PU.1 inhibition in Alzheimer's disease: A double-edged sword with stage-dependent strikes on amyloid and neuroinflammation?

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SPI1 (encoding the transcription factor PU.1) was identified as a genetic risk factor for Alzheimer's disease (AD) in human genetic studies. We recently demonstrated that SPI1 overexpression ameliorates amyloid-associated pathology, and its knockdown exacerbates phenotypes in 4-month-old amyloidosis mouse models (*Kim, et al., Nat. Commun*). However, a recent study by *Ralvenius, et al., (J. Exp. Med, 2023)* reported that A11, a functional PU.1 inhibitor, attenuated AD-related phenotypes in 12-month-old 5xFAD mice. To investigate the effect of A11 on AD-related pathology in a model with a moderate-stage of amyloid accumulation, we intraperitoneally injected A11 or vehicle to five-month-old App^{SAA} knock-in (SAA-KI) mice (n=18 per group) daily for six weeks. In 6.5-month-old SAA-KI mice, A11 administration did not significantly affect the levels of insoluble Aβ peptides compared to vehicle control. Consistent with the Aβ peptide levels, immunohistochemical analysis revealed that A11 treatment did not alter plaque accumulation in the brain. However, we observed a reduction in hippocampal LAMP1+ dystrophic neurites. Complementary *in vitro* study demonstrated that A11 treatment significantly attenuated immune response in BV2 microglia cells.Notably, these findings contrast with the reported efficacy of A11 in an older 5xFAD mouse model, suggesting that therapeutic outcomes of PU.1 inhibition may depend on the disease stage. This apparent discrepancy underscores the necessity for further investigation into the temporal and context-specific roles of PU.1 in the onset and progression of AD.

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