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New research reveals how alpha-synuclein interacts with cell membranes in Parkinson's disease

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The accumulation of α-synuclein, a small, negatively charged protein, in neural cells, is one of the hallmarks of Parkinson's disease. It has been suggested that oligomeric α-synuclein causes membranes to become permeable, or to form channels on the outer cell membrane. Now, a group of scientists from Sweden has found a way to reliably replicate α-synuclein aggregation on cell membranes to investigate how different forms of α-synuclein interact with membranes under different conditions and to learn if any of the α-synuclein species can penetrate these membranes. Their results are published in the current issue of the *Journal of Parkinson's Disease*.

"We found that on-pathway oligomers and α-synuclein fibrils associate with negatively charged model membranes. Furthermore, when investigating seeded α-synuclein aggregation in the presence of giant unilamellar vesicles (GUVs), we find lipid and α-synuclein co-localized in the GUV membrane," explains lead author Marie Grey, of Lund University and the Wallenberg Neuroscience Center in Lund, Sweden. "Importantly, no transport of α-synuclein was seen, indicating that the ability of α-synuclein to enter cells is more complex than diffusive transport over cell membranes."

The scientists generated GUVs containing a small amount of a lipid-conjugated red emitting dye (rhodamine B) and varied the membrane charge by using different molecular ratios of phosphatidyl choline

(DOPC), a common phospholipid in human cell membranes with a neutral charge, with the negatively charged lipids phosphatidyl serine (DOPS), a major component of the plasma membrane in human cells, or cardiolipin (CL), abundant in mitochondrial membranes. They then used confocal fluorescence microcopy to examine how monomer, fibril, and on-pathway α-synuclein species labeled with a green emitting fluorophore interacted with phospholipid bilayers of the GUV. The study achieved unique, reproducible aggregation without addition of stirring bars, chemicals, and vigorous shaking as had been used in previous studies. These gentler methods make the results more physiologically relevant while still yielding the desired reproducibility.

"On-pathway oligomers are difficult to isolate and enrich due to their dynamic nature. Using our reproducible protocol, we could compare the outcome when adding the different species of α-synuclein to the GUVs," notes Dr. Grey.

The researchers found that on-pathway and aggregated forms of α-synuclein species bound to lipid membranes, but α-synuclein monomers did not. α-synuclein was particularly strongly associated with GUVs containing the negatively charged anionic lipids CL or DOPS, but did not associate with GUVs containing only the neutrally charged DOPC. α-synuclein progressively accumulated at the surface of the GUVs, typically in distinct areas rather than uniformly covering the membrane. They did not observe transport of α-synuclein over the GUV bilayer.

"Our results indicate that alpha-synuclein does not readily traverse any biological lipid membrane, but that there most likely are required proteins that regulate the transport, possibly with some degree of specificity. This is good news for future attempts to develop treatments that prevent transport of synuclein across membranes, as proteins provide better drug targets than do lipid membrane constituents," concludes Dr. Grey.

More information: The article is "Membrane Interaction of α-Synuclein in Different Aggregation States," by M. Grey, S. Linse, H. Nilsson, P. Brundin, and E. Sparr. *Journal of Parkinson's Disease*. 1(2011) 359-371. DOI 10.3233/JPD-2011-11067