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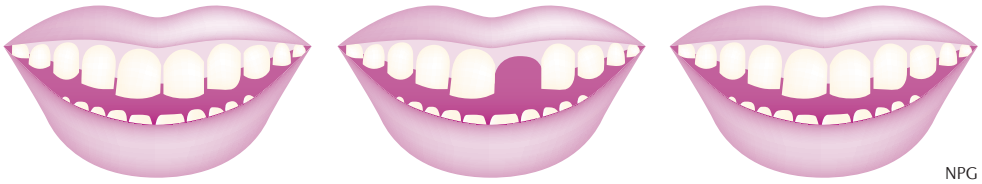
SIGNALLING

Finding the GAPs in mTORC1 signalling



NPG

Tsun and colleagues have identified folliculin (FLCN), a tumour suppressor that is implicated in Birt–Hogg–Dubé hereditary cancer syndrome, as a GTPase-activating protein (GAP) that regulates the nucleotide status of the RAG proteins. The RAG proteins are crucial for the nutrient-sensing response and activation of mTOR complex 1 (mTORC1) kinase.

The RAG GTPases directly interact with mTORC1 to form a heterodimer that consists of RAGA or RAGB (RAGA/B) bound to RAGC or RAGD (RAGC/D); the interaction of this heterodimer with mTORC1 is required for mTORC1 activation. In addition, the nucleotide status (that is, whether the RAGs are in a GTP-bound or a GDP-bound form) is also important in mTORC1 activation. Thus, the GAPs, which promote conversion of GTP to GDP, and guanine nucleotide exchange factors (GEFs), which promote conversion of GDP to GTP, are crucial to mTORC1 regulation. Although RAGA/B have been reasonably well studied, the role of RAGC/D in mTORC1 signalling has been less clear.

> “FLCN–FNIP activity is required for mTORC1 activation.”

Tsun and colleagues first re-examined the nucleotide (GTP- or GDP-bound) status of each of the RAGs. GTP-bound RAGA/B was previously reported to be the major determinant of mTORC1 binding, but this was inferred by examining RAGA/B-mutant proteins, which preferentially had an affinity for either GTP or GDP. Tsun and colleagues sought to conclusively ascertain whether RAGA/B is the major determinant by individually examining the nucleotide state of each RAG, including RAGC and RAGD. Surprisingly, they found that the nucleotide state of RAGC was the most important; specifically, it had to be GDP-bound for mTORC1 binding and activation. Following this, the authors attempted to identify regulators of the nucleotide state of RAGC. They applied an immunoprecipitation–mass-spectrometry approach using epitope-tagged RAG proteins, which consistently identified FLCN as a RAG interactor. They further showed that FLCN, and its binding partner folliculin-interacting protein (FNIP), is a GAP that is specific for RAGC/D and not for RAGA/B, and that FLCN–FNIP activity is required for mTORC1 activation. Moreover, the authors found that the interaction between FLCN–FNIP and the RAGs in cell culture was strengthened in the absence of amino acids. This suggests that FLCN–FNIP is part of the mTORC1 nutrient-sensing machinery. Furthermore, when FLCN is knocked down by short hairpin RNAs, mTORC1 fails to properly localize and does not become active in response to amino acid stimulation, which suggests that FLCN–FNIP is required for nutrient-sensitive activation of mTORC1.

This study raises several interesting questions, which include why FLCN (a tumour suppressor that is lost in several tumour types) activates the growth-promoting mTORC1 kinase. The authors speculate that in tumours with FLCN loss other growth-promoting pathways are activated, and they observe that there are reports of pathways such as MAPK being hyperactivated in FLCN-deleted tumours. Alternatively, there may be other, undescribed proteins that compensate for FLCN loss. This study provides further insight into the molecular components of mTORC1 signalling, in particular those relevant to amino acid sensing, and it describes one of the first molecular roles for FLCN.

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ORIGINAL RESEARCH PAPER Tsun, Z.-Y. *et al.* The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2013.09.016 (2013)