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Untangling alpha synuclein fibrils by graphene quantum dots

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Abundant evidence from genetic, neuropathological, and animal studies has highlighted a key role for the aggregation of the protein α -synuclein into insoluble amyloid fibrils in the progression of genetic and familial Parkinson's disease¹. For this reason, considerable effort has been focused on identifying strategies that inhibit this fibrilization of α -synuclein². Despite these efforts, more work is needed to identify strategies that not only inhibit α -synuclein fibrilization, but also induce disaggregation of existing α -synuclein fibrils.

In a recent issue of *Nature Nanotechnology*, Kim et al. investigated a novel approach to target α -synuclein fibrils using a carbon-based nanomaterial, graphene quantum dots (GQDs)³. The researchers show that GQDs can inhibit α -synuclein fibrilization and induce disaggregation of assembled fibrils. Using structural biology techniques and molecular dynamics simulations, they provide compelling insight into the mechanism through which GQDs interact with and dissociate these fibrils. Application of GQDs in primary neurons significantly rescued toxicity induced by α -synuclein pre-formed fibrils (PFF) including mitochondrial respiration deficits, α -synuclein aggregation, and cell-to-cell transmission of α -synuclein aggregates.

In addition, the authors reported excellent in vivo outcomes. Using a PFF mouse model, the researchers found that GQDs were fully brain penetrant and that biweekly intraperitoneal injections for 6 months led to significant protection against PFF-induced toxicity in dopaminergic neurons of the substantia nigra. As a result, mice treated with GQDs displayed reduced motor deficits relative to untreated mice. Importantly, the treated mice displayed no toxicity associated with GQD treatment.

This study represents an exciting new strategy to target α -synuclein fibrils, but there are several questions that remain. The authors provide only sparse details regarding the synthesis of the GQDs. Publication of these details will be important for independent replication of these data. While the data shows a clear disassembly of large α -synuclein fibrils, the resulting protein does not appear completely monomeric raising concerns of potential toxicity from these smaller soluble oligomers⁴. Further studies are necessary to understand the fate of these oligomers in the cell. The researchers showed widespread brain

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penetrance of the GQDs and hypothesized that the GQDs distribute in the brain through endocytosis and release, but future studies are needed to understand GQDs absorption, distribution, and metabolism in the brain and in other parts of the body.

In summary, the present work suggests that the use of carbon-based nanomaterials is a promising novel therapeutic approach to combat amyloid diseases like Parkinson's disease through disaggregation of α -synuclein fibrils.

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