Researchers discover a new protein fold with a transport tunnel

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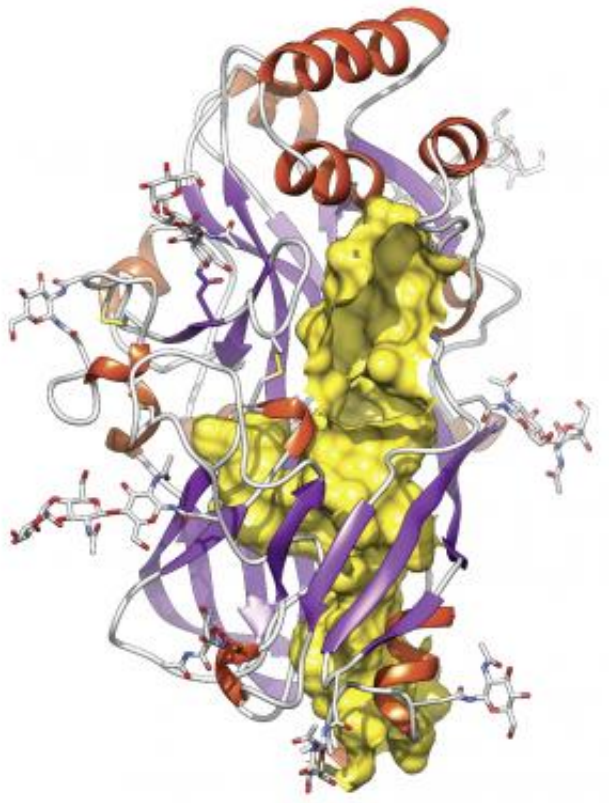

The Bielefeld chemist Michael Schwake and his colleagues have discovered a new protein fold. At its head (the red helices), this protein can bind enzymes and viruses. The tunnel in the protein structure is coloured yellow. Credit: Nature

The protein LIMP-2 is vital for both humans and animals. If it is absent – due, for example, to a hereditary disease – substances of an unknown

nature, probably lipids, accumulate in the organism. Up to now, scientists were unsure what the protein looks like and how exactly it functions. Privatdozent [senior lecturer] Dr. Michael Schwake from the Faculty of Chemistry at Bielefeld University (Germany) is doing research on the protein – and thereby preparing the way for future therapies. Together with colleagues in Kiel, Toronto, and Boston, he has now discovered that the protein LIMP 2 possesses a novel protein fold together with a nanomicroscopically small transport tunnel. The researchers have published their findings on Sunday (27 October) in the globally renowned scientific journal *Nature*.

Proteins are composed of amino acids. Although these are lined up as if along a string, they produce a twisted three-dimensional structure of helices and sheets. It is only this pleating that enables them to influence biological cells. 'We are decoding the structure and function of proteins in order to find out how biochemical processes within them take place,' says Schwake.

To study LIMP-2, Schwake's colleagues from the Canadian University of Toronto have crystallized the protein. Then they can use X-ray diffraction analysis to ascertain its crystalline structure. 'When analysing the images, we detected a protein fold that has not been described in any other protein up to now,' says Schwake.

LIMP-2 is present in every cell of the human body. It is found mostly in the lysosomes of the cells where it ensures that a specific enzyme reaches them. Lysosomes are the 'stomachs' of the cells and they break down harmful and unusable substances. A specific enzyme called beta-glucocerebrosidase is responsible for breaking down lipids. If this enzyme is defect or does not reach the lysosomes, these lipids will accumulate. Biochemists suspect that this is what causes Gaucher's disease that leads to an enlarged liver and spleen.

Schwake's studies confirm how LIMP-2 transports this enzyme. The protein has a 'head' consisting of several helices on which the enzyme docks. 'We also managed to show that the protein is equipped with a tunnel through which it transports substances through membranes,' Schwake reports. The biochemists have determined that it is highly probable that this channel is used to transport lipids away from the lysosome. 'We determined that by comparing the structure of LIMP-2 with that of related proteins,' says Schwake. Two of these proteins are known to bind and transport lipids. The comparison suggests that LIMP-2 must possess the same ability.

As a biochemist, it is not Schwake's job to develop a therapy – his interest is in basic research, that is, in finding out how the proteins work in the cells. 'Our findings could be used to develop substances to cure diseases,' he explains. 'Through our research, we now how ligands bind to the head and lipids are transported through the tunnel. One way to prevent this would be to deliberately disrupt the binding at these locations,' says Schwake.

More information: Neculai, D. et al. Structure of LIMP-2 provides functional insights with implications for SR-BI and CD36, *Nature*, October 27, 2013. dx.doi.org/ 10.1038/nature12684

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