

P010 The Rag proteins mediate amino acid signalling to mTORC1

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mTOR Complex 1 (mTORC1) integrates signals from growth factors, amino acid availability, cellular energy content and different stresses to regulate cell growth via its downstream effectors S6K1 and 4EBP1. Downstream of growth factor signaling, mTORC1 activator small GTPase Rheb and inhibitor PRAS40 regulate its activity, both *in vitro* and *in vivo*. Regulation of mTORC1 downstream of amino acid signaling has been controversial and poorly understood. Although Rheb is necessary for activation of mTORC1 by amino acids, constitutively active Rheb cannot overcome mTORC1 inhibition upon amino acid starvation, suggesting that other proteins must be involved in amino acid signaling to mTORC1. In order to find new mTORC1 interacting proteins, we did mass spectrometry analysis of mTORC1 purifications and found RagC as an mTORC1 interacting protein. RagC, and related Rag A, B, D proteins form the Rag family of GTPases. A Rag mutant that is constitutively bound to GTP interacts strongly with mTORC1 and its expression within cells makes the mTORC1 pathway resistant to amino acid deprivation. Conversely, expression of a GDP-bound Rag mutant prevents stimulation of mTORC1 by amino acids. The Rag proteins do not directly stimulate the kinase activity of mTORC1, but, like amino acids, promote the intracellular localization of mTOR to a compartment that also contains its activator Rheb.