Research breakthrough paves the way for understanding serious diseases

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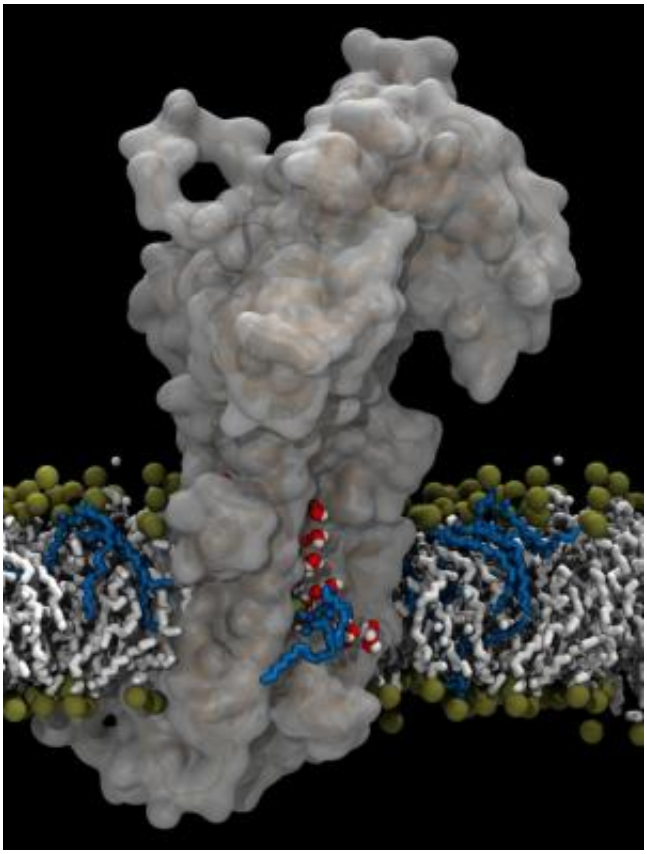

The model of the ATP8A2 flippase transport mechanism developed by the researchers is shown. The flippase molecule is the large grey area and you can see the lipid molecule with the blue 'tail' moving along an open channel in the protein, which also contains water molecules (red spheres with white spots). Credit: Anna Lindeløv Vestergaard

New basic research reveals how the body's cells transport lipid. Defects in the mechanism can lead to serious neurological diseases, liver diseases and involuntary childlessness, and the new knowledge is an important step on the way to understanding and treating these diseases.

A few years ago researchers described a Turkish family whose family members moved around on all fours. It turned out that they lacked the sense of equilibrium. This was caused by the rare neurological disease CAMRQ, which is the result of a mutation in the lipid pump in the cells. On the other hand, it was not known why the genetic error had such serious consequences.

The discovery provided inspiration for a Danish study of the mechanism for the vital lipid pump function, the so-called flippase, which transports lipids in the membrane that surrounds every single cell in the body. Researchers from Aarhus University have now presented a hypothesis that can explain how the flippase functions - and they have thus found the answer to a basic research question that has preoccupied researchers for years. The study has just been published in the recognised scientific journal *PNAS*.

Fundamental question for researchers around the world

14 different types of flippases are found in the cells. In collaboration with colleagues from Switzerland and Canada, the Danish researchers have put forward a model for how the transfer of lipid molecules takes place between the two layers in the cell membrane. The researchers created the model by mimicking the mutations from the Turkish family in the laboratory on one of the flippases - the so-called ATP8A2 - and then using computer simulations to study the structural changes of the flippase.

"With the model we have found a possible answer to the question known as 'the giant substrate problem.' It has not previously been possible to explain how a relatively small protein could transport large lipid molecules in the membrane. This fundamental question has occupied researchers around the world since the existence and size of the flippase protein became known. With the new knowledge we can understand how the mutation interferes with the lipid transport mechanism and thus, in this way, triggers disease," says postdoc Anna Lindeløv Vestergaard, who is one of the researchers behind the project.

Research based on Danish Nobel Prize research

The study is based on the research tradition that Nobel Prize winner Jens Christian Skou laid the groundwork for when he became the first person to discover a pump function in the cells in the 1950s, the so-called sodium potassium pump.

The flippase and the sodium potassium pump belong to a group of a total of 36 different pump proteins that are found in the cell membranes in the body's cells. The pumps are vital and genetic defects in flippases contribute - in addition to the Turkish family's illness - to the deadly Byler's disease of the liver, involuntary childlessness and neurological diseases such as e.g. Alzheimer's disease.

"14 out of the 36 pumps in the cells are flippases. For that reason alone there is every reason to believe that they play an important role. Genetic errors in the flippases are probably the cause of many more diseases than we currently recognise. The basic scientific understanding is the first step. In the long term it can lead to us becoming better to diagnose and treat diseases that are caused by errors in a flippase," says postdoc Anna Lindeløv Vestergaard, before continuing:

"The new knowledge can also be used for the development of new drugs

as the flippases can also transport lipid-soluble medicines. Once we know how the medicine can get into the cell, it can be designed so that the treatment is more carefully targeted and effective."

Important step towards greater knowledge

The flippases ensure that there is asymmetry between the two lipid layers in the cell membrane, so that the membranes bend, which is necessary so that the cells can divide or fuse. This also means that the flippases are of significance during e.g. embryo development, fertilisation and the excretion of hormones from the cells into the blood.

"We surmise that the basic mechanism which we have discovered is universal for all flippases in humans and animals. So this is the first step towards far greater knowledge than we have today," says Professor Jens Peter Andersen, who has headed the study in collaboration with Anna Lindeløv Vestergaard.

More information: www.pnas.org/content/111/14/E1334.abstract

Provided by Aarhus University