TIPRL, THE MAMMALIAN ORTHOLOG OF TIP41, DIRECTLY INTERACTS WITH THE CATALYTIC SUBUNITS OF TYPE 2A PHOSPHATASES

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Type 2A phosphatases are part of the PPP subfamily that is formed by PP2A, PP4 and PP6, which are the mammalian orthologues of yeast Pph21/22, Pph3 and Sit4, respectively. These phosphatases are key players in the TOR pathway and share as common regulators the yeast Tap42 protein and its mammalian orthologue α4. The yeast Tip41 protein was previously identified in a yeast two-hybrid screen as a binding partner for Tap42 and genetic analyses suggested that it functions as a negative regulator of the TOR signaling pathway. In this study, we performed a yeast two-hybrid screening with the human orthologue of Tip41, TIPRL (TIP41, TOR signaling pathway regulator-like), in order to find a functional context for this protein. Surprisingly, we found that TIPRL interacts directly with the C-terminus of the catalytic subunits of type 2A phosphatases, but not with α4. The TIPRL:α4 complex was reconstituted in vitro only in the presence of PP2Ac, which shows that TIPRL and α4 can bind PP2Ac simultaneously. TIPRL regulates the activity of PP2A in vitro and forms a rapamycin-sensitive complex with PP2Ac in human K562 cells. These findings suggest the existence of a novel rapamycin sensitive PP2A heterotrimeric form (α4:TIPRL:PP2Ac) which structurally resembles the A:B:C complex.

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