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Chemico-genetic discovery of molecules underlying tripartite-synaptic function in vivo

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Neuronal synapses are intimately ensheathed by abundant astroctytic perisynaptic processes, which is critical for synapse formation and function. In contrast to well-studied neuronal synaptic compartments, however, the molecular mechanisms of how astrocytic perisynaptic structures govern neuronal synapses remain ill-defined. Here, we develop a new in vivo chemico-genetic approach, Split-TurboID-GRAPHIC, that uses a cell surface fragment complementation strategy combined with informatics to identify the molecules at astrocyte-synapse junctions in vivo. We identify more than 100 proteins enriched at astrocyte-neuronal junctions. We find novel adhesion molecules highly expressed in cortical astrocytes whose deletion dramatically alters excitatory/inhibitory synaptic balance and also impairs spatial learning. Using Split-TurboID-GRAPHIC we thus establish a new mechanism by which astrocytes coordinate inhibitory synaptic balance with excitation via a chemo-affinity code of the tripartite synapse.