HDAC3 inhibition ameliorates dystrophic axons and memory function via M2 microglia in a transgenic mouse model of Alzheimer's disease

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Amyloid β (Aβ) skews microglia to M1 phenotype and induces inflammation and neurodegeneration. On the other hand, another type of microglia, M2, shows anti-inflammatory and neurotrophic effects. We previously clarified that HDAC3 inhibition induced predominance of M2 microglia and axonal growth, and recovered locomotor function in spinal cord injured mice. Therefore, this study aimed to clarify that HDAC3 inhibition skewed to M2 microglia and restored memory function in Alzheimer's disease model mice. In cultured microglia, a treatment with an HDAC3 inhibitor, RGFP966, skewed to M2 microglia when treated 24 h after Aβ addition. Conditioned medium collected from RGFP966-treated microglia recovered Aβ-induced collapse of axonal growth cones. RGFP966 was intraperitoneally administered to 5XFAD mice, a transgenic model of Alzheimer's disease. RGFP966 decreased degenerated axons overlapping with Aβ plaques and improved novel object recognition memory. When microglia in the brain of 5XFAD mice were eliminated by intracerebroventricular administration of clophosome, the effects of RGFP966 were diminished. These results suggest that HDAC3 inhibition increased predominance of M2 microglia, recovered axonal degeneration, and ameliorated memory deficit in 5XFAD mice.