Effects of amyloid beta plaque on different brain cells

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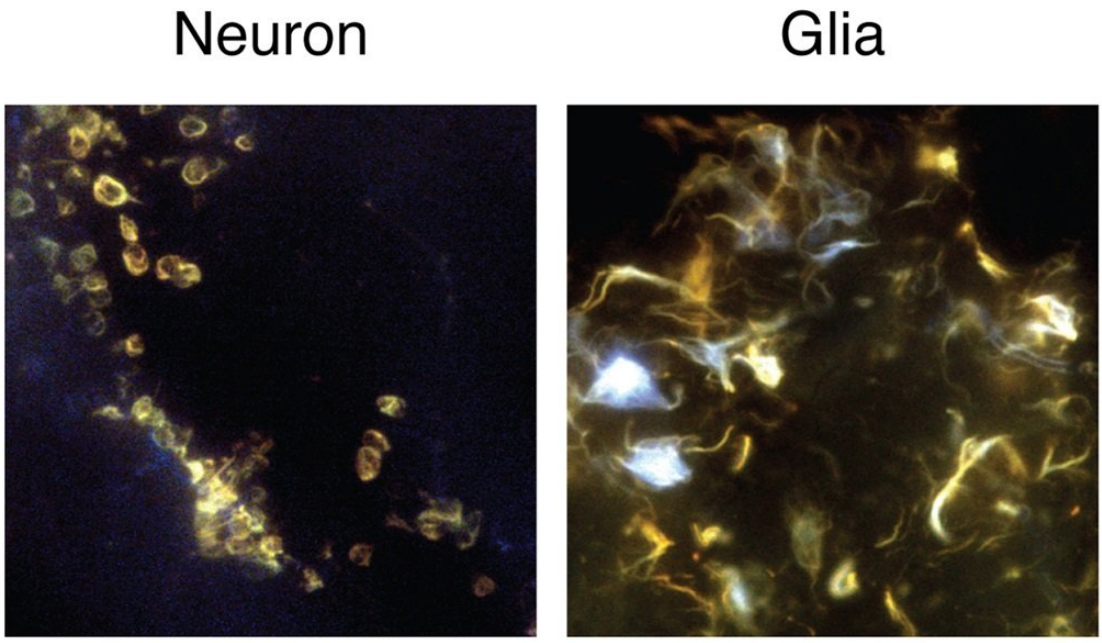

In nerve cells, the immature form of amyloid beta fibrils dominates (ring-shaped structures in yellow) while glial cells form the more mature structure (pointed structures in yellow, and cyan structures). Credit: Maria Jonson, Linköpings universitet

Amyloid beta, a protein linked with Alzheimer's disease, has different properties in different cell types in the brains of fruit flies. This is the conclusion of a study led by researchers at Linköping University in

Sweden. While amyloid beta is highly toxic for nerve cells, it seems that certain other types of cell are unaffected by aggregates of the protein.

The study, which has been published in *Cell Chemical Biology*, describes investigations by Swedish researchers into the sensitivity of different brain cells for one of the proteins closely associated with Alzheimer's disease. In advanced Alzheimer's disease, huge numbers of nerve cells in the brain are dead. Research has long been focused on the process by which nerve cells are damaged via erroneously folded forms of the amyloid beta protein. These forms build up and eventually form plaques in the brain. But the erroneously folded forms of amyloid beta do not accumulate only in nerve cells. Amyloid deposits are also found in the blood vessels of the brain, in the retina, and in cells known as glial cells. The latter have support functions in the brain, and it is unclear whether this plays a role in the development of disease. For this reason, the researchers wanted to investigate whether amyloid beta can form in these different types of cell, and whether it is toxic for other cells than nerve cells.

The researchers used fruit flies (Drosophila melanogaster) in their work. These have been extensively used in research to understand neuronal development and diseases, including Alzheimer's disease. They used fruit flies that had been modified to produce high levels of human amyloid beta 1-42, which is the more harmful of the two most common variants. The researchers could control which cells expressed the amyloid, and compared flies in which it was expressed in different cell types. The group had previously shown that the higher the amount of amyloid aggregate present in the nerve cells, the more severe was the disease in the flies.

"In this study, we expressed the amyloid beta 1-42 in glial cells instead, and observed that huge amounts of aggregate accumulated around these cells. The flies, however, were hardly affected by the disease. They were

affected to a certain degree, compared with control groups, but nowhere as much as flies with amyloid beta in their nerve cells. This was a great surprise," says Maria Jonson, research student in the Department of Physics, Chemistry and Biology and first author of the article.

The researchers wondered why amyloid did not harm the glial cells as much as nerve cells, and thus studied the structure of the aggregate in detail. Amyloid beta with faulty folding can be produced in various forms, and these are classified by, among other things, the degree of maturity. Mature amyloid appears in the microscope as thin, tightly packed strands, almost like a bundle of uncooked spaghetti. When immature, it looks more like cooked spaghetti, and forms tangles. Previous studies by the researchers in mice and humans have shown that both forms can be present, but this is the first time that neuron degradation was linked to the structure of the amyloid.

"We noted that glial cells seem to produce the mature, less harmful form of amyloid beta, while neurons cannot. The amyloid ends up outside the glial cells as bundles of fibres, while the same protein in its immature form gets stuck inside the neurons, and they die. This raises the question of the molecular mechanism that lies behind the high toxicity of amyloid beta for neurons, while glial cells can survive even with high levels, at least in fruit flies," says Per Hammarström, professor in the Department of Physics, Chemistry and Biology, and leader of the study.

One important advantage of using fruit flies rather than mice as experimental model is that high levels of the amyloid beta aggregate in the flies leads to neurodegeneration and a considerably shorter lifetime, which is the same as in humans. Stefan Thor's research group at the Department of Clinical and Experimental Medicine has developed the fruit flies used in the study.

More information: Maria Jonson et al, Aggregated Aβ1-42 Is

Selectively Toxic for Neurons, Whereas Glial Cells Produce Mature Fibrils with Low Toxicity in Drosophila, *Cell Chemical Biology* (2018). DOI: 10.1016/j.chembiol.2018.03.006