proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 109, September 2009

www.proteinspotlight.org

another dark horse

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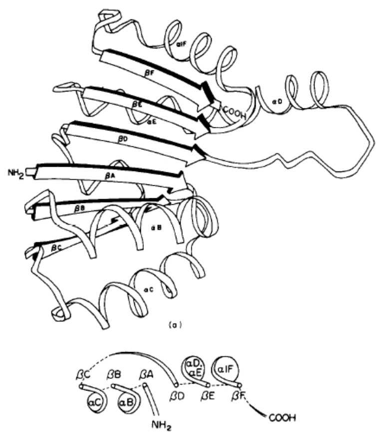
Life is sustained thanks to a continuous flow of chemistry within cells and between cells. Molecules of all shapes and sizes are being scooped up, modified, and released – albeit in a different form – to produce fuel, trigger off a metabolic process or indeed put an end to one, act as a messenger or simply become waste product. Until fairly recently, lactate was thought to be just that: a dead-end by-product following muscular effort for example. And for many a year, it was stashed away in the backs of minds as something which had no future. But it does. In the past decade or so, scientists have discovered that lactate has a life after all; it is not only being shuttled inside a cell but also from cell to cell, and may well have a role in telling our brain when a muscle is tired, or helping us to perceive muscular pain. As for most chemical entities, there are always proteins involved in binding to them, breaking them down or adding something onto them. One enzyme in particular is directly involved in lactate's career: lactate dehydrogenase, or LDH.



LDH monomer, illustrating two Rossmann folds, hand-drawn by the late Audrey Rossmann (ref.3)

Courtesy of Prof. Michael G. Rossmann

The study of lactate metabolism dates as far back as the 1700s when it was first isolated in 1780 by the Swedish chemist Karl Wilhelm Scheele (1742-1786) – a scientist who was in the habit of tasting what he had discovered, and may well have died at the early age of 43 because he licked a little too much mercury… Jöns Jacob Berzelius (1779-1848), yet another Swedish chemist and the man who coined the term 'protein' in 1816, offered the beginnings of an understanding of lactate metabolism. He was the first to observe that lactate accumulated following intensive activity. This was seen as a sort of passive poisoning of the body which brought on exhaustion. As a consequence, lactate's role was not seen as a constructive one and, for the best part of 200 years, it was considered a waste product. However, in the past few years, scientists have shown that lactate is not just a useless by-product of exercise but that it is actually a mobile metabolite, able to move within a cell, travel from cell to cell, and even extend its travellings to other organs.

Lactate dehydrogenase, LDH, is the key enzyme in lactate production. It can make pyruvate from lactate, or lactate from pyruvate, with the concomitant production of NADH or NAD+. And when concentrations of lactate are high – as in intense exercise for instance – the excess lactate creates a negative feedback on LDH, thereby decreasing its activity. Present in all kingdoms, LDH has many isoforms, which are all tetramers of two different kinds of subunit: the H (from heart) subunit, or the M (muscle) subunit. It is the combination of these subunits which give a specific LDH its properties. Typically, tetramers of M subunits only have a turnover which is twice that of tetramers made up solely of H subunits. Similarly, their levels of inhibition are also different as are their substrate affinity and enzyme activity. This said, the greatest structural differences between LDH isozymes are not those observed between species but those that occur when LDH undergoes various conformational changes during catalysis.

One of the first LDH structures to be defined was solved in the 1970s by Michael Rossmann, a German-American physicist and microbiologist. He also observed a particular fold in the enzyme where three parallel β-strands enclose two α-helices (BABAB) – a conformation now known as the Rossmann fold – and which occurs very frequently in protein sequences. In those days, computer programs which could predict the 3D structures of proteins and readily produce an image were unheard of. Everything was done by hand. Calculations and illustrations alike. The first hand drawn 'cartoon' sketches of proteins, or indeed parts of proteins, were beginning to emerge with ribbons, cylinders and arrows used to illustrate recurrent structures. Michael Rossmann's wife, Audrey Rossmann was one of the first to make ink sketches of the structure of LDH, amongst which the Rossmann fold.

In the 1970s, it was still widely believed that lactate had no life to speak of and it had been lying for the best part of two centuries in the dark corners of minds and laboratories. But in the late 1980s, scientists were beginning to realise that there was more to this molecule than met the eye. It was becoming clear that lactate acts a little like a pseudo-hormone – it seems to have the ability to signal a state of stress to the central nervous system following intensive muscular activity. Such a signal is then translated into a sensation of pain, so that exercise is reduced or stopped, and the body can recuperate. All in all, lactate could well be a metabolite with an aim to protect, able to send out a "Give yourself a break" warning signal.

LDH is then part of a fundamental metabolic process: one which gives an organism the means to dialogue between cells, between tissues and between organs. Without this sort of communication – where molecules are shuttling back and forth, triggering off metabolic processes and inhibiting others – life is not possible. LDH is by far not what defines life but it certainly is part of the hugely complex network which makes up the fabric of life. What is more, other roles for lactate are also emerging. It could have a role in the selection of fuel used by a cell for instance, and may also increase muscle contractility. The level of LDH is also measured by doctors nowadays because high levels can indicate the existence of internal tissue breakdown, a cardiac arrest, tumours or meningitis for example. LDH, and its substrate lactate, are just one example of something put aside as uninteresting simply because the time is not right. It's a law of life. As it is a law of research. Only the ready mind can see.

Cross-references to Swiss-Prot

L-lactate dehydrogenase B (LDH heart subunit), *Homo sapiens* (Human) : P07195
L-lactate dehydrogenase A (LDH muscle subunit), *Homo sapiens* (Human) : P00338

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