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Bioinformatics in Action

on a tightrope

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Too much of anything is never good. Excess alcohol, and our faculties are impaired. Excess heat, and drought spreads. Excess cold, and vineyards die. Too much, too, of what is paradoxically essential to life frequently turns out to be toxic. Consider oxygen, iron, zinc or vitamins to name but four. Though we may be acquainted with the symptoms of what 'too much' entails, these are merely the superficial echo of cells under stress. Over the aeons, and throughout the living kingdom, organisms have had to deal with periodical over-abundances of many things. While selecting systems to use them in small doses, they promoted others to keep them in check. As an illustration, iron is vital for ferrying oxygen in organisms, and it is crucial in DNA synthesis, DNA repair and other fundamental cellular processes. Yet, too much iron will kill a cell – a process known as ferroptosis. Though this may be an ideal way of ridding a tissue of unhealthy cells, alternative processes have also evolved to stabilise things and prevent ferroptosis. One of these processes involves a protein known as ferroptosis suppressor protein 1, or FSP1.

Danseuse, by Helen Phillips

The Annex Galleries, Santa Rosa, California

Ferroptosis is defined as the death of a cell brought about by an overwhelming presence of iron. Though iron is vital for all species – as it is required to transport and deliver oxygen to organs, to ferry electrons in mitochondria or as a cofactor for instance – too much of it can be toxic as it can hinder a cell's antioxidant capacity. This means that noxious 'lipid reactive oxygen species' begin to accumulate, ultimately leading to oxidative cell death where, in the case of ferroptosis, plasma membranes typically rupture and mitochondria shrink while the cells, swell. This is unlike other programmed cell deaths, such as apoptosis for instance where cells typically bleb and diminish in size, which is why scientists regard ferroptosis as a category apart.

What exactly is meant by 'oxidative cell death'? In the case of ferroptosis, this implies lipid peroxidation that is driven by an iron-containing enzyme lipoxygenase. Lipid peroxidation involves the degradation of lipids caused by the addition of molecular oxygen which attacks their carbon-carbon double bonds. As the main constituent of plasma membranes are phospholipids, these present an ideal target for peroxidation modification which interferes not only with the assembly of plasma membranes but also with its structure and dynamics. As a result, if nothing is done to counter peroxidation, plasma membranes are damaged and the cell eventually dies.

Molecules known as antioxidants regulate the level of oxidation in a cell. CoQ_{10} is one. When CoQ_{10} was first discovered, it was called 'vitamin Q_{10}', where 'Q' stands for 'quinone' and '10' refers to the number of isoprenyl chemical subunits in the molecule's tail. In time, vitamin Q_{10} was renamed 'ubiquinone' because of its ubiquitous presence in lipid membranes. CoQ_{10} is a lipid-soluble antioxidant meaning that it can slip into the plasma membrane of

cell organelles, such as the mitochondrion, the endoplasmic reticulum or the Golgi apparatus. Here, ubiquinone must remain in a reduced state – $CoQ_{10}H_2$ also known as ubiquinol – so as to halt the propagation of lipid peroxides. How is ubiquinol kept in a reduced state in animals? Thanks to FSP1.

Ferroptosis suppressor protein 1 (FSP1) is an enzyme or, more specifically, a CoQ_{10} plasma membrane oxidoreductase. This is where the 'Co' springs from in CoQ_{10} since the molecule is also referred to as 'coenzyme Q_{10}' as it is required by FSP1 for its catalytic activity. Like its coenzyme, FSP1 is also present in plasma membranes and probably targeted there thanks to a post-translational modification known as myristoylation which is the addition of a long fatty acid at the enzyme's N-terminus. Myristoylation not only directs FSP1 towards plasma membranes but also helps it squeeze between the phospholipids. So now we have CoQ_{10} and FSP1 in the plasma membrane – and all we need to suppress ferroptosis is a source of hydrogen which is supplied by the omnipresent and universal cofactor NADPH. Thanks to NADPH, FSP1 can produce the reduced form of ubiquinone, $CoQ_{10}H_2$ or ubiquinol, which is then armed to fight lipid peroxidation.

Having sorted out this rather complex biochemistry, another molecule popped up: vitamin K. Vitamin K, like CoQ_{10}, belongs to the family of quinones and is prescribed in substantial doses to patients taking warfarin, a popular blood thinner. Why? Because vitamin K counters warfarin poisoning – but no one really understood why. It turns out that vitamin K is also involved in suppressing ferroptosis. Indeed, vitamin K and CoQ_{10} happen to share similar structural properties. Consequently, vitamin K can take the place of CoQ_{10} in FSP1, where it is reduced. The resulting reduced vitamin K (VKH_2), like $CoQ_{10}H_2$ is also a potent inhibitor of lipid peroxidation. Scientists then realised that the reduction of vitamin K led by FSP1 is also responsible for the effect vitamin K has against warfarin poisoning.

Cells are able to cope with certain levels of lipid peroxidation; it just must never reach levels that become detrimental to the cells. It all comes down to equilibrium. This said, FSP1 is not the only enzyme involved in taming ferroptosis; there are other pathways too, each of which seem to supplement the other. In recent years, medical scientists have taken a growing interest in ferroptosis as it seems to be at the heart of neurodegenerative diseases such as Alzheimer's and Parkinson's but also diseases like cancer. Promoting ferroptosis could kill cancer cells for example while, in neurodegenerative diseases, checking ferroptosis could keep neurons alive. This would make FSP1 an ideal therapeutic target besides proving, perhaps, to be a good biomarker.

Life certainly tiptoes along a narrow tightrope. From an evolutionary point of view, the involvement of components as biologically vital as iron and vitamin K in ferroptosis is intriguing. Iron has an essential role in life that dates back billions of years. When oxygen started to accumulate in the Earth's atmosphere and organisms began to use oxygen to drive many of their vital processes which were already dependent on iron, they were concomitantly building one of Nature's conundrums: she was going to have to find a way of keeping toxicity at bay. In this light and long before the existence of FSP1, vitamin K could actually be the most ancient member of anti-ferroptotic quinones since ferroptosis is a cell-death mechanism that has been conserved from prokaryotes to plants and mammals. Fascinating.

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