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Are we ready to repurpose dimethylfumarate for Parkinson's disease? Lessons learnt from preclinical studies

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A promising approach to neurotherapeutics involves activating the nuclear-factor-E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling, which regulates expression of antioxidant, anti-inflammatory, and cytoprotective genes. Tecfidera, a putative Nrf2 activator, is an oral formulation of dimethylfumarate (DMF) used to treat multiple sclerosis. We compared the effects of DMF and its bioactive metabolite monomethylfumarate (MMF) on Nrf2 signaling and their ability to block 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced experimental Parkinson's disease (PD). We show that in vitro DMF and MMF activate the Nrf2 pathway via S-alkylation of the Nrf2 inhibitor Keap1, and by causing nuclear exit of the Nrf2 repressor Bach1. Nrf2 activation by DMF but not MMF was associated with depletion of glutathione, decreased cell viability, and inhibition of mitochondrial oxygen consumption and glycolysis rates in a dose-dependent manner, whereas MMF increased these activities in vitro. However, both DMF and MMF up-regulated mitochondrial biogenesis in vitro in a Nrf2-dependent manner. Despite the in vitro differences, both DMF and MMF exerted similar neuro-protective effects against MPTP-neurotoxicity in mice, and DMF blocked MPTP-neurotoxicity in wild type but not in Nrf2 null mice and attenuated associated oxidative damage and inflammation. Our data suggest that DMF and MMF exhibit neuroprotective effects against MPTP-neurotoxicity owing to their distinct Nrf2-mediated antioxidant, anti-inflammatory and mitochondrial function/biogenesis, but MMF does so without depleting glutathione and inhibiting mitochondrial and glycolytic functions. Given that oxidative damage, neuroinflammation and mitochondrial dysfunction are implicated in PD pathogenesis, our results provide pre-clinical evidence for the development of MMF rather than DMF as a novel PD therapeutic.

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High content screening of epigenetics compound library in two Huntington's disease cell lines: Importance of p53 in HD cell lines

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Huntington's disease (HD) is characterized by a variety of aberrations in basic cellular processes, including epigenetic dysregulation – all attributed to the downstream effects of mutant huntingtin. The phosphorylation of two serine residues within the first 17 amino acids in huntingtin is critical in modulating the toxicity of mutant huntingtin. Increase in N17 phosphorlyation has been shown to ameloriate HD pathology, and presents a novel pharmacetical target. Epigenetic compound inhibitors were screened for a change in level of N17 phosphorlyation, and restoration of normal epigenetic regulation. An epigenetics compound screen on two cellular models of HD shows a drastic effect histone deacetylase inhibitors (HDAC) have on the level of N17 phosphorylation. Furthermore, the p53-active TruHD hTERT cell line is affected by a variety of different epigenetic compound classes such as, PARP, Aurora kinase inhibitors etc., in addition to the HDAC inhibitors found only to be effective in the p53-inactive ST Hdh Q111/Q111 cell line. TruHD hTERT cell line seems to present alternative pathways mediated through active p53 to elicit different epigenetic regulation; while ST Hdh Q111/Q111 with their inactive p53 do not show novel targets. This demonstrates the importance of having active p53 to model the true cellular physiology in Huntington's disease. Most importantly, high content screening for therapeutic intervention should screen through TruHD hTERTs, rather than the commonly used stritals ST Hdh Q111/Q111.

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