proteinspotlight
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Issue 50, September 2004
www.proteinspotlight.org

A virus for life

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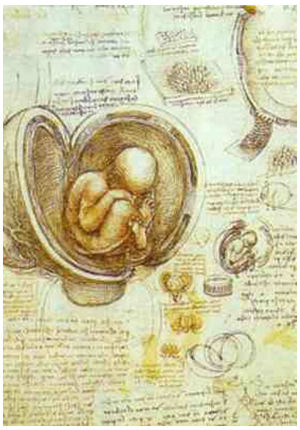
Who would have thought that a virus could have anything to do with a tissue as important to life, and its development, as the placenta? A viral protein, now known as syncytin, whose gene was probably integrated into the primate genome over 25 millions years ago, is hugely expressed in placental tissue – especially at the beginning of embryonic development – and is giving signs of bearing an essential role in placental architecture. Could it be that placental evolution – and indeed mammalian evolution – finds its origins in the doings of a virus?

The virus in question is a retrovirus known as human endogenous retrovirus : HERV-W. The human genome – like many other eukaryotic genomes – is sprinkled with retroviral genes and harbours up to 8% of endogenous retroviral sequences. With the passing of time, many of them have become dysfunctional due to mutations but a number of them have survived and their sequences can be translated into functional proteins. It is not always clear how their expression could benefit the host's biology but the discovery, in the year 2000, of the retroviral protein syncytin is a fascinating example of how a retroviral product can be integrated into a host's genome, kept relatively intact throughout time, and whose function – possibly via natural selection – has ended up by serving the host's purpose.

Syncytin is a 538 amino-acid viral envelope protein, with a transmembrane and a cytoplasmic subunit, which are probably posttranslationally cleaved and meet up again at the cell's membrane. In general, a viral envelope protein mediates cell fusion and participates in building up the virus' envelope. What was discovered was that syncytin seems to fulfill the same purpose in humans – i.e. cell fusion – but at the level of the placenta.

On the mother's side, the placenta is lined by a tissue known as the syncytiotrophoblast – from where the protein's name derives. The syncytiotrophoblast is an essential tissue for the proper development of the embryo, acting as a place of nutritional exchange between the mother and her child, besides being a centre for hormone synthesis and having a role in the foetus' immunity. The syncytiotrophoblast is a one-celled layer formed via the fusion of cells known as trophoblasts. Trophoblasts accompany the foetus in the very early stages of development, giving it all it needs while helping it to anchor itself in the womb. The fusion of trophoblasts creates the syncytiotrophoblast, the tissue which embraces the placenta.



The Foetus in the Womb
Leonardo da Vinci

In 'normal' circumstances – i.e. in the event of viral infection – syncytin would be synthesized via the host's translating machinery and would then appear at the surface of a viral cell. From there it would recognise a specific receptor on a second viral cell, dock to it, and mediate cell fusion. Syncytin has been squatting the human genome for millions of years now; it still does use our machinery to be expressed but instead of initiating viral envelope formation, it is involved in mediating trophoblast fusion. The expression of syncytin during placental

formation is high and besides some expression in the testes, the placenta seems to be the only place where the protein is really expressed.

Syncytin not only has a role in placental morphogenesis but it may also have a role in driving off viral infection – via receptor interference. When syncytin drives trophoblast fusion to form the syncytiotrophoblast, it probably does so by using cell receptors that are used by other 'healthy' invading viruses. If syncytin grabs the receptor before another viral envelope protein gets the chance to, it is in effect interfering with the formation of invading viruses and hence viral infection of the foetus. So here is a virus which is not only at the heart of an essential tissue – the human placenta – but is also capable of fighting off ... viral infection of the human foetus.

Hence, from an evolutionary point of view, syncytin could have an important role in placental development. So far though, it seems that HERV-W is only shared between humans and higher primates, which wouldn't make much of a basis for a major role in placental evolution. However, there are a number of different HERV-W families which are dispersed in various mammals. Could it be then that various viral families are at the heart of the diverse types of placenta observed in mammals today? Certainly, syncytin does appear to have something to do with certain malfunctions of the placenta such as pre-eclampsia (high blood pressure, weight gain and convulsions) or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome because, in these instances, it is not expressed at the normal levels.

All this raises hopes in the field of biotechnology and the search for treatments against such diseases during pregnancy – although both diseases are multisystem disorders, and cell fusion is a far more complicated process than the mere recognition of a membrane receptor by syncytin. However, the discovery of specific amino acids within the syncytin sequence – which are paramount in receptor recognition – could provide a basis for the genetic engineering of the syncytin polypeptide. In this respect, when the fusogenic protein is expressed in tumour cells, it can cause the cells to fuse and subsequently cause tumour cell death. Unfortunately, in the same vein, syncytin could also participate in envelope formation of invading viruses, such as HIV-1 for instance, thus contributing to its pathogenesis. There are always two sides to a story.

Cross-references to Swiss-Prot

Syncytin, human endogenous retrovirus-W (HERV-W): Q9UQF0

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Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).