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Strain-specific accumulation of human transgenic TDP-43, inclusion formation and microglia activation in a mouse model for frontotemporal lobar degeneration

R. SHAHIDEHPOUR[1], L. KUKREJA[1], G. KIM[1], K. SADLEIR[2], C. SPENCER[1], H. DONG[3], M. MESULAM[1], R. VASSAR[2], C. GEULA[1]

[1]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis. (MCCNAD), [2]Dept. of Cell and Mol. Biol., [3]Dept. of Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL

Accumulation of TDP-43 inclusions is one of the pathological hallmarks of frontotemporal lobar degeneration (FTLD). Mouse models have shown that overexpression of wild-type or mutant human TDP-43 (hTDP-43) results in the formation of inclusions and neuronal loss. To investigate the temporal sequence of inclusion formation and degeneration, we employed a conditional transgenic mouse model expressing hTDP-43 under the control of tetracycline operator sequences (tTA). TTA and hTDP-43 transgenic mice were initially bred on 129SVE and FVB backgrounds respectively. Transgenic pups were weaned, and brains examined after 14 and 28 days, as well as 8, 15, and 24 weeks of TDP expression and immunohistochemically stained for phosphorylated TDP-43 (pTDP-43), hTDP-43 and the microglia marker, Iba-1. Bigenic mice on the 129SVE/ FVB background showed inclusions and microglial activation as early as 5 days after TDP-43 expression, followed by a rapid increase in number and size of inclusions, peaking at 14 days of post-weaning expression. After 8 and 24 weeks of transgene expression, microglial activation was significantly decreased and inclusions were rarely encountered, but the brains showed the most severe degeneration. Past studies have shown that in the 129SVE and FVB lines, tTA possesses toxicity independent of hTDP-43, which was rescuable by moving the transgene onto a congenic C57BL/6 background (B6). To avoid tTA-specific degeneration, we backcrossed hTDP-43 overexpressing mice with B6 mice for 6 generations and bred pups with B6 mice expressing the tTA transgene. Unlike 129SVE/ FVB transgenic mice, bigenic mice on the B6 background displayed pTDP-43 inclusions at a much later age (starting at 24 weeks of expression), and increased progressively over time. Protein analysis and staining for wild-type human TDP-43 confirmed significant slowing of hTDP-43 accumulation in B6 mice compared to the original 129SVE/ FVB mice. These observations indicate that backcrossing hTDP-43 overexpressing mice onto a full B6 background delays accumulation of hTDP and inclusion formation. Iba-1 staining suggests microglial activation in B6 mice mirroring the progression of pathology. Our TDP-43 mouse model serves as a valuable tool in examining the temporal sequence of TDP-43 inclusion formation and its association with neuronal degeneration.

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