



Press Release

How Alzheimer's Peptides Shut Down Cellular Powerhouses

Freiburg biochemists discover new mechanisms of the brain disease

The failing in the work of nerve cells: An international team of researchers led by Prof. Dr. **Chris Meisinger** from the Institute of Biochemistry and Molecular Biology of the University of Freiburg has discovered how Alzheimer's disease damages mitochondria, the powerhouses of the cell. For several years researchers have known that the cellular energy supply of brain cells is impaired in Alzheimer's patients. They suspect this to be the cause of premature death of nerve cells that occurs in the course of the disease. Little is known about the precise cause of this neuronal cell death, and many approaches and attempts to find an effective therapy have failed to make an impact. What is certain is that a tiny protein fragment by the name of "amyloid-beta" plays a key role in the process. Meisinger, a member of the Cluster of Excellence BIOSS Centre for Biological Signalling Studies of the University of Freiburg, and his team have now demonstrated how this protein fragment blocks the maturation of protein machines that are responsible for the production of energy inside the cellular powerhouses. The researchers demonstrated this with the help of model organisms and with brain samples from Alzheimer's patients. "The elucidation of this key component of the disease mechanism will enable us to develop new therapies and improve diagnostics in the future," explains Meisinger. The findings were published in the journal *Cell Metabolism*.

Mitochondria are made up of around 1500 different proteins. Most of them need to migrate to the cellular powerhouses before taking up their work. This import is facilitated by a so-called signaling sequence – tiny protein

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extensions that transport the protein into the mitochondria. Once the protein is inside, the signaling sequence is normally removed. **Dirk Mossmann** and Dr. **Nora Vögtle** from Meisinger's research team have now discovered that the amyloid-beta peptide prevents mitochondria from removing these signaling sequences. As a consequence, incomplete proteins accumulate in the mitochondria. Since the signaling sequences remain attached, the proteins are unstable and can no longer adequately carry out their function in energy metabolism. The researchers demonstrated that modified yeast cells producing the amyloid-beta protein generate less energy and accumulate more harmful substances.

In the brain, the mechanism probably leads to the death of nerve cells: The brain shrinks and the patient suffers from dementia. The researchers are currently developing an Alzheimer's blood test to detect the accumulation of mitochondrial precursor proteins. They suspect that the mitochondrial alterations observed in nerve cells will also be detected in the blood cells of Alzheimer's patients.

Original Publication:

Mossmann, D., Vögtle, F.N., Taskin, A.A., Teixeira, P.F., Ring, J., Burkhart, J.M., Burger, N., Pinho, C.M., Tadic, J., Loreth, D., Graff, C., Metzger, F., Sickmann, A., Kretz, O., Wiedemann, N., Zahedi, R.P., Madeo, F., Glaser E. & Meisinger, C. (2014). Amyloid- β peptide induces mitochondrial dysfunction by inhibition of preprotein maturation. *Cell Metabolism*.

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Caption:

In patients suffering of Alzheimer's disease, mitochondria (green) inside cells are blocked.

Source: Christ Meisinger/BIOSS

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The University of Freiburg achieves top positions in all university rankings. Its research, teaching, and continuing education have received prestigious awards in nationwide competitions. Over 24,000 students from 100 nations are enrolled in 188 degree programs. Around 5,000 teachers and administrative employees put in their effort every day – and experience that family friendliness, equal opportunity, and environmental protection are more than just empty phrases here.

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