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Press Release

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Cholesterol transporter structure decoded

The three-dimensional structure of the transport protein TSPO opens up novel paths for the diagnosis and treatment of brain diseases

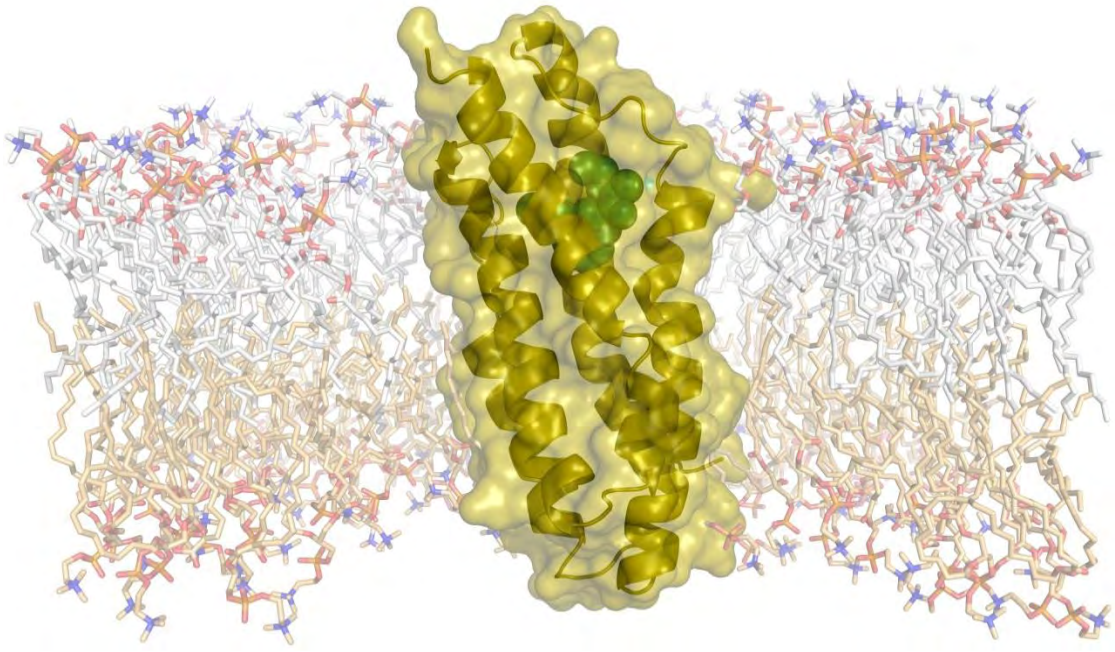
The word "cholesterol" is directly linked in most people's minds with high-fat foods, worrying blood test results, and cardiovascular diseases. However, despite its bad reputation, cholesterol is essential to our wellbeing: It stabilizes cell membranes and is a raw material for the production of different hormones in the cell's power plants – the mitochondria. Now, for the first time, scientists in Göttingen have solved the high-resolution structure of the molecular transporter TSPO, which introduces cholesterol into mitochondria. This protein also serves as a docking site for diagnostic markers and different drugs, such as Valium. The detailed knowledge of its three-dimensional shape and function opens up new diagnostic and therapeutic perspectives. *(Science, March 21, 2014)*

Not only are mitochondria the most important energy supplier in living cells. They also produce steroid hormones such as testosterone and oestradiol, which control many processes in the body. The raw material for the production of steroid hormones is cholesterol, which must first be transported into mitochondria across two membranes. This difficult task is carried out by a molecular transport protein named TSPO in the outer mitochondrial membrane. Using nuclear magnetic resonance spectroscopy, two teams working with the Göttingen-based scientists Markus Zweckstetter and Stefan Becker have now shown the complex three-dimensional structure of the protein “at work” in atomic detail.

The researchers achieved this methodical breakthrough by applying an ingenious trick: In their experiments, they coupled the transporter to an important diagnostic marker called PK11195; it was this complex that first gave the scientists analyzable results. In fact, the TSPO structure delivers more than just clues about how cholesterol is transported into the mitochondria. "We now also have a much better understanding of how TSPO recognizes and binds to diagnostic markers and drugs", explains Markus Zweckstetter, head of research groups at the German Center for Neurodegenerative Diseases (DZNE), at the Max Planck Institute for Biophysical Chemistry, and at the Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB) at the University Medical Center of Göttingen (UMG).

TSPO has long been successfully used in diagnostics and treatment of a number of diseases. "When the brain is injured or inflamed, its cells produce more TSPO. This fact is used in the diagnosis of neurodegenerative diseases such as Parkinson's and Alzheimer's", explains Stefan Becker, a protein chemist and Max Planck researcher who works next door to Zweckstetter.

Physicians also use radioactively tagged molecules such as PK11195 to visualize inflamed areas of the brain. A detailed understanding of how TSPO binds to such markers opens up novel paths for diagnostic imaging and could constitute an important step along the way to early detection of such diseases and inflammations.



The cholesterol transporter TSPO in the outer mitochondrial membrane serves as a docking site for important diagnostic markers and for a number of drugs such as diazepam. (*Image: Łukasz Jaremko, Mariusz Jaremko, Markus Zweckstetter / DZNE, Max Planck Institute for Biophysical Chemistry and UMG*)

TSPO also binds several medicinal drugs such as diazepam, also known by the trade name of Valium. Not only is diazepam a widely prescribed sedative; it is also used in the treatment of anxiety and epileptic seizures. The Göttingen researchers hope that detailed information about the transporter's structure will help to develop new TSPO-binding drugs. (fk/cr)

Original article:

Łukasz Jaremko, Mariusz Jaremko, Karin Giller, Stefan Becker, Markus Zweckstetter: Structure of the mitochondrial translocator protein in complex with a diagnostic ligand. *Science,* March 21, 2014, doi: 10.1126/science.1248725

Further information:

www.dzne.de/standorte/goettingen/forschergruppen/zweckstetter.html – Website of the Research Group "Structural Biology in Dementia", German Center for Neurodegenerative Diseases (DZNE)

www.mpibpc.mpg.de/de/zweckstetter – Website of the Research Group "Structure Determination of Proteins using NMR", Max Planck Institute for Biophysical Chemistry

www.cnmpb.de – Website of the Cluster of Excellence and German Research Foundation (DFG) Research Center "Nanoscale Microscopy and Molecular Physiology of the Brain" (CNMPB)

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