proteinspotlight
> ONE MONTH, ONE PROTEIN <

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support

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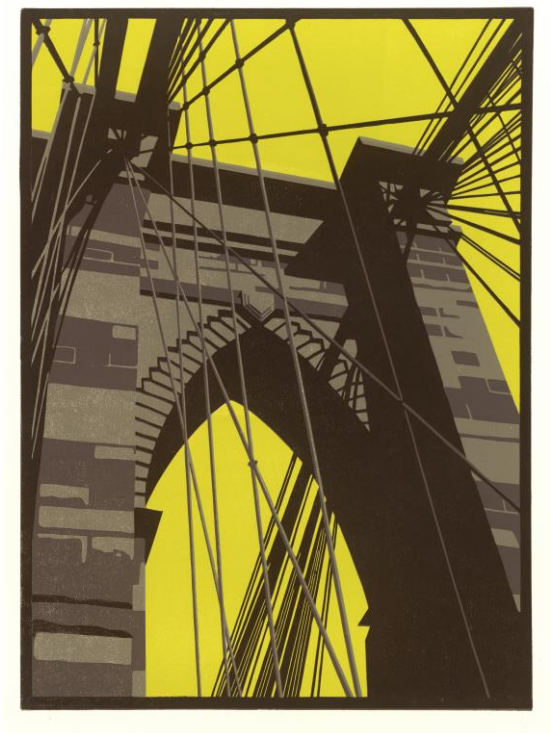
You've arrived at the supermarket, and your trolley token is missing. It's not where you usually keep it – on your keyring, or in your bag. Flustered, you search for something to replace it. A coin of sorts. What you find, thank goodness, fits. So, you pull your trolley away from its fellow partners feeling both relieved and gratified. What you have just done is put something right that could have gone wrong. And you did it by way of an intermediate that mimicked what lacked. Situations such as these sometimes occur inside us. Enzymes may be temporarily out of order – not because they are deficient in any way but because their substrate is lacking. As a result, they do nothing. This has been shown to happen to UXS1, an enzyme involved in forming part of our extracellular matrix which is crucial to our well-being. In the absence of an intermediate compound (UDP-4-ketoxylose), UXS1 remains inactive – which can create downstream complications. However, researchers discovered that a second enzyme, TGDS, comes to the rescue by producing an intermediate (UDP-4-keto-6-deoxyglucose) that is able to replace the one that is missing. UXS1 is thus revived and can resume its role.



Brooklyn Bridge by Paul Catherall

courtesy of the artist

The extracellular matrix (EM) is the matter in which all cells are immersed. Until the early 1900s, the EM was described as connective tissue because it was, clearly, a tissue that connected an organism's outer skin, inner organs and skeleton to one another. Its nature was also fibrous – something that had been observed for centuries. In fact, in the Middle Ages, a living organism was thought to be a sum of fibres of different kinds that were organised in different ways. Such an arrangement kept an organism's global internal architecture together while allowing the flow of fluid, gas and various other secretions. This led to the belief that life must arise spontaneously from within such fibres; a theory which has been dubbed the fibre theory of life. Surprisingly, at least with the knowledge we now have, the fibre theory lasted until the early 1800s when the German naturalist Lorenz Oken stated that life, surely, can only arise from life.

It was around this time that scientists began to understand the internal organisation of cells. Cells, it seems, were the seat of life. Then cells were spotted in connective tissue, which gave the fibre theory its last blow. The cellular theory of life surfaced – a theory which fitted beautifully with the idea that life can only emerge from life. Scientific interests shifted: is anything going on between cells and connective tissue? If so, what? Answers began to surface in the 1930s with the development of chemical and physical methods that assisted scientists in characterising the molecules which made up the connective tissue. It was during these times that the term 'extracellular matrix' began to replace that of 'connective tissue' as it became gradually apparent that the cells themselves

were secreting the substances they soak in. Thanks to the continuous evolution of technologies since the beginning of the 20th centruy, we now know that the extracellular matrix is not just a listless mass whose only role is to support what bathes in it. In fact, it turns out that cells are dependent on the EM they make, as the EM is dependent on the cells that make it. One cannot survive without the other.

The EM is a complex network of fibrous proteins and polysaccharides that fills in the space between cells providing them both with a means to anchor and mechanical support. But the EM does much more than that: it also mediates communication between cells as it regulates crucial cell activities such as migration, proliferation, differentiation and tissue repair. In particular, the main polysaccharide chains that constitute the EM are known as glycosaminoglycans (GAGs). GAGs form a kind of molecular sponge able to resist compression while providing cells with a bouncy support. But GAGs also keep the EM hydrated while forming a basis for cell-signalling and trafficking. These are two crucial tasks since faulty cell-signalling or trafficking can give rise to serious disorders – such as skeletal dysplasia, which affects the growth of bone and cartilage. Dwarfism is an example.

UDP-glucuronic acid decarboxylase 1, or UXS1, is an enzyme involved in synthesizing GAGs. In a first step, with the help of cofactor NAD+, UXS1 catalyses the decarboxylation of UDP-glucuronic acid to produce both the intermediate sugar UDP-4-ketoxylose and bound NADH. In a second step, UXS1 reduces the keto group of the intermediate sugar to produce bound NAD+ and UDP-xylose (uridine diphosphate xylose) – which is vital for producing GAGs. So, NAD+ remains bound to UXS1 and switches between a reduced and an oxidised state depending on the enzyme's activity. Sometimes, the UDP-4-ketoxylose intermediate escapes (!) thus leaving UXS1 twiddling its thumbs, unable to continue its job because its cofactor has been reduced (NADH) and there's nothing to restore it to its oxidised form. UXS1 needs NAD+ to be active.

It so happens that a second enzyme, UDP-D-glucose 4,6-dehydratase (TGDS), which is geographically close to UXS1 in cells, converts UDP-glucose to UDP-4-keto-6-deoxglucose. Now, just like the coin you used to replace the trolley token, UDP-4-keto-6-deoxglucose can act as UXS1's intermediate and oxidise NADH so that UXS1 can complete its cycle and produce UDP-xylose – vital for GAG formation. Why not provide UXS1 with some of its cofactor NAD+, you may wonder? Scientists suggest that it might have to do with the proximity of the two enzymes within cells. Like offering your hand to help your aging mother climb the stairs, if TGDS can lend a helpful hand to UXS1, why not?

UXS1 is thus involved in building the extracellular matrix, specifically by producing GAGs that are vital for an organism's development. UXS1 seems to be dependent on TGDS because, when lacking NAD+, TGDS provides UXS1 with a rescue metabolite. Such circumstances are particularly intriguing for scientists. The notion that a functionally-deficient enzyme could lead to downstream damage is straightforward enough. But what if various metabolites (such as UDP-4-keto-6-deoxglucose) that are produced by our own metabolism, or that come from food we eat or from our microbiota, can mimic enzyme substrates? What if such mimics were the cause of enzyme inactivation and clinical symptoms? It is something for researchers to reflect upon. Alternatively, a greater understanding of substrate mimics, similar to those that occur between TGDS and UXS1, could help in the development of therapeutic approaches to reactivate enzymes whose inactivation is the cause of a disease – such as Catel-Manzke syndrome, a hereditary skeletal disorder precisely caused by TGDS deficiency.

Cross-references to UniProt

UDP-D-glucose 4,6-dehydratase, *Homo sapiens* (Human): O95455
UDP-glucuronic acid decarboxylase, *Homo sapiens* (Human): Q8NBZ7

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