The mechanisms underlying neuronal development and synaptic formation in the brain depend on intricate cellular and molecular processes. The neuronal membrane glycoprotein GPM6a promotes neurite elongation, filopodia/spine formation, and synapse development, yet its molecular mechanisms remain unknown. Since the extracellular domains of GPM6a (ECs) command its function, we investigated the interaction between ICAM5, the neuronal member of the intercellular adhesion molecule (ICAM) family, and GPM6a's ECs. Our study aimed to explore the functional relationship between GPM6a and ICAM5 in hippocampal culture neurons and cell lines. Immunostaining of 15 days in vitro (DIV) neurons revealed significant co-localization between endogenous GPM6a clusters and ICAM5 clusters in the dendritic shaft. These results were further corroborated by overexpressing GPM6a and ICAM5 in N2a cells and hippocampal neurons at 5 DIV. Moreover, results from the co-immunoprecipitations and cell aggregation assays prove the cis and trans interaction between both proteins in GPM6a/ICAM5 overexpressing HEK293 cells. Additionally, GPM6a and ICAM5 overexpression additively enhanced neurite length, the number of neurites in N2a cells, and filopodia formation in 5 DIV neurons, indicating their cooperative role. These findings highlight the dynamic association between GPM6a and ICAM5 during neuronal development, offering insights into their contributions to neurite outgrowth, filopodia formation, and cell-cell interactions [1)]

1)
Gutiérrez Fuster R, León A, Aparicio GI, Brizuela Sotelo F, Scorticati C. Combined additive effects of neuronal membrane glycoprotein GPM6a and the intercellular cell adhesion molecule ICAM5 on neuronal morphogenesis. J Neurochem. 2024 Oct 1. doi: 10.1111/jnc.16231. Epub ahead of print. PMID: 39352694.