

## Characterisation of the CNS expression and function of Notum, a negative regulator of Wnt signalling pathway.

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The Wnt signalling pathway regulates several aspects of brain development and function, including synapse formation, synaptic transmission and maintenance in the adult, as well as blood brain barrier formation and maintenance. There is some evidence suggesting that the Wnt signalling pathway is downregulated in Alzheimer's disease (AD) and that this could contribute to AD pathogenesis.

Signal transduction by Wnt proteins is tightly regulated. For example, Wnt signalling is downregulated by Notum, a secreted carboxylesterase that removes the palmitoleoylate moiety normally appended on Wnts in the secretory pathway to ensure binding to Frizzled receptors and signal transduction. The contribution of Notum in the mammalian central nervous system has yet to be explored.

Here we describe the expression of Notum in the mouse brain. We show that Notum is expressed in specific cell types throughout the brain and spinal cord and is specifically enriched in some thalamic nuclei. The expression of Notum in human brain was also examined. Additionally, mouse models of AD as well as biopsies of human frontal cortex from AD patients were used to determine whether Notum expression is affected during the progression of the disease. To investigate the roles of Notum, we developed several mouse models including a conditional knock-out and a reporter line. Together with small molecule inhibitors (see Mahy et al poster) these genetic tools will enable the assessment of Notum function in the mammalian brain.

**300 words max**