Does Nrf2 help nerves to survive?

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Dimethyl fumarate (DMF) has recently been approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) after showing beneficial effects on clinical and radiologic endpoints in 2 phase 3 clinical trials.[1,2] While DMF's mode of action is not completely understood, experimental data suggest that putative neuroprotective properties may be mediated by the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway.[3,4] Specifically, DMF leads to translocation of Nrf2 to the nucleus, thereby enhancing the expression of antioxidant enzymes and promoting neuroprotection in cell culture models.[4] In line with this, DMF improved the clinical course and preservation of myelin, axons, and neurons in an animal model of MS. These effects were lost in Nrf2-deficient mice, suggesting a central role for Nrf2 in mediating neuroprotection.[3]

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Metz et al.[5] report on a patient with RRMS who after more than 1 year of DMF treatment underwent brain biopsy for a large unusual left occipital lesion. Histopathologic workup of this lesion revealed a more than 6-fold higher number of Nrf2-positive nuclei than control lesions from patients with MS not treated with DMF. The most prominent nuclear Nrf2 signal was observed in astrocytes, whereas other cell types such as oligodendrocytes and lymphocytes displayed a predominantly cytoplasmic staining. Metz et al. could also analyze biopsied lesions from 3 patients with psoriasis who had developed progressive multifocal leukoencephalopathy (PML) as a rare complication of ongoing fumarate treatment. Lesions from 2 of those 3 patients likewise exhibited higher numbers of Nrf2-positive nuclei than control PML lesions.

Although based on only a few cases, these data provide circumstantial evidence that DMF treatment may induce nuclear translocation of Nrf2 in CNS cells in vivo, thus potentially preventing oxidative damage of neurons and glial cells in vivo. Nevertheless, the findings of Metz et al. are derived from single biopsies and therefore do not permit us to draw conclusions on the temporal dynamics of Nrf2 expression. Another note of caution is that the MS lesion was biopsied 8 weeks after the last DMF dosage, raising the question as to whether levels of DMF would have been sufficiently high to exert biological functions at that time. Although the results of Metz et al. therefore do not formally prove Nrf2 nuclear translocation in patients treated with fumarate, they are consistent with previous observations in cell culture experiments and allow for the possibility that a similar mechanism may operate in vivo.

Do these intriguing findings indicate that Nrf2 helps nerves to survive? Findings from the experimental autoimmune encephalomyelitis model indeed suggest that DMF treatment may be associated with an ameliorated disease course, in particular in the late stages of the disease.[3] However, answering the question of whether DMF's interesting effects in cell culture and animal models translate into measurable and clinically meaningful neuroprotective effects in patients will require carefully designed long-term studies with appropriate endpoints. In this regard, 2 recent phase 3 trials of DMF for RRMS have evaluated the effects of DMF treatment on the reduction of brain atrophy, an MRI surrogate measure of neuroprotection.[6,7] In the DEFINE study, relative reductions in brain atrophy over a 2-year period were statistically significant only for DMF twice daily but not 3 times daily.[6] In the CONFIRM study, reductions in brain atrophy with DMF compared with placebo did not reach statistical significance over a 2-year period.[7] Thus, these studies do not yet seem to provide definitive evidence for neuroprotective effects of DMF, at least as measured by the reduction of brain atrophy on MRI. MRI studies with a longer follow-up appear to be warranted to further analyze those effects. Finally, and perhaps most importantly,

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the ultimate measure of neuroprotective properties of any disease-modifying therapy for MS will be the demonstration of beneficial effects on the patients' overall level of functioning, including cognitive and motor capacities, in the long term.

NOTE ADDED IN TEXT

DMF's safety profile is generally considered favorable; however, a recent case of PML underscores the necessity for further pharmacovigilance.[8]

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