron-dependent lipid peroxides. How exactly GPX4-Sec does this is still a mystery. Does the enzyme clean up the toxic mess? Or does it have more of a protective role against it? What came as a surprise is that, unlike other selenoenzymes, GPX4-Sec cannot be replaced by its cysteine-containing homolog. Researchers realised this while studying the role of GPX4-Sec in interneurons, brain cells that act as relays between neurons. Mice embryos did develop normally with GPX4 in which Sec had been replaced by Cys, but after birth the mice were prone to seizures and had to be sacrificed. To cut a rather long story short, this would imply that the chemical element selenium is essential for life.

Not so long ago, selenium was believed to be a highly toxic nutrient that could cause hair loss, diarrhoea, vomiting and even cancer. Today, we know that, once incorporated into an enzyme, it can actually sustain life. A huge responsibility for one chemical element… Nevertheless, evolution has chosen a very costly way of dealing with ferroptosis. It takes just that little more energy and effort to turn a stop codon into a "don't mind me" codon, while making minor transformations to the replication machinery for a Sec residue to be added to a nascent protein sequence. Why would you do things in such an energy-consuming way? Can ferroptosis not be prevented otherwise? Well, it may be less a question of preventing ferroptosis than the need a cell has for iron, which may be important in cell-signalling say some scientists. Ferroptosis would then simply be an unfortunate side effect. Whatever it is, Nature has decided to bear the costs and keep selenocysteine in a few select proteins. And she no doubt has her reasons.

Cross-references to UniProt

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Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).