Postnatal brain development dysregulations in a novel microglial Tyrobp mouse model

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Tyrobp (TYRO Protein Tyrosine Kinase-Binding Protein, aka Dap12 or KARAP) is an adaptor protein expressed by cells of the myeloid lineage represented by microglia within the brain parenchyma. Here, Tyrobp is involved in removing apoptotic neurons and maintaining inflammatory homeostasis. Recent research has focussed on the causal link between Tyrobp and age-related neurodegenerative pathologies such as Alzheimer's disease. However, the role of Tyrobp during brain development, in which microglia perform critical functions such as synaptic pruning, remains yet underexplored. To address this, we have used CRISPR gene editing to generate a mouse model in which the signalling domain of Tyrobp is rendered non-functional. By characterising this model during critical points of postnatal brain development, we observed a marked decrease in the number of microglial cells compared with littermate controls. The remaining microglia population showed, surprisingly, brain area-dependent dysfunction in their phagocytic activity. However, by 6 months of age, both microglial numbers and phagocytic levels returned to what is observed in littermate controls. Analysis of the total brain proteome at birth revealed dysregulations in critical signalling pathways related to neuronal development. Using this data, we are now employing immunohistochemistry to identify the most affected brain cell populations and regions in the Tyrobp mutant mice. We expect our results to reveal novel aspects of perinatal microglial physiology, with potential implications for the healthy adult brain.