Border control: Study shows how proteins permit entry to a cell

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The means by which proteins provide a 'border control' service, allowing cells to take up chemicals and substances from their surroundings, whilst keeping others out, is revealed in unprecedented molecular detail for the first time today (16 October) in *Science* Express.

The scientists behind the new study have visualised the structure of a protein called Microbacterium hydantoin permease, or 'Mhp1', which lives in the oily membrane that surrounds bacteria cells. It belongs to a group of proteins known as 'transporters' which help cells take up certain substances from the environment around them. This is the first time scientists have been able to show how a transporter protein opens and closes to allow molecules across the membrane and into the cell, by accurate analysis of its molecular structure in different states.

Professor So Iwata from Imperial College London's Division of Molecular Biosciences in the Department of Life Sciences, one of the authors of the new study, explains that solving the structure of the Mhp1 bacterial transporter protein is very important because hundreds of similar transporters are found in the membranes of human cells:

"Transporter proteins play an important role in the human body - they are responsible for letting different substances, including salts, sugars and amino acids, into our cells and are targets for a large number of drugs. Understanding the details of how this transport mechanism works may help researchers to design new, more effective, drugs in the future," he said.

The group's research into this protein began in 2000 with a joint project with the Ajinomoto Company from Japan. This company work with a bacterium called Microbacterium liquefaciens which has the Mhp1 protein in its cell membranes. The project revealed that Mhp1 helps the uptake of amino acid-like molecules called hydantoins across the otherwise impermeable cell membrane.

Professor Peter Henderson from the University of Leeds, co-author of the study, said: "The major problem was to produce enough protein for the structural studies. We developed methods for the amplified expression of the Mhp1 protein in a genetically-engineered host organism, Escherichia coli, and procedures for the subsequent efficient purification of the protein from the cell membranes. We could then maintain a 'pipeline' to supply an exceptional amount of the membranes containing the excess Mhp1 protein to our colleagues at Imperial".

Professor Iwata and his colleagues analysed the structure of Mhp1 using the facilities at the Membrane Protein Laboratory (MPL), which is an Imperial College outstation at the Diamond Light Source national synchrotron facility in Oxfordshire. They used the MPL, which is a dedicated facility for membrane protein structural studies, to build an accurate picture of the Mhp1 protein binding to hydantoin.

The researchers analysed the structure of Mhp1 before and after it had taken in a hydantoin molecule from outside the cell, and also used the structure of a related transporter, vSGLT, for insight into the latter stages of the take-up process. These three structures revealed new molecular-level detail of how Mhp1 transports a hydantoin molecule across the cell membrane.

The researchers saw that the Mhp1 protein opens up on its outer-facing side, allowing the hydantoin molecule to move inside. Once the hydantoin is bound, the 'door' to the outside world closes behind it,

ensuring that no other substances have been let in. Then the gate on the inward-facing side opens to release the hydantoin into the cell.

Professor Iwata comments on the significance of the discovery, saying: "Our research has revealed the detailed molecular function of an important membrane protein. We now know how the protein facilitates the movement hydantoin across the cell membrane without letting any other substances through at the same time. This mechanism is likely to be shared by many cell membrane proteins, including those in the human body, so this is an important step forward in our understanding of the fundamental processes which occur in our cells."

Source: Imperial College London