Ependymal VPS35 promotes ependymal cell differentiation, suppresses microglial activation, and prevents neonatal hydrocephalus

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Hydrocephalus is a pathological condition with accumulation of cerebrospinal fluid (CSF) in the brain. This condition may be congenital or acquired, and often associated with neurodegenerative diseases, such as Alzheimer's disease (AD). Hydrocephalus is frequently linked with ciliary dysfunctions. It thus is of considerable interest to investigate the cellular and molecular mechanisms underlying ependymal cell (EpC) regulation of hydrocephalus. Here, we report that vacuolar protein sorting-associated protein 35 (VPS35) is critical for EpC differentiation and ciliogenesis, and preventing neonatal hydrocephalic deficit. VPS35 is abundantly expressed in EpCs. Knocking out (KO) VPS35 in mouse embryonic or postnatal EpCs progenitors results in an enlargement of lateral ventricle (LV) and hydrocephalus-like deficit. Further studies reveal marked reductions in EpCs and their cilia in VPS35 KO mice, which are likely due to an impairment in EpC differentiation. Remarkably, microglia surrounding LV became activated in ependymal VPS35 KO mice, depletion of microglia by PLX3397, an antagonist of colony stimulating factor 1 receptor (CSF1R), restores EpCs and diminishes hydrocephalus-like deficit in VPS35 KO mice. Taken together, these observations suggest an unrecognized function of VPS35 in EpC differentiation and ciliogenesis in neonatal brain, and reveal pathological roles of locally activated microglia in EpC homeostasis and hydrocephalus development.