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PDE4B as a key regulator of out of control microglia

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Microglia are responsible for excessive synaptic loss, taking place as early as the prodromal phase in the pathophysiology of Alzheimer's Disease (AD). Phosphodiesterase 4 (PDE4) has been extensively studied in the inflammatory environment witnessed in late-stage AD. However, the function of breaking down cyclic adenosine monophosphate (cAMP) influences the microglial cells' capacity for phagocytosis. We hypothesized that PDE4, and in particular PDE4B which is the most abundant in microglial cells, regulates microglia-mediated synaptic elimination in the hippocampus, resulting in cognitive deficits as witnessed in APP/PS1 mice.

We showed that disrupted PDE4B signaling alters microglial cells' phagocytic capacity of synaptosomes and amyloid beta. Additionally, we show that sustained PDE4 inhibition during synapse pruning leads to notable effects on cognition in mice of the APP/PS1 model. Interestingly, we witnessed significantly improved working memory as well as longer term spatial memory in animals treated with the selective PDE4B inhibitor A33, four months after treatment ended. These results show that PDE4 signaling is an important regulator of microglial phagocytosis and poses an interesting target for early prophylactic intervention.