

Neurology[®]

Molecular mechanisms of cortical degeneration in Parkinson disease

Joshua M. Shulman and Julie A. Schneider

Neurology; Published online before print September 26, 2012;
DOI 10.1212/WNL.0b013e31827040c6

This information is current as of October 15, 2012

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/content/early/2012/09/26/WNL.0b013e31827040c6>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2012 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.



Molecular mechanisms of cortical degeneration in Parkinson disease

Joshua M. Shulman,
MD, PhD
Julie A. Schneider, MD,
MS

Correspondence & reprint
requests to Dr. Schneider:
julie_a_schneider@rush.edu

Neurology® 2012;79:1750–1751

In Parkinson disease (PD), dopaminergic neuronal death within the substantia nigra generates characteristic motor manifestations, while synuclein pathology in cortical regions often causes additional symptoms, including cognitive impairment and dementia.¹ Therefore, a comprehensive understanding of PD pathogenesis requires the evaluation of cell death mechanisms both within the brainstem and extranigral sites. In the current issue of *Neurology*®, Jiang et al.² begin to reveal the potential molecular pathways responsible for cortical degeneration in PD.

Apoptosis, also known as programmed cell death, depends on an intricate molecular circuitry that is hardwired into nearly all cell types, including neurons.³ These biochemical pathways have established roles in neural development and maintenance, as well as in immunity and inflammation, and it is becoming clear that apoptosis is also important in PD and other neurodegenerative diseases. Broadly, apoptotic degeneration can be initiated by either extrinsic or intrinsic cellular signals. Extrinsic apoptotic induction is initiated by cell surface “death receptors,” including tumor necrosis factor receptor I (TNFRI), which respond to secreted or membrane-tethered ligands. In the intrinsic pathway, mitochondria play a central role responding to cellular insults—such as DNA damage or starvation—by releasing cytochrome *c* and other factors into the cytoplasm that trigger apoptosis. Both signaling pathways converge on effector cysteine proteases, called caspases, which cleave a large number of cellular substrates, setting in motion downstream cell death mechanisms (membrane blebbing, nuclear fragmentation). Interestingly, the protein Bid (*BH3* interacting domain death agonist) has been identified as a mediator of cross-talk between the extrinsic and intrinsic apoptotic signaling pathways, potentially functioning as an amplification mechanism.^{4,5} Specifically, death receptor signaling can promote cleavage of Bid to the active form, tBid, which promotes mitochondrial membrane permeabilization and cytochrome *c* release.

In their revealing study, Jiang et al. focus on autopsy material from 15 clinically and pathologically well-characterized PD cases and 15 controls. Although all were without dementia, the duration of PD in cases was fairly advanced (mean = 14 years), and most brains showed moderate Lewy body (LB) pathology, involving both the brainstem and limbic areas, but only sparse if any LBs in the temporal or other neocortical regions. Controls neither had a clinical diagnosis of PD nor did they show substantial LB pathology. Looking for evidence of apoptotic signaling in PD temporal cortex, the authors found increased levels of TNFRI as well as the downstream adaptor protein, TRADD. Further, levels of Bid protein and more importantly, the activated form tBid, were also increased in PD temporal cortex, and particularly within mitochondria. Finally, Jiang et al. found an increase in cytoplasmic cytochrome *c* (and reciprocal decrease of mitochondrial cytochrome *c*), along with evidence of caspase-3 activation. The authors interpret their findings as consistent with increased TNFRI signaling in PD temporal cortex, and further, that this signal, via Bid, converges on mitochondria to promote cytochrome *c* release, thereby triggering activity of caspase-3. They speculate that TNFRI/Bid-mediated apoptotic signaling may contribute to PD cortical pathogenesis, and ultimately to cognitive impairment.

The Jiang et al. study has important strengths, including the evaluation of numerous apoptotic pathway components, and cases with detailed clinical and pathologic assessments. Short postmortem intervals in the study increase confidence in the protein measurements. Moreover, by focusing on the neocortex of individuals without dementia, they potentially isolate early pathogenic mechanisms of cognitive impairment in PD. Study limitations include a small sample size, advanced age, and long duration of PD, which potentially restricts generalizability. Several key questions remain unresolved. First, what is the time course of TNFRI-Bid activa-

See page 1767

From the Departments of Neurology and Molecular and Human Genetics (J.M.S.), Baylor College of Medicine, Houston, TX; Jan and Dan Duncan Neurological Research Institute (J.M.S.), Texas Children's Hospital, Houston; and Departments of Pathology and Neurological Sciences (J.A.S.), Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.

tion relative to overall PD pathogenesis? Although Jiang et al. studied cases without dementia, all subjects for whom data were available had limbic synuclein pathology, and almost all had some neocortical pathology. Future studies would be enhanced by including more subjects with earlier or later pathologic PD stages (brainstem only or neocortical, respectively), as well as considering temporal cortex alongside other affected brain regions. In addition, more detailed clinical information, such as Hoehn & Yahr PD stage and cognitive assessments, would clarify the relationship of apoptotic signals to clinical progression. Second, what cell types are responsible for the molecular changes in PD cortex? The biochemical assays used do not discriminate among a mixed population of cells (neurons, astrocytes, and microglia), and the finding of changes in total protein levels (TNFRI, TRADD, Bid) could be explained in part by altered proportions of cell types. Although immunohistochemistry suggests a gradient of Bid expression (neurons > astrocytes > microglia), tBid would be the preferred marker to determine the cell type in which the pathway is maximally activated. Related to the question of where the apoptotic signal originates is whether there is even only a single activated pathway. For example, neuronal apoptosis might be dually triggered by extrinsic signals, such as TNFRI ligands released during inflammation, and intrinsic signals, for example due to misfolded/aggregated α -synuclein. Finally, what is the specificity of TNFRI-Bid signaling to PD pathology compared to other common coexisting age-related pathologies, such as Alzheimer disease (AD)? The authors perform secondary analyses to suggest that comorbid AD pathology did not contribute

to their current findings; however, their prior work indicates that TNFRI activation can be observed in AD brains.⁶

With the availability of medical and surgical treatments that delay disability associated with PD motor symptoms, there is increasing need to develop similarly effective therapies for common nonmotor manifestations, including cognitive impairment and dementia. Although much work remains, if TNFRI-Bid signaling is indeed an early and pervasive correlate of cortical degeneration and subsequent cognitive deterioration in PD, this could potentially yield an attractive target pathway for therapeutic intervention.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Shulman JM, De Jager PL, Feany MB. Parkinson's disease: genetics and pathogenesis. *Annu Rev Pathol* 2011;6:193–222.
2. Jiang H, He P, Adler CH, et al. Bid signal pathway components are identified in the temporal cortex with Parkinson disease. *Neurology* 2012;79:1767–1773.
3. Bredesen DE, Rao RV, Mehlen P. Cell death in the nervous system. *Nature* 2006;443:796–802.
4. Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* 1998;94:481–490.
5. Li H, Zhu H, Xu CJ, Yuan J. Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell* 1998;94:491–501.
6. Cheng X, Yang L, He P, Li R, Shen Y. Differential activation of tumor necrosis factor receptors distinguishes between brains from Alzheimer's disease and non-demented patients. *J Alzheimers Dis* 2010;19:621–630.

Molecular mechanisms of cortical degeneration in Parkinson disease

Joshua M. Shulman and Julie A. Schneider

Neurology; Published online before print September 26, 2012;

DOI 10.1212/WNL.0b013e31827040c6

This information is current as of October 15, 2012

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/early/2012/09/26/WNL.0b013e31827040c6
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addir.xhtml#reprintsus

