nature publishing group
webfocus oncelldivision

Milestone 5

This bud's for you!

When Lee Hartwell and his colleagues launched the study of cell-cycle genetics, detailed morphological descriptions of the cell cycle were available in several organisms. But nothing was known about the mechanisms for achieving the orderly progression of cell-cycle events. The leap of faith taken by Hartwell was that the cell cycle might depend on a set of genes — cell division cycle or *cdc* genes — whose function is required at specific timepoints in the cycle. He found evidence for these genes by identifying mutants that arrested the cell cycle at a specific stage.

Courtesy of Steve Reed and Steve Haase

The organism that Hartwell chose to study was the budding yeast, *Saccharomyces cerevisiae*. Because the cell cycle is an essential process, mutagenized yeast cultures were screened for temperature-sensitive mutants that grew and divided normally at the permissive temperature, but arrested cell division with a characteristic phenotype at the restrictive temperature. The first paper to describe *cdc* mutants was by Hartwell, Culotti and Reid, who also coined the term 'execution point' — the stage in the cell cycle when the gene function is required. In this paper, three *cdc* genes were described, which paved the way for the identification of many more such genes, and for the discovery of the molecules and mechanisms controlling the cell cycle.

Although routine methods for cloning yeast genes were still ten years away, Hartwell's work went much further. With thoughtful and elegant genetic analysis, Hartwell used the mutants as tools to block the cell cycle at specific stages and to ask questions about the interdependence of yeast cell-cycle events. For example, in his *J. Mol. Biol.* paper, Hartwell concluded that DNA synthesis is required for later events, such as nuclear division. By contrast, the formation of the bud is not dependent on DNA replication, although DNA replication does prevent further bud initiation in the same cell cycle.

Three years on and yeast cell-cycle genetics was well established — as demonstrated by the synthetic model of the cell cycle that was presented in *Science*. Genetics had divided the cycle into two parallel pathways, which comprised two sets of dependent steps and involved a total of 19 *cdc* genes. At the beginning of the cell cycle, both pathways depend on the completion of a step that Hartwell *et al*. termed 'start'. This event is defined by the famous *cdc28* mutant (famous because the *cdc28* gene was later shown to encode the founding member of the cyclin-dependent kinase family), and is also the event at which yeast mating factor arrests cell division to prepare cells for mating. With amazing prescience, the authors speculated that 'start' would turn out to be an important control point for the cell cycle in many eukaryotes. Cell cycle genetics was out of the blocks and off to a flying start of its own.

Mark Patterson, Editor, *Nature Reviews Genetics*

References

ORIGINAL RESEARCH PAPERS
Hartwell, L. H., Culotti, J. and Reid, B. Genetic control of the cell-division cycle in yeast I. Detection of mutants. *Proc. Natl Acad. Sci. USA* **66**, 352-359 (1970)

Hartwell, L. H. Genetic control of the cell-division cycle in yeast II. Genes controlling DNA replication and its initiation. *J. Mol. Biol.* **14**, 183-194 (1971)

Hartwell, L. H. *et al*. Genetic control of the cell division cycle in yeast. *Science* **183**, 46-51 (1974)