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CELL DIVISION

CDK1 in the driving seat

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The division of mammalian cells is thought to require the sequential activation of at least four cyclin-dependent kinases (CDKs) — CDK2, CDK3, CDK4 and CDK6 — during cell-cycle interphase, followed by the activation of CDK1 (which is encoded by *Cdc2a*). However, Barbacid and colleagues now show that CDK1 activity alone can drive the mammalian cell cycle through cell division, as is the case in unicellular organisms such as yeast.

Based on previous evidence that mice can survive without individual interphase CDKs and that mouse cells proliferate even when they lack up to three of these CDKs, the authors generated triple knockout (TKO) mouse embryos that lacked the interphase kinases CDK2, CDK4 and CDK6 (most laboratory strains, including this TKO strain, lack CDK3 owing to a naturally occurring mutation). The resulting embryos underwent organogenesis and developed to mid-gestation, which indicates that CDK1 alone is sufficient for completion of the cell cycle. Despite the lack of interphase CDKs, these TKO embryos showed normal expression levels of other cell-cycle regulators, including CDK1 and various cyclins. CDK1 bound G1–S cyclins and phosphorylated the retinoblastoma (RB) protein normally, which resulted in the inactivation of RB and the subsequent release of E2F transcription factors to activate genes that are required for cell-cycle progression.

> “…CDK1 activity alone can drive the mammalian cell cycle through cell division…”

Primary mouse embryonic fibroblasts (MEFs) obtained from these TKO embryos displayed reduced cell proliferation owing to a slower cell cycle. By inactivating RB-family members using a retrovirally encoded fragment of the simian-virus-40 large T antigen, the proliferation rates of TKO MEFs were restored to wild-type levels, which indicates that the slower cell cycles are a result of incomplete inactivation of RB proteins and, thus, reduced E2F activity.

Barbacid and colleagues then investigated whether CDK1 was essential for cell division by crossing mice that were heterozygous for a mutant *Cdc2a* gene in an attempt to produce homozygous *Cdc2a* mutants. No embryos could be detected, even in the morula stage (16–64 cells), which suggests that CDK1 may be essential for cell division. This result also implies that the activity of CDK1 cannot be replaced by the presence of interphase CDKs during development.

The intriguing question that remains is how interphase CDKs function in driving cell division in specialized cell types, in which CDK1 cannot compensate for their absence. The authors suggest that “interphase CDKs, but not CDK1, might phosphorylate substrates that are unique to those cell types in which they are essential.”

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ORIGINAL RESEARCH PAPER Santamaria, D. *et al.* Cdk1 is sufficient to drive the mammalian cell cycle. *Nature* **448**, 811–815 (2007)
FURTHER READING Bloom, J. & Cross, F. R. Multiple levels of cyclin specificity in cell-cycle control. *Nature Rev. Mol. Cell Biol.* **8**, 149–160 (2007)