CELL CYCLE

Timed cyclin'

The periodic activation of cyclin-dependent kinases (CDKs) by the binding of distinct cyclins is required to drive the cell cycle through S phase and M phase. Loog and Morgan now report in *Nature* that cyclins use different mechanisms to promote the phosphorylation of S-phase- and M-phase-specific substrates.

The Morgan laboratory had previously identified 181 budding yeast Cdk1 substrates. In this recent study, Loog and Morgan measured the rates of phosphorylation of 150 of these substrates by complexes combining the S-phase cyclin Clb5 or the M-phase cyclin Clb2, and Cdk1. Activities of the two complexes were normalized against a nonspecific substrate. About 110 were equally good substrates for Clb5–Cdk1 and Clb2–Cdk1, with most of the remaining substrates being more specific for Clb5–Cdk1. Among these, 14 substrates had between a 10-fold and 800-fold higher specificity for Clb5–Cdk1. No highly Clb2–Cdk1-specific substrates were found.

So what determines the high Clb5 specificity of some substrates? The authors mutated a previously identified cyclin region, known as the hydrophobic patch, that interacts with a sequence motif on some CDK substrates. Mutation of the hydrophobic patch in Clb5 abolished the Clb5 specificity of selected substrates. Loog and Morgan also identified a single KXL motif in the Clb5-specific substrate Fin1, which was responsible for the Clb5 specificity of Fin1 phosphorylation.

Surprisingly, the authors found that Clb2–Cdk1 was ~10–20-fold more active than Clb5–Cdk1 in the phosphorylation of a nonspecific substrate. The authors suggest that this might allow Clb2–Cdk1 to function as a highly efficient kinase for a range of substrates, whereas Clb5–Cdk1 uses its hydrophobic patch to focus on a small subset of S-phase-specific substrates. This also implies that different cyclins can modulate the properties of the CDK in two ways — by influencing the substrate specificity or the intrinsic catalytic activity.

Next, using a yeast strain in which the open reading frame of *CLB5* was replaced by that of *CLB2*, Loog and Morgan analysed whether Clb5-specific substrate phosphorylation also occurs *in vivo*. Whereas two Clb5-specific substrates were fully phosphorylated in early S phase in the wild-type strain, the replacement of Clb5 by Clb2 in the mutant strains delayed the onset, and reduced the extent, of substrate phosphorylation.

The authors conclude that there are probably several mechanisms by which different cyclins help to drive the correct timing of CDK substrate phosphorylation during the cell cycle — and that substrate-specific targeting of CDKs by cyclins is a highly effective one.

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References and links

ORIGINAL RESEARCH PAPER Loog, M. & Morgan, D. O. Cyclin specificity in the phosphorylation of cyclin-dependent kinase substrates. *Nature* **434**, 104–108 (2005)
FURTHER READING Wittenberg, C. Cyclin guides the way. *Nature* **434**, 34–35 (2005)