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CELL SIGNALLING

Rho1 keeps an eye on TORC1

PHOTODISC

> Rho1 is a key mediator of stress signals to TORC1

Target of rapamycin complex 1 (TORC1) in yeast couples cell growth and metabolism with extracellular conditions. As such, TORC1 is regulated by stress, including treatment with the antiproliferative drug rapamycin and nitrogen starvation. Exactly how this regulation occurs has been unclear, but Jiang and colleagues now show that the small GTPase Rho1 is a key mediator of stress signals to TORC1.

TORC1 inactivation by rapamycin involves the dissociation of Tap42-2A phosphatase, which is then free to dephosphorylate downstream targets of TOR kinase. The authors observed that other stresses, such as caffeine treatment and heat, also induced Tap42-2A release. This suggests that these stress signals may exert their effects via a common pathway, such as the cell wall integrity (CWI) pathway, which controls cell wall expansion in response to the cell cycle and stress. A key node in the CWI pathway is Rho1, which the authors find can be activated by several stress stimuli. Thus, they examined whether Rho1 might also transmit these stress signals to TORC1. Indeed, rapamycin treatment triggered a transient interaction between Rho1 and the TORC1 component Kog1, and Rho1 inactivation led to Tap42-2A dissociation from Kog1 and, consequently, TORC1.

Most small GTPases directly bind to their targets to exert their effects, so the authors investigated the interaction between Rho1 and Kog1. They observed that Rho1 directly interacted with the RNC (RAPTOR amino-terminal conserved) domain of Kog1. Importantly, only GTP-bound Rho1 (active Rho1) with an intact effector domain could bind to Kog1 following rapamycin treatment.

But what effect does Rho1 binding have on TORC1? The authors observed that active Rho1 inhibits TOR kinase activity and that this inhibitory effect depends on the Rho1–Kog1 interaction, as Rho1 mutants that cannot bind Kog1 had no effect on TOR kinase activity. Interestingly, both Rho1 and Tap42-2A were found to interact with the RNC domain of Kog1, which suggests that they may compete for binding to Kog1. Indeed, GTP-bound, but not GDP-bound, Rho1 was able to reduce the binding of Tap42-2A to Kog1; this may therefore be the mechanism by which Rho1 inactivates TORC1 following stress-mediated activation.

Together, these findings suggest that in response to stress, Rho1 binds to the TORC1 component Kog1, thereby releasing the TORC1 effector Tap42-2A. Surprisingly, Jiang and colleagues also found that this regulation is mutual, as TORC1 can sense stress signals directly and acts as an upstream regulator of Rho1, promoting Rho1 activation. This reveals a complex mechanism by which yeast cells can integrate their spatial expansion (regulated by Rho1) and growth (regulated by TORC1).

Rachel David

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