Movement Disorders
CLINICAL PRACTICE

The Role of Poly(ADP-ribose) in α-Synuclein Neurodegeneration: Another Piece of the Puzzle for α-Synucleinopathies

Kam T, Mao X, Park H, et al. Poly(ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. *Science* 2018;362(6414).

In the last few years, the involvement of poly (ADP-ribose) (PAR) polymerase-1 (PARP-1) in the cellular death process known as parthanatos, which is thought to underlie many neurodegenerative disorders[1] has been gaining interest, mainly because PARP inhibitors (drugs currently used as adjuvant treatments in patients with oncologic diseases) could potentially be repurposed as promising disease-modifying agents.[2]

In a recent study, Kam et al.[3] describe a molecular cascade, explaining a way in which α-synuclein (α-syn) aggregates produce neurotoxicity both in vitro and in vivo. The authors investigated the role of PARP-1 and PAR in α-syn-induced neurotoxicity. α-Syn preformed fibrils (PFF) produced DNA damage through nitric oxide (NO) production, causing the activation of DNA-repair enzyme PARP-1, and an elevation in PAR, which induced cell death and loss of dopaminergic (DA) neurons with a consequent reduction in motor performance. All of these changes could be avoided or reduced in PARP-1 knockout (KO) or CRIPS-Cas9 deletion models, as well as in mice treated with PARP-1 inhibitors. Another observation of this study was that PAR bound to α-syn and facilitated its aggregation, producing more misfolded and compact strains, resulting in higher resistance to enzymatic digestion, and proved to be 25-times more neurotoxic than α-syn PFF alone. When added to neuronal cultures or injected intrastriatally, PAR-α-syn PFF induced earlier and greater deposition of α-syn, a higher rate of cell death, and greater cell-to-cell transmission than α-syn PFF, also causing more prominent motor deficits. Finally, in PD patients, as compared to controls, PAR levels are elevated both in CSF and substantia nigra, and correlate with disease severity and duration.

This study provides the first evidence for the potential role of PARP-1 inhibition in modifying the course of α-synucleinopathies, by halting or reducing not only the deposition of α-syn, and its more toxic PAR-bound strain, but probably its propagation from cell-to-cell as well. The findings on PAR levels in CSF warrant further studies to evaluate its role as a potential biomarker of disease progression and target engagement, critical to the development of future clinical trials in Parkinson's disease and other α-synucleinopathies. It may take time to translate these findings to clinical practice, but one by one, the pieces are falling into place.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.
P.M-V.: 3A

Disclosures

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