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# constructive futility

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**Idleness is not encouraged in our parts of the world. With our twisted notion of *Carpe diem*, the days are filled with things we have to do and things we would like to do. Many of which we do. Adolescents, lost in the depths of a settee, are told by their parents to "go out and do something". Dreamers are told that they are wasting their time. The only time a lack of productivity is tolerated is when, lying on our back in a cot, we can stare for hours on end at objects dangling above us. This is because we know that though, for adults, it may just be a case of suspended shapes, for a baby it is like reading a book: the baby is learning, its senses are awakening. Nature, too, sometimes opts for what may seem counter-productive. Though life usually depends on a subtle balance between what is produced and what is gained with as little loss as possible, there are instances when the production of excess is actually vital. Body heat relies on this. When temperatures drop, to keep our system warm, our body fat produces excess chemical energy which is not used but rather 'lost' in the form of heat. For this, fat cells need to kickstart a process known as the futile creatine cycle. One of the enzymes involved in such a cycle is 'tissue nonspecific alkaline phosphatase', or TNAP.**

Passion de lignes

Sophie Taeuber-Arp (1889-1943)

Were we to sit in a fridge, our body would have to maintain its temperature by producing heat to counterbalance heat loss – a process known as adaptive thermogenesis. This may bring a smile to your face but such experiments were actually carried out in the last centuries in an attempt to understand the physics and chemistry of heat. Towards the end of the 18$^{th}$ century, French scholars Pierre-Simon Laplace (1749-1827) and Antoine Levoisier (1743-1794) published a pioneering study on heat – *Mémoire sur la chaleur* – despite a winter that had not been as harsh as they had hoped. Their results, they suggested, would benefit scientists who lived further up North. The point of their study was to develop precise instruments able to measure heat, since heat increases and decreases and is therefore subject to calculation.

Though Laplace and Levoisier were developing ways of quantifying heat, they had no understanding of how heat was actually produced in organisms. For this, they would have had to wait another century or two. In fact, it is only recently that there is a renewed interest in brown fat tissue, whose primary function turns out to be thermogenesis and thermoregulation. How is body heat produced? Body heat relies on a sort of energy spilling by way of what has been called the futile creatine cycle. Futile cycles are defined as cycles in which chemical energy is dissipated without being used to perform mechanical or chemical work. In the futile creatine cycle, energy is dissipated in the form of heat.

Creatine is the organic compound thermogenesis depends upon. It is found in all vertebrates – especially in muscle and brain tissue which demand a lot of energy in the form of adenosine triphosphate (ATP). Phosphocreatine is both a shuttle and a reservoir of high-energy phosphate. When a muscle is being used for instance, the energy it needs is supplied by phosphocreatine which donates its phosphate group to

adenosine diphosphate (ADP) to form ATP. When muscle effort ceases, any excess ATP is converted to ADP in the reverse reaction, where creatine is phosphorylated to recreate phosphocreatine. These two reactions – dephosphorylation of phosphocreatine and phosphorylation of creatine – occur in a coupled manner and form the basis of the creatine futile cycle.

Brown fat thermogenesis needs a cycle such as the one described above, where the energy charge is not used to create subsequent work but simply dissipates it as heat. In turn, the cycle requires enzymes to phosphorylate and dephosphorylate creatine. Scientists knew about the creatine kinase that uses ATP to create phosphocreatine and ADP, but, until recently, they had not found which enzyme performed the reverse reaction. This turned out to be a tissue nonspecific alkaline phosphatase (TNAP) that hydrolyses the high energy charge of phosphocreatine to free a phosphorous compound. The existence of TNAP in the mitochondrion – came as a surprise since, up to that point, all TNAPs were believed to be anchored to cell membranes.

TNAPs belong to a larger group of alkaline phosphatases that have been classified into two types: tissue-specific and, precisely, tissue nonspecific alkaline phosphatases. Alkaline phosphatases located in the intestine, the placenta and germinal tissue are tissue-specific; those that are tissue nonspecific are found in the blood serum and travel throughout our system. Membrane-bound, all alkaline phosphatases catalyse the hydrolysis of organic phosphate esters to free inorganic phosphate. Though these enzymes are found in many tissues throughout the body – and probably present a diversity of roles via various post-translational modifications –, no one knows which pathways they are involved in. Save for the above-mentioned TNAP which is anchored not to cell membranes, as would have been expected, but to mitochondrial membranes!

TNAPs are enzymes whose active site requires three metal ions, namely one $Mg^{2+}$ and two $Zn^{2+}$. Acting as dimers, TNAPs are usually tethered, via a GPI-anchor, to the extracellular side of cell membranes. In brown fat cells, however, they are anchored in the same way to the inner mitochondrial membrane. A domain baptised the crown domain – because of its shape – mediates interactions either with the extracellular matrix or the mitochondrial matrix, depending on the TNAP's location, to produce inorganic phosphorous. In brown tissue, TNAPs initiate the futile cycle of creatine dephosphorylation and phosphorylation to produce thermogenic heat.

TNAPs are found in several tissues where they take part in various biological processes – namely bone and teeth mineralization but also the development of the nervous system with roles in visual, sound and olfactory perception. With such scattered locations, chances are that TNAPs are also engaged in pathologies related to them, such as atherosclerosis and age-related diseases like arteriosclerosis but also type-2 diabetes, cardiovascular diseases and loss of weight due to certain cancers. Adaptive thermogenesis, itself, has gained interest in the past few years because it could help develop targeted therapies against obesity in patients who have insufficient brown fat. Certainly, that body heat should be the fruit of something described as futile comes as a surprise because it is a form of futility most of us are happy to embrace when the cold of Winter kicks in.

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