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Cell signaling

Yeast enzyme regulator recognized

A highly conserved cellular pathway is triggered by the presence — and absence — of glucose in yeast

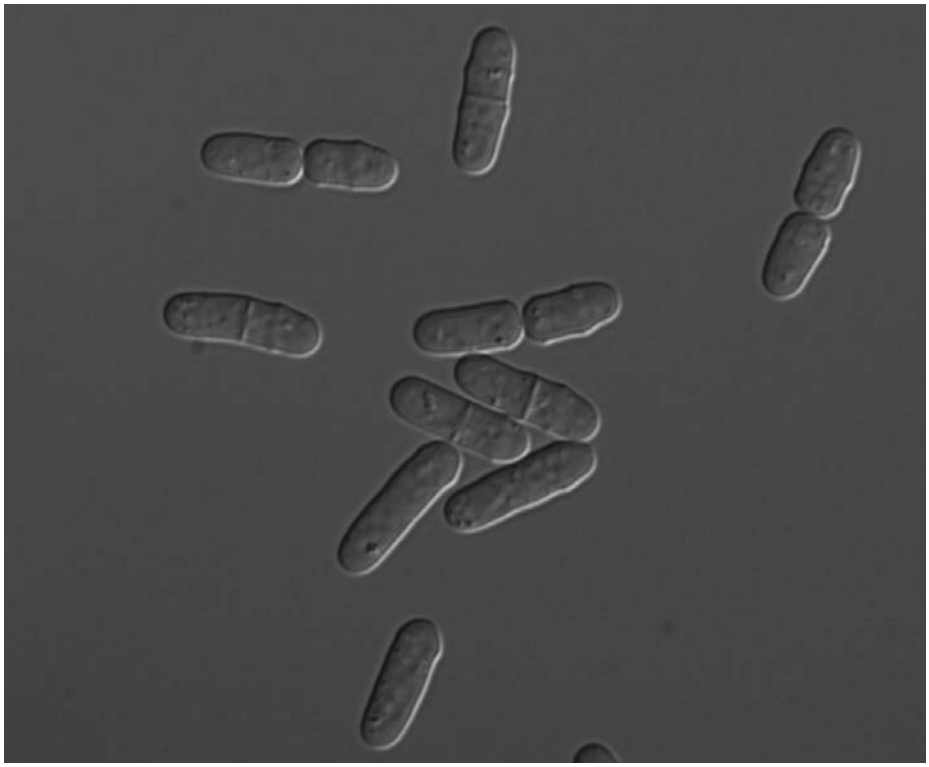
Glucose both positively and negatively controls the activity of an enzyme in a model yeast essential for cell growth, division and stress resistance, find NAIST researchers[1]. This finding could help uncover the regulatory mechanism driving the enzyme's human homologue, which is active in certain cancers.

The enzyme target of rapamycin (TOR) has been conserved during the evolution of various species, indicating its critical importance for the viability of life forms. TOR forms two protein complexes, each of which is controlled by, and controls, a distinct set of upstream and downstream proteins. Recent studies have shown that the essential nutrients nitrogen and carbon activate the TOR complex 1 (TORC1) protein pathway — but the critical trigger for TORC2 had remained elusive.

Previously, the NAIST researchers had demonstrated that a protein belonging to the small GTPase family of enzymes Rhy1 interacts with TORC2 to promote the phosphorylation of another enzyme — Gad8[2]. But they were keen to uncover the whole story. "Nobody knew what stimuli or signals regulate fission yeast Ryh1 and TORC2," explains NAIST's Hisashi Tatebe, who led the study.

After testing the TORC2–Gad8 pathway's responsiveness to nitrogen, which proved tenuous, the researchers considered glucose. They transferred cells of the fission yeast *Schizosaccharomyces pombe* (see figure) from standard growth media containing 3 per cent glucose to media with only 0.02 per cent glucose. Within 5 minutes, the glucose-starved yeast cells stopped dividing and showed no sign of Gad8 phosphorylation.

To identify the role of Ryh1 in the glucose-induced signaling process, the team tried the same experiment with yeast models lacking the Ryh1 protein. Given sufficient glucose in its diet, the mutant yeast showed reduced phosphorylation, confirming the importance of Ryh1 in activating the TORC2–Gad8 pathway.



An important cellular pathway for cell growth, division and resistance to stress in the fission yeast *Schizosaccharomyces pombe* is triggered by both the presence and absence of glucose.

However, after about 30 minutes of surviving under glucose stress, both normal and Ryh1-lacking yeast strains made a surprising recovery, phosphorylating Gad8 at rates similar to those under glucose abundance. This finding suggests an alternative, Ryh1-independent, mechanism of TORC2–Gad8 activation, triggered by the virtual absence of glucose.

"It was totally unexpected that the fission yeast TORC2 pathway is regulated by the paired positive and negative regulatory mechanisms," says Tatebe.

The researchers will conduct genetic screens in yeast to investigate the mysterious resurgence and are eager to find a small GTPase in humans that plays a similar regulatory role to Ryh1 in yeast. "TORC2 activity is indispensable in various cancer cells, but not in normal cells," says Tatebe. "Our findings may offer many clues about TORC2 in humans."

Reference

1. Hatano, T., Morigasaki, S., Tatebe, H., Ikeda, K. & Shiozaki, K. Fission yeast Ryh1 GTPase activates TOR Complex 2 in response to glucose. *Cell Cycle advance online publication*, 15 January 2015 (doi: 10.1080/15384101.2014.1000215).
2. Tatebe, H., Morigasaki, S., Murayama, S., Zeng, C. T. & Shiozaki, K. Rab-family GTPase regulates TOR complex 2 signaling in fission yeast. *Current Biology* **20,** 1975–1982 (2010).

More information about the group's research can be found at the Laboratory of Cell Signaling webpage:
http://bsw3.naist.jp/shiozaki/?cate=207