IL-1 receptor accessory protein like1 (IL1RAPL1) complex at the excitatory synapse

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IL1RAPL1 belongs to the IL1/Toll receptor family and shares 52% homology with the IL-1 receptor accessory protein (IL-1RacP). Similar to other members of the IL-1 receptor family, it is characterized by three extracellular Ig-like domains, a transmembrane domain and an intracellular TIR domain. However, unlike the family members, 150 additional amino acids are located at the C-terminus. The homology with IL-RacP is evenly distributed throughout the protein with the exception of the last 150 amino acids, which are present only in IL1RAPL1 and its paralog, IL1RAPL2. The first identified mutation in the *IL1RAPL1* gene was associated with a non-syndromic form of intellectual disability (ID). Similar to some other genes involved in cognitive impairment, *IL1RAPL1* and *IL1RAPL2* mutations are associated with a spectrum of cognitive impairments ranging from ID to autism. We have demonstrated that the C-terminal tail of IL1RAPL1 interacts with PSD-95 and regulates PSD-95 localization to synapses by stimulating c-Jun N-terminal kinase (JNK) phosphorylation at Ser-295. We also found that both IL1RAPL1 and IL1RAPL2 can induce excitatory pre-synapse differentiation and dendritic spine formation. Interestingly, although the extracellular domain is sufficient for inducing pre-synaptic differentiation, both extracellular and intracellular TIR domains are required for dendritic spine formation. Using affinity chromatography, we identified protein tyrosine phosphatase delta (PTPδ) as a binding partner of IL1RAPL1 through its extracellular domain. Using yeast two-hybrid screening, we found that the IL1RAPL1 intracellular TIR domain interacts with RhoGAP2, which is localized at the excitatory post-synaptic density. The interaction of IL1RAPL1 with RhoGAP2 is required to induce dendritic spine formation. Our data indicate that IL1RAPL1 and IL1RAPL2 are part of trans-synaptic signalling pathway that regulates excitatory synapse and dendritic spine formation.