Séminaire

CONFÉRENCIER INVITÉ

Vendredi 22 Février 2019 à 11h

Salle des séminaires

Institut de biologie structurale - 71 avenue des Martyrs CS 10090 38044 Grenoble Cedex 9 - T.+33 (0)4 57 42 85 00

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Pseudo-atomic structure of TOROID and its implications on the regulation of TORC1 activity

The Target of Rapamycin Complexes (TORC1/2) play key roles in the maintenance of metabolic homeostasis in eukaryote cells. TORC1 localises at the surface of the autophagy-related organelles (vacuole in yeast or lysosomes in mammals) where it sets the balance between macromolecule biosynthesis and turnover according to the presence or absence of nutrient and other types of stress. Yeast TORC1 is a 1.2 Mega Dalton complex formed by the atypical protein kinases Tor1 or Tor2, the WD40 repeat containing proteins Lst8 and Kog1, and protein lacking obvious domains known as Tco89. We have shown that, upon glucose starvation, TORC1 relocalizes into a single condensate on the surface of the vacuole. Purification of these condensates and subsequent electron microscopy (EM) analyses revealed that these condensates represent a regularly ordered assembly of TORC1 dimers that form the biggest helicoidal structure described to date. Our previous low-resolution cryo-electron microscopy (cryo-EM) structure shows that the kinase active sites are occluded by adjacent protomers within the helix which prevents substrate phosphorylation. Thus we called these helices TORC1 Organised in Inhibited Domains (TOROIDs). We also demonstrated that TOROID formation is dependent on the activity of the known TORC1 regulators, the Rag-family GTPases, Gtr1/2. However, the molecular mechanism of this regulation is unclear. We have now determined a high resolution cryo-electron microscopy structure of yeast TOROIDs and the first atomic model of the yeast TORC1. Inspired from these structures, we used CrispR/Cas9 mutagenesis to confirm the roles of conserved residues involved in TOROID assembly. Presently, we are probing possible TOROID - Gtr1/2 interfaces with the hope of understanding how the Rag-GTPases initiate TOROID assembly and disassembly.

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