Atomistic Equilibrated Full-Length Models of mTORC1 in the Presence and Absence of RHEB Activator.

Abstract: The mammalian Target of Rapamycin Complex 1 (mTORC1) is a large (~1.2Mega-Dalton) complex which acts as a central regulator of cell growth and synthesis by sensing nutrient, energy and stress levels. The dimeric complex consists of 2 protein chains each of mTOR, mLST8, RAPTOR[i]. Dysregulation of mTORC activity has been known to be the reason for many cancers[ii]. Some known effectors[iii,iv,v] cause an increase in mTOR activity whereas other effectors[vi,vii] inhibit mTOR activity. However, the structural, energetic and dynamic basis for the functioning and selectivity of mTORC1 remain poorly understood at present. Recently Cryo-EM studies have provided the first structural views of mTORC1 complex shedding light on the movement of domains in the complex upon binding to molecular effectors[1]. However, the resolution of these structures are too low (3.4 A^0, 3 A^0) to resolve residue-level interactions. Further, these structures lack coordinates for large stretches of residues (2-108) in every protein chain of mTORC1. We have used homology modelling to build structural models of each chain using cryo-EM structure and AlphaFold-2 structures as templates. We have been successful in designing chain assembly protocol to successfully assemble the individual proteins into mTORC1 preserving the protein-protein interactions. The subsequent model have then been equilibrated using classical Molecular Dynamics Simulations to produce a high-resolution refined model of mTORC1. In my AWS I will be presenting analysis of the initial static structures modelled by me and discuss the results of model refinement by equilibration.

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[vi] Yasemin Sancak,*Mol. Cell,***2007** ,25,903-915

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