

Astrocytic YAP

Cholesterols are the main components of **myelin** and are mainly synthesized in **astrocytes** and transported to **oligodendrocytes** and **neurons** in the adult **brain**. It has been reported that Hippo/yes-associated protein (**YAP**) pathways are involved in cholesterol synthesis in the **liver**, however, it remains unknown whether **YAP** signaling can prevent the **demyelination** through promoting cholesterol synthesis in experimental **autoimmune encephalomyelitis** (EAE), a commonly used **animal model** of **multiple sclerosis** characterized by **neuroinflammation** and **demyelination**. Zhang et al. found that YAP was upregulated and activated in astrocytes of **spinal cords** of EAE mice through suppression of the **Hippo signaling pathway**. YAP deletion in astrocytes aggravated EAE with earlier onset, severer inflammatory infiltration, demyelination, and more loss of neurons. Furthermore, we found that the neuroinflammation was aggravated and the proliferation of astrocytes was decreased in YAPGFAP-CKO EAE mice. Mechanically, RNA-seq revealed that the expression of cholesterol-synthesis pathway genes such as HMGCS1 was decreased in YAP^{-/-} astrocytes. qPCR, western blot, and immunostaining further confirmed the more significant reduction of HMGCS1 in spinal cord astrocytes of YAPGFAP-CKO EAE mice. Interestingly, upregulation of cholesterol-synthesis pathways by diarylpropionitrile (DPN) (an ERβ-ligand, to upregulate the expression of HMGCS1) treatment partially rescued the demyelination deficits in YAPGFAP-CKO EAE mice. Finally, activation of YAP by XMU-MP-1 treatment promoted the expression of HMGCS1 in astrocytes and partially rescued the demyelination and inflammatory infiltration deficits in EAE mice. These findings identify unrecognized functions of astrocytic YAP in the prevention of demyelination through promoting cholesterol synthesis in EAE, and reveal a novel pathway of YAP/HMGCS1 for cholesterol synthesis in EAE pathology ¹⁾.

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Zhang J, Xu X, Liu H, Jin L, Shen X, Xie C, Xiang W, Yang D, Feng W, Wang J, Wang M, Dong T, Qiu H, Wu L, Wang Y, Zhang X, Huang Z. Astrocytic YAP prevents the demyelination through promoting expression of cholesterol synthesis genes in experimental autoimmune encephalomyelitis. *Cell Death Dis.* 2021 Oct 5;12(10):907. doi: 10.1038/s41419-021-04203-8. PMID: 34611127.

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