**Structure of Small GTPase Human Rheb Provides a Structural Basis for its Unique Biological Function and Reveals a Novel GTP Hydrolysis Mechanism**

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Small GTPase Rheb functions as an important mediator between the tumor suppressor proteins TSC1/TSC2 and the mTOR to stimulate cell growth and possesses unique biological features different from other small GTPases. Structures of human Rheb in complexes with GDP, GTP, and GppNHp reveal unique structural features that provide molecular basis for these distinct properties. During GTP/GDP cycling, switch I undergoes conformational change whereas switch II maintains a stable, unusual extended conformation. The unique switch II conformation results in a displacement of Gln64, making it incapable of participating in GTP hydrolysis and thus accounting for the low intrinsic GTPase activity of Rheb. This rearrangement also creates space to accommodate the side chain of Arg15, avoiding the steric conflict with the catalytic residue and explaining its noninvolvement in GTP hydrolysis. A closed GTP-binding site appears to prohibit the insertion of a potential arginine finger from its GAP. Taken the genetics, biochemical, biological, and structural data together, we propose that Rheb forms a new group of the Ras/Rap subfamily and uses a novel GTP hydrolysis mechanism.

**Keywords: small GTPase, Rheb, mTOR signaling**