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> ONE MONTH, ONE PROTEIN <

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on a tangent

Vivienne Baillie Gerritsen

Years ago, primatologist Jane Goodall described wild chimpanzees using sticks to fish for termites. Inserting the tips into a mound, the chimps then withdrew them covered with termites, which they conscientiously pecked off the wood the way humans peck at corn on the cob. The news was ground-breaking in animal behaviour circles because it showed that great apes showed signs of being just as smart as their close cousins, humans, by using tools to help them in their daily chores. Using tools – and even more so, crafting them – to make life easier is a form of intelligence. Perverting something from its original purpose, such as a branch, so that it can be used to one's advantage is yet another form of intelligence, and it is a phenomenon that is widely used by living beings across all kingdoms. Even on the molecular level, cells sometimes acquire the capacity to divert metabolic pathways for their own benefit. Tumour cells show particular skills in this way and will literally hijack biological molecules to do this. An example is the enzyme PCK1, a phosphoenolpyruvate carboxykinase, whose major role is to produce glucose and which certain cancer cells, for their survival, subvert to produce mainly fats.

The Escalator (linocut)

Cyril Edward Power (1872-1951)

In Nature, examples of entities – for want of a better word – whose original role is deflected to make living easier, are many. A chimpanzee fishing for termites in the way humans scrape for the remains of the honey at the bottom of a jar is one example. But take species that are not so close to us, such as crows who, from a height, let walnuts still in their shells drop onto the tarmac below to smash them open and recover the nut inside. Or spiders who anchor their webs to the corners of window frames or in between the iron rods of gates to catch a distracted insect. Or ivy that uses garden walls or neighbouring trees to grow and reach more light. Or viruses, possibly the supreme example, which make a living out of deflecting the activities of entire cells.

In the case we discuss here, the enzyme phosphoenolpyruvate carboxykinase (PCK1) which is known to trigger off the production of glucose – a process known as gluconeogenesis – is side-tracked by cancer cells to favour the production of lipids, a process known as lipogenesis. In the first case, a cell will produce more sugar; in the other, more fats. What difference does it make? Gluconeogenesis occurs when an organism needs energy as, for example, during periods of fasting or starvation, of intensive physical effort or when food lacks carbohydrate. The trick is to generate glucose from non-carbohydrate carbon substrates, and it is a process which is used throughout all kingdoms – plants, animals, fungi and bacteria. Lipogenesis, on the other hand, produces fats which, like glucose, are also a source of energy. So why prefer one source of energy to another? The thing is, besides energy, fats are the main constituent of membrane phospholipids, the essential components of cell membranes – and of course tumour cell membranes.

As for all metabolic pathways, dozens of different enzymes are involved in specific steps, gradually breaking down or building up a given metabolite. Under normal circumstances, PCK1 which is situated

in the mitochondrion, activates one of the upstream events in gluconeogenesis by catalysing the formation of phosphoenolpyruvate (PEP) from oxaloacetate with the help of GTP – or ATP in plants, bacteria and fungi. There is little sequence identity between the mammalian and bacterial enzymes but residues at the active site have been conserved across all species. Once PEP has been formed, it continues to undergo a series of modifications, finally producing glucose.

In animals, PCK1 actually plucks an atom of phosphorus off GTP to phosphorylate oxaloacetate and form PEP. In order to do this and without causing any dramatic conformational change in PCK1, GTP lodges neatly into a guanine-binding pocket on the enzyme's surface. Once inside, GTP is held firmly in place by way of three phenylalanine residues, where it gives up one phosphorus to make PEP. This is the enzymatic reaction PCK1 is known for. However, recently, scientists discovered that in certain cancers, PCK1 can itself be phosphorylated which sets it off on an unexpected path ultimately leading to the formation of fats, and not sugar.

How does it happen? When PCK1 is phosphorylated by tyrosine kinase, this causes the enzyme to translocate from the mitochondrion to the endoplasmic reticulum where it uses GTP to phosphorylate two proteins: INSIG1* and INSIG2*. This triggers the release of a small complex of three proteins already bound to them: SCAP* and SREBP1* and SREBP2*, which are then translocated to the Golgi apparatus where they separate. SREBP1 and SREBP2 are concomitantly activated, finally leading to the transcription of genes involved in lipogenesis. In a nutshell, the phosphorylation of PCK1 causes the enzyme to leave the mitochondrion and translocate to the endoplasmic reticulum where it triggers off a pathway leading to not to gluconeogenesis but to lipogenesis which is better at supporting and enhancing tumour cell proliferation.

It may well be that PCK1 has a lipogenic role in healthy tissues too. However, certain cancer cells seem to be able to increase lipogenesis significantly by pushing PCK1 firmly in that direction while diverting it from entering the process of gluconeogenesis. Metabolic pathways and gene expression are paramount in cell proliferation and, not surprisingly, have become the playing fields of tumour cells. As a consequence, the enzyme's unique guanine-binding site is an attractive target for drugs, and inhibiting PCK1 could provide a strategy in treating human hepatocellular carcinoma for instance. Likewise, with regards to gluconeogenesis, inhibiting PCK1 could help reduce glucose production in the treatment of the wide-spread disease, diabetes. As scientists are learning to twist nature to meet their needs, life – in its many forms, good and bad – has been doing it from the moment it emerged on this planet, finding a way to burgeon either by shunning what could hinder it or by shifting the power to its side.

**the full names of each of these proteins can be found in Ref.1*

Cross-references to UniProt

Phosphoenolpyruvate carboxykinase, cytosolic [GTP], *Homo sapiens* (Human): P35558

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