SynGAP

The SynGAP protein is a major regulator of synapse biology and neural circuit function. Genetic variants linked to epilepsy and intellectual disability disrupt synaptic function and neural excitability. SynGAP has been involved in multiple signaling pathways and can regulate small GTPases with very different functions. Yet, the molecular bases behind this pleiotropy are poorly understood.

Gou et al. hypothesize that different SynGAP isoforms will mediate different sets of functions and that deciphering their spatio-temporal expression and subcellular localization will accelerate understanding their multiple functions. Using isoform-specific antibodies recognizing SynGAP in mouse and human samples we found distinctive developmental expression patterns for all SynGAP isoforms in five mouse brain areas. Particularly noticeable was the delayed expression of SynGAP-α1 isoforms, which directly bind to PSD-95, in cortex and hippocampus during the first two weeks of postnatal development. Suggesting that during this period other isoforms would have a more prominent role. Furthermore, we observed subcellular localization differences between isoforms, particularly throughout postnatal development. Consistent with previous reports, SynGAP was enriched in the postsynaptic density in the mature forebrain. However, SynGAP was predominantly found in non-synaptic locations in a period of early postnatal development highly sensitive to SynGAP levels. While, α1 isoforms were always found enriched in the postsynaptic density, α2 isoforms changed from a non-synaptic to a mostly postsynaptic density localization with age and β isoforms were always found enriched in non-synaptic locations. The differential expression and subcellular distribution of SynGAP isoforms may contribute to isoform-specific regulation of small GTPases, explaining SynGAP pleiotropy [1)].

1)
Gou G, Roca-Fernandez A, Kilinc M, Serrano E, Reig-Viader R, Araki Y, Huganir RL, de Quintana-Schmidt C, Rumbaugh G, Bayés À. SynGAP Splice Variants Display Heterogeneous Spatio-Temporal Expression And Subcellular Distribution In The Developing Mammalian Brain. J Neurochem. 2020 Feb 18:e14988. doi: 10.1111/jnc.14988. [Epub ahead of print] PubMed PMID: 32068252.