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Journal of Glycomics & Lipidomics

ISSN: 2153-0637

Perspective

Formation of α-Synuclein Amyloid Protein in Parkinson's Disease

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DESCRIPTION

Accumulation of the protein α-Synuclein (αSyn) in the form of amyloid deposits, Lewy bodies, coincides with the loss of dopaminergic neurons in Parkinson's disease. αSyn is a 140 amino acid residue protein that is present at high concentration in the presynaptic terminal of neurons. In its normal function, αSyn is associated with processes involving trafficking of synaptic vesicles, neurotransmitter release and dopamine regulation. While the detailed pathological role of αSyn is unclear, the aggregation of monomers into β-sheet-rich amyloid fibrils can potentially deplete functional αSyn or produce neurotoxic intermediate species. In the living system, the protein aggregation process that lead to the formation of Lewy bodies takes place in a complex environment containing many other proteins as well as lipid membranes.

As the aggregation of αSyn is largely driven by hydrophobic interactions, lipids may interfere with the aggregation process and associate with the forming of amyloid aggregates. Such co-assembly is supported by recent *in vivo* findings of large contents of lipids in Lewy bodies. *In vitro* examination also states that lipids may co-assemble with αSyn in the fibrillation process. Similarly, lipid-protein co-assemblies have also been reported for other amyloid-forming proteins.

The co-assembly of lipids together with proteins in amyloid deposits may have large consequences for the protein aggregation process in itself. The presence of lipids in the aggregates may also affect the physical-chemical properties of the formed amyloid aggregates, which can in turn modulate interactions between aggregates and other molecules and cells. Finally, the co-assembly of protein and lipids implies extraction of components from the membrane, which likely affects the membrane structure and function and may have pathological consequences.

Gangliosides are anionic lipids that are primarily found in the outer plasma membrane. These lipids are enriched in the brain and on nerve cells where they act as cell surface recognition and regulation molecules. Gangliosides have also been identified in cell-derived vesicles, for example, exosomes which have to accelerate αSyn aggregation. Secretion of αSyn *via* exosomes has also been proposed to amplify and propagate Parkinson's disease pathology.

The gangliosides are glycosphingolipids that consist of a glycosphingolipid with one or more sialic acids that are linked to an anionic and relatively large oligosaccharide headgroup, which may influence the physical properties of membrane interfaces. Observations of an elevated concentration of GM3 in the plasma of Parkinson's disease patients have suggested that dysfunction of GM3 metabolism may affect αSyn pathology in Parkinson's disease. The major brain gangliosides (GM1, GM3, GD1a, GD1b and GT1a) are all biosynthesized via the common precursor GM3 and make up 97% of brain gangliosides in adult humans. Ganglioside GM3 is mainly concentrated in non-neuronal tissues, but as a precursor for the more complex gangliosides GM3 will determine the amount of GM1, GD1a, GD1b and GT1a in neuronal tissues. Parkinson's disease has been suggested to be both related to misfolding of αSyn and as a membrane disorder involving gangliosides, which has led to the development of therapeutical peptides that compete with αSyn for GM3 and GM1 binding.

CONCLUSION

The possible relation between GM3, αSyn and Parkinson's disease, the aggregates formed by αSyn in the presence of GM3-containing vesicles are the lipids membranes present in the supernatants after the aggregation processes has been completed. Samples were collected at the end of the aggregation process, for which amyloid structure of αSyn was first confirmed by X-ray scattering, and then analyzed by NMR spectroscopy. Based on complementary solid-state- and solution NMR experiments, that lipids were present in the aggregates. Then quantified the lipid uptake in the sediment aggregates and supernatant for different sample conditions, varying both the GM3 content and lipid-to-protein ratio. To further bring light on the lipid-protein interactions within the co-assembled aggregates, the compared lipid and protein molecular dynamics in the aggregates to that in systems composed of only lipids or only protein using 13C MAS NMR with dynamics-based spectral editing. Finally, the morphology of the co-assembled aggregates was analyzed using cryo-TEM.

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Received: 29-Nov-2022, Manuscript No. JGL-23-21517; **Editor assigned:** 01-Dec-2022, Pre QC No. JGL-23-21517(PQ); **Reviewed:** 15-Dec-2022, QC No. JGL-23-21517; **Revised:** 22-Dec-2022, Manuscript No. JGL-23-21517(R); **Published:** 29-Dec-2022, DOI: 10.35248/2153-0637.22.11.326.

Citation: Paul D (2022) Formation of α-Synuclein Amyloid Protein in Parkinson's Disease. J Glycomics Lipidomics. 11:326.