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Journal club

DECONSTRUCTING THE CELL CYCLE

When I was an undergraduate student, knowing three key concepts would ensure success in 'Cell Cycle 101': that oscillations of cyclin–cyclin dependent kinase (CDK) complexes drive the cell cycle; that directionality is ensured by the irreversibility of periodic proteasome-mediated cyclin degradation; and that checkpoints ensure the dependence of later cell cycle steps on the completion of earlier events. A recent study by Coudreuse and Nurse now suggests that only the first concept may be fundamentally essential for cell cycle progression.

> "cell cycle directionality is established by increasing CDK activity."

Using the fission yeast, the authors generated a translational fusion of its only CDK (Cdc2) and the major cyclin, Cdc13. This monomolecular module drives normal cell cycle progression even in the absence of the endogenous CDK and major cyclins. The authors then introduced mutations affecting cyclin function or proteasome-mediated destruction, and generated a CDK moiety that could be chemically inhibited, to demonstrate three major features.

First, they showed that cell cycle progression through S phase and M phase are driven by distinct thresholds of CDK activity, with M phase requiring a higher level than S phase. Remarkably, natural oscillations in cyclin levels through protein degradation can be functionally replaced with oscillations in CDK activity by modulating exogenous chemical inhibitor levels. Second, cells with high CDK activity can enter mitosis from any cell cycle stage, without activating the S phase checkpoint. This establishes that M phase exists independently of passage through S phase, and that the S phase checkpoint requires intermediate CDK levels. Thus, cell cycle directionality is established by increasing CDK activity. Finally, this system becomes much less dependent on normal CDK regulation by stoichiometric inhibitors and inhibitory phosphorylation, especially for cell size control, indicating that known regulatory mechanisms can be bypassed by forcing cyclin–CDK complex formation, and that other regulatory mechanisms must exist.

Although cell cycle regulation in extant eukaryotes is exceedingly complex, these studies suggest how a simplified oscillatory system may have driven the cell cycle in primitive eukaryotic cells.

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ORIGINAL RESEARCH PAPERS Coudreuse, D. & Nurse, P. Driving the cell cycle with a minimal CDK control network. *Nature* **468**, 1074–1079 (2010)