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Positive effect of microglia repopulation on the Alexander disease pathology, the primary astrocyte disease

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Alexander disease (AxD) is a rare neurodegenerative disease caused by mutations in GFAP, the main intermediate filaments of astrocytes. The typical histological feature of AxD is Rosenthal fiber (RF), an aggregate in astrocyte that is composed of GFAP and $\alpha\beta$ -crystallin. In addition to this aberrant feature of astrocyte, activation of microglia which plays orchestrated roles with astrocyte is observed in the AxD brain. We have previously reported that microglia could suppress the progression of the AxD pathology using the AxD model mice expressing human GFAP with R239H mutation (60TM mice). However, the positive effects of naïve microglia seemed to be limited, so we attempted to enhance it by microglia renewal. We used on/off protocol of PLX5622 (PLX), a CSF-1 receptor antagonist, to repopulate microglia. We depleted microglia by PLX-on for one week and then repopulate microglia by PLX-off. Two weeks after the repopulation, the Fluoro-Jade B (FJB) signals, a marker for RF, significantly decreased in 60TM mice. Surprisingly, two more weeks after the repopulation, the FJB as well as GFAP-positive signals showed further decreases. These results suggest that microglia repopulation could enhance the positive role of microglia in AxD and could be the innovative therapeutic strategy to AxD, the primary astrocyte disease.