proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 126, February 2011
www.proteinspotlight.org

our hollow architecture

Vivienne Baillie Gerritsen

We get on with our day-to-day life largely unaware of the continuous battles that are being led within us. Indeed, it is thanks to unceasing cellular hostilities inside our bodies that we are able to get on with our lives as we do. Unwelcome entities such as viruses, but also tumours, would use our bodies as a playground, spreading havoc in their wake, were it not for a system that Mother Nature has offered every multicellular being, namely an immune system. In particular, natural killer cells and cytotoxic T lymphocytes are able to recognise infected cells in the body, into which they inject various molecules that ultimately destroy them. But how is the death sentence relayed? By way of pores. And these pores are formed by proteins known as perforins which assemble into large aggregates to form a barrel-shaped tunnel through which the poison flows from one cell to another.

Big Bang, by Emanuela Lucaci*

Tubes, tunnels, pores, subways, holes, shafts, you name it, are all very straightforward ways of getting something from one place to another. Engineers build them to go through mountains and under seas. Electricians use them as motorways for electrons. On a far smaller scale, nanoengineers design them so that matter can flow from one place to another. But that is all very recent. Nature devised hollow architecture billions of years before anyone else. From bacteria to tulips and humans, all sorts of pores are used to relay all kinds of messages either within a cell, or from one cell to another. These minute biological passageways are used as a means to relay messages, and are involved in events as diverse as defence, sex, smell, transpiration, sleep and the beating of a heart.

When a cell has become unwelcome – because it has been infected or has become malignant – the immune system triggers off an initial response, known as the innate response. This immune reaction is immediate. Natural killer cells armed with poison are deployed and are able to recognise the hostile cells. Upon recognition, various enzymes make their way into the infected cells' cytosol by way of perforin pores and, together, they trigger off cell apoptosis. How exactly the killer enzymes reach the cytosol remains obscure. To date there are two theories.

The first suggests a simple strategy. A natural killer cell approaches a target cell and releases perforin and other enzymes into a cleft between them. Here perforin monomers assemble to form a multimeric barrel-shaped pore which is then inserted into the hostile cell's plasma membrane. The apoptotic enzymes are then able to flow into the infected cell and get on with their business. The second theory is very similar; the difference is geographical. Indeed, perforins together with the killer enzymes are believed to enter the infected cell by way of endocytosis. Pore formation then occurs within an endocytic lysosome. Once assembled, the pores are inserted into the lysosome's membrane, and the apoptotic enzmyes are released into the infected cell's cytosol.

Whichever the strategy, the end result is the assembly of perforin monomers to form transmembrane pores through which flow apoptotic enzymes. A perforin monomer has a key-like structure. The main body of the structure is an intricate mass of alpha helices which embrace a series of beta sheets. The "tail" of the key-like structure is formed by yet another series of beta sheets. And the two regions are joined by a domain which is highly flexible, and vulnerable. When pore formation is launched, about twenty perforin monomers assemble neatly to form a barrel-shaped pore large enough for the passage of apoptotic enzymes. It seems that the pores are formed before they are actually inserted into the plasma membrane. In order to do this, the alpha helices stretch and flatten out alongside the existing beta strands, and the now smooth barrel-shaped structure is ready to glide and lodge itself into the lipid bilayer.

Perforins, however, are more than just pore-forming entities. Indeed, without them, the apoptotic enzymes – in particular enzymes known as granzymes – are unable to carry out their toxic effect. This would imply that the presence of perforins in the immune response is more than merely architectural. To date though, nothing more is known about alternative perforin activity. There remains an intriguing question however. How can perforin and its accompanying killer enzymes destroy unwelcome cells and yet not affect the cells that release them? As logic would suggest, the system could easily act against the killer cells themselves. It has been implied that soluble perforins are covered in a bulky protective coat of proteoglycans, which would prevent them from turning onto the cells which carry them.

Needless to say, perforin is so essential to the immune response that a faulty version of it, or its absence, can only spell disaster. And indeed, there is a hereditary disorder known as HLH (hemophagocytic lymphohistiocytosis) in which patients suffer from a total loss of lymphocyte cytotoxic function because of a loss of perforin activity. What is more, it has been observed that severely immunosuppressed transplant patients are prone to developing cancers – which may well be due to the drastic down regulation of cytotoxic cells caused by a counter performance of their perforins. This is why it is so important to get to know perforin better so that, in the near future, drugs will be designed which could either restore incorrect perforin folding or perhaps replace perforin altogether to recover a healthy immune response.

***** Another kind of tunnel. This painting by the Swiss artist Emanuela Lucaci covers the outer doors of the ALICE magnet which is part of the LHC tunnel at the European Organisation for Nuclear Research (CERN).

Cross-references to UniProt

Perforin-1, *Homo sapiens* (Human) : P14222
Perforin-1, *Mus musculus* (Mouse) : P10820

References

1. Voskoboinik L, Dunstone M.A., Baran K., Whisstock J.C., Trapani J.A.
   Perforin: structure, function, and role in human immunopathology
   Immunological Reviews 235:35-54(2010)
   PMID: 20536554

2. Law R.H.P., Lukoyanova N., Voskoboinik L., Caradoc-Davies T.T., Baran K., Dunstone M.A., D'Angelo M.E., Orlova E.V., Coulibaly F., Verschoor S., Browne K.A., Ciccone A., Kuiper M.J., Bird P.I., Trapani J.A., Saibil H.R., Whisstock J.C.
   The structural basis for membrane binding and pore formation by lymphocyte perforin
   Nature 468:447-453(2010)
   PMID: 21037563

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