Alzheimer-linked protein complex at super resolution

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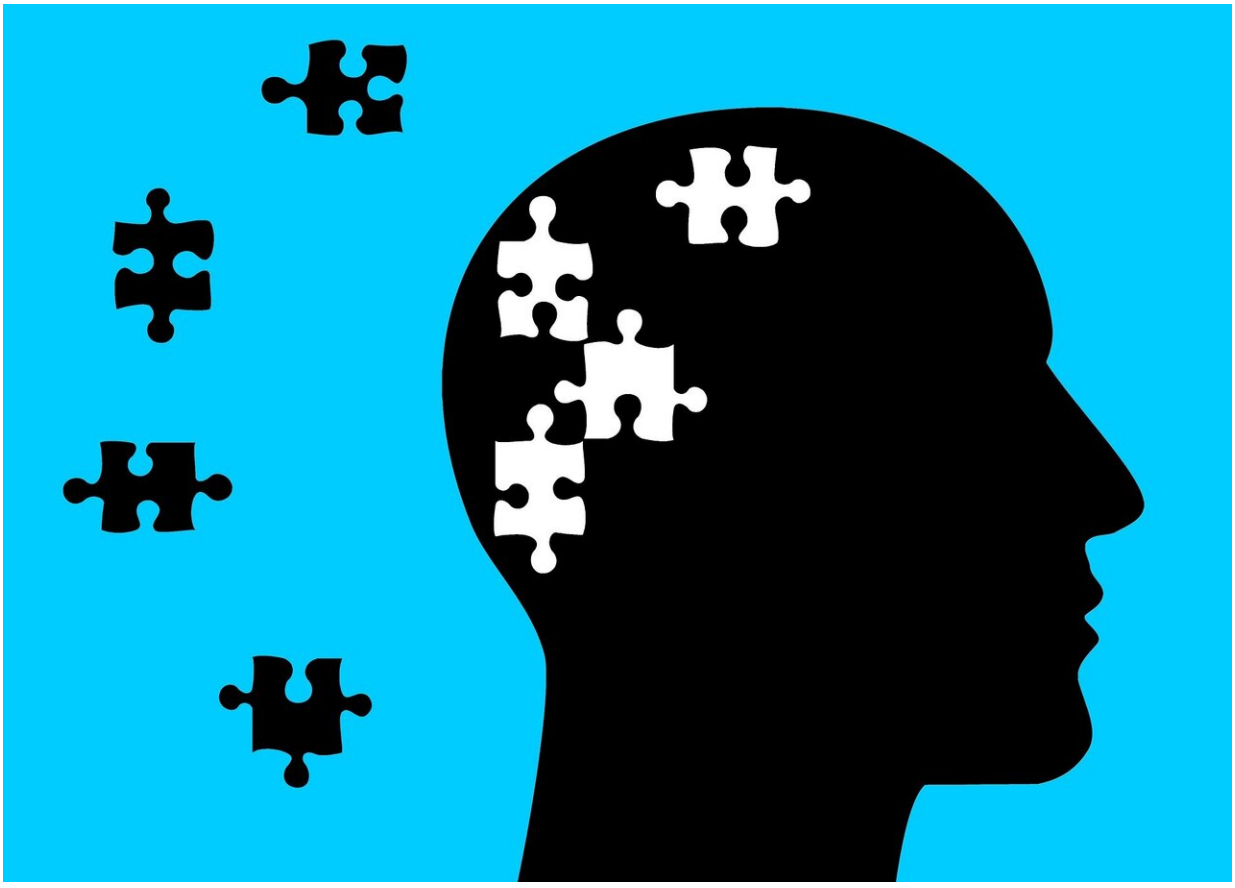

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With the advent of super-resolution microscopy, scientists can study close protein associations better than ever before. In the latest edition of

eLife, the team of Wim Annaert (VIB-KU Leuven) combines state-of-the-art imaging techniques to investigate the distribution of γ-secretase, a protein complex associated with both Alzheimer's disease and cancer.

γ-Secretase is a transmembrane enzyme complex consisting of four different protein subunits. It has received a lot of research attention because of its link to Alzheimer's disease and cancer but because of a lack of resolution, it has for long been difficult to directly visualize protein associations within and between these complexes.

"While enormous progress has been made in the past years to unveil γ-secretase protein structure at atomic resolution, we were still lacking direct visual evidence on its distribution in membranes of living cells," says prof. Wim Annaert from the VIB-KU Leuven Center for Brain & Disease Research.

His team studies the molecular biology of membrane transport in health and disease, and took advantage of advances in super-resolution microscopy to analyze the distribution of γ-secretase complexes.

Open configuration options

Visualizing single γ-secretase complexes

"Given the diffraction limit of light, conventional microscopy is limited to ~200 nm lateral resolution, which means that proteins that are closer together cannot be distinguished from one another," explains Abril Escamilla-Ayala, Ph.D. student in the lab of Annaert. "This dramatically changed with the introduction of super-resolution and quantitative microscopy. Now we can really look at subcellular structures in close up, and study the nano-scale distribution of single proteins and complexes in their native context."

The team used complementary imaging strategies to show—for the first time— the stoichiometry of the γ-secretase complex while embedded in its natural environment. They found that the majority of the complexes present at the cell surface are either monomers or dimers, whereas higher order assemblies are rare.

Hotspots

Secretases—such as γ-secretase—trim pieces off other proteins embedded in the cell membrane. Annaert and his team looked at associations between γ-secretase and two of its substrates (the amyloid precursor protein and N-cadherin) and between γ-secretase and two other secretases (ADAM10 and BACE1). They detected associations within 100 nm distance between γ-secretase and its substrates, but not other secretases—although there were dynamic hotspots for secretase recruitment.

"In contrast to earlier studies, our findings do not support the notion of so-called mega-associations of γ-secretase with other secretases. Rather, our findings suggest that 'hotspots' are frequented transiently by different secretases," says Annaert. Interestingly, treatment with γ-secretase inhibitors resulted in a decrease in hotspots.

The findings highlight the power of super-resolution microscopy for the study of γ-secretase distribution and dynamics in the membrane in real-time. When it comes to its role in Alzheimer's disease, Annaert believes that nanoscale resolution studies will be the way forward: "Characterizing the distribution, associations and dynamics of the enzyme complex at neuronal contact sites will give a much more detailed insight on the molecular mechanisms driving the disease."

More information: Abril Angélica Escamilla-Ayala et al. Super-resolution microscopy reveals majorly mono- and dimeric presenilin1/γ-

secretase at the cell surface, *eLife* (2020). DOI: 10.7554/eLife.56679

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