proteinspotlight
> ONE MONTH, ONE PROTEIN <

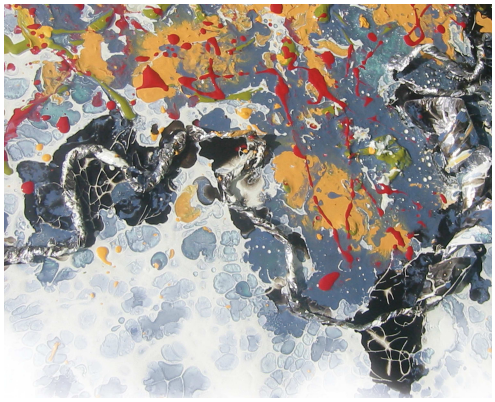
Issue 76, November 2006

www.proteinspotlight.org

Life shuttle

Vivienne Baillie Gerritsen

There is no life without energy. Much in the way a car needs petrol to run, we also need something essential to keep us going. And it is called adenosine tri-phosphate or ATP. ATP runs through every nook and cranny of our body to keep our heart pumping, our fingers moving and our thoughts alive. But – like petrol – we do not get it for free. We have to make it. So, in the great majority of our cells, we have powerhouses – known as mitochondria – that spend their time synthesizing ATP and distributing it where need be. Not surprisingly, hordes of proteins are involved in this process, one of which has been known for decades: cytochrome c. Human cytochrome c happens to be the very first protein sequence that was entered into the Swiss-Prot database. And the beginning of an adventure which is heading into its 21st year.



'Cytochrome c' by Julia Baillie*

Courtesy of the artist

Cytochrome c has been around for a very long time – almost as long as life really – which has made it an ideal candidate for evolutionary studies. In fact, Linus Pauling was one of the first to imagine the concept of a molecular clock based on comparisons of the sequences of haemoglobin and cytochrome c. The protein was discovered in the early part of the 20th century and besides becoming a paradigm in evolutionary research, cytochrome c has been a choice model in studies of electron transport, protein folding, molecular immunology, and at the heart of pioneering studies of site-directed mutagenesis.

If cytochrome c has been so popular in the study of electron transport, it is because that is what it does. It delivers electrons into the respiratory pathway, giving it the wherewithal to drive a proton pump which in turn will synthesize ATP. The respiratory pathway is lodged in the inner membrane of the mitochondrion. By way of electrostatic interactions, cytochrome c bounces between two of the respiratory chain complexes – cytochrome reductase and cytochrome oxidase – where it transfers electrons from one to the other, respectively. Cytochrome c shuttles electrons thanks to its haem – iron-protoporphyrin IX – that is harboured within its centre and protrudes just enough to grab hold of an electron for transfer.

Despite the fact that mitochondria carry their own DNA, apo-cytochrome c is synthesized in the nucleus as a precursor molecule that has been described as a molten globule because of its apparent lack of defined structure, though linear and supple. Cytochrome c biogenesis is a process which involves many factors and researchers have distinguished three types. Surprisingly, mammalian cytochrome c biogenesis is the most straightforward – thereby demonstrating that evolution does not always rhyme with complexity… Once the precursors have made their way through the mitochondrion's outer membrane, like a father presenting the groom to the bride, haem lyase presents a haem ligand to the apo-cytochrome. The apo-cytochrome then wraps itself around the haem ligand, adopting its final conformation, and leaving the tip of the haem free to catch an electron. Cytochrome c's final conformation is both directed by haem binding and stabilised thanks to strong thioether bonds between the ligand and the cytochrome itself.

Cytochrome c's main role is to participate in the making of ATP. However, it is also involved in a number of other instances, one of which is apoptosis, or programmed cell death – thus giving the protein something of a Dr Jekyll and Mr Hyde quality. In the event of apoptosis, it is seen to leave the mitochondrion – possibly following swelling and the subsequent rupture of the mitochondrial outer membrane – and collaborate with factors which are themselves directly involved in cell apoptosis: the caspases. Besides ganging up with the caspases, the growing loss of cytochrome c will also eventually interrupt the synthesis of ATP, and hence the fuel the cell needs to survive.

Researchers' imagination continues to be sparked by cytochrome c. It has been combined with plastics in an attempt to create novel biosensors, by depositing a film of polymer on a surface of gold or platinum electrodes. The polymer was fashioned in such a way that it would accept electrons from cytochrome c. The electrons were then passed onto the electrodes where they produced an electric current that was directly proportional to the amount of cytochrome c used. Such techniques could be used for detecting biological molecules both for medical and industrial purposes. A clinical technique known as LLLT – Low Level Laser Therapy – which uses laser light to stimulate cell regeneration is suspected to be driven by cytochrome c activity. The 670 nm laser light wavelength may well increase the cytochrome's activity, thereby increasing the synthesis of ATP and, as a consequence, sustaining tissue repair.

Like insulin, cytochrome c is yet another protein that has shed light on many biological processes and pioneered numerous studies. It certainly seems to tiptoe along the line between life and death, and for just this reason, it is fitting that human cytochrome c was the first protein ever to make it into Swiss-Prot.

* On the occasion of the 20th anniversary of the Swiss-Prot database, the artist made her personal interpretation of the 3D structure of human cytochrome c. The illustration is a detail of the full painting. Acrylic, 2006.

Cross-references to Swiss-Prot

Cytochrome c, *Homo sapiens* (human) : P00001
Cytochrome c, *Equus caballus* (horse) : P00004

References

1. Stevens J.M., Uchida T., Daltrop O., Ferguson S.J.
   Covalent cofactor attachment to proteins: cytochrome c biogenesis
   Biochem. Soc. Trans. 33:792-795(2005)
   PMID: 16042600

2. Wrinkler J.R.
   Cytochrome c folding dynamics
   Curr. Opin. Chem. Biol. 8:169-174(2004)
   PMID: 15062778

3. Maneg O., Malatesta F., Ludwig B., Drosou V.
   Interaction of cytochrome c with cytochrome oxidase : two different docking scenarios
   Biochim. Biophys. Acta 1655:274-281(2004)
   PMID: 15100042

4. Cytochrome c: Can't live with it – can't live without it
   Reed J.C.
   Cell 91:559-562(1997)
   PMID: 9393848

Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB). Authorization to photocopy or reproduce this article for internal or personal use is granted by the SIB provided its content is not modified. Please enquire at spotlight@isb-sib.ch for redistribution or commercial usage.