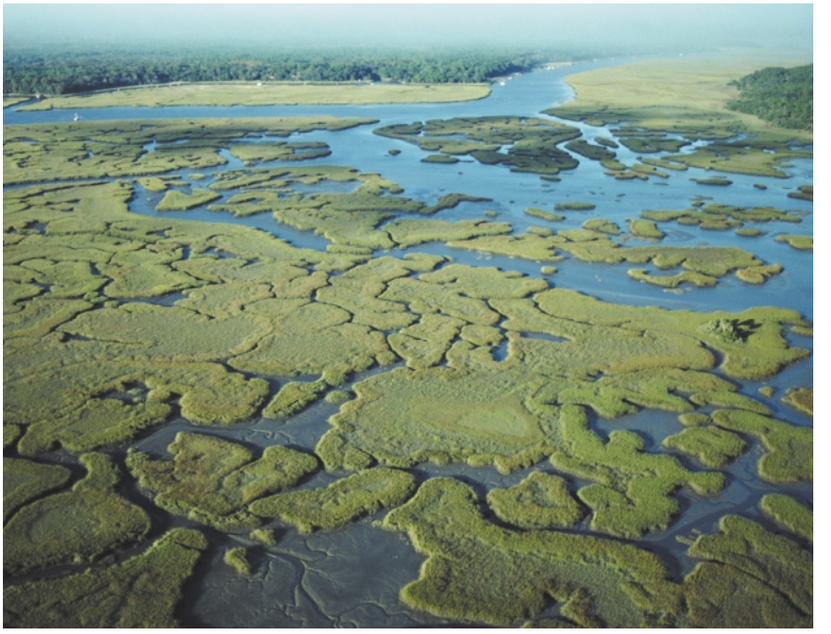
HIGHLIGHTS

CELL CYCLE

Deadly Archipelago



Cyclin E, as its name suggests, is expressed in a cyclical fashion — it accumulates at the G1–S boundary, where it controls entry into S phase, and is then destroyed by ubiquitin-mediated proteolysis. Defects in the proteolysis of cyclin E can lead to accelerated entry into S phase, genetic instability and tumorigenesis; hence the need to identify the factor that targets it for destruction. Two papers in *Nature* and one in *Science* now not only uncover the identity of this factor, but also show that it is mutated in several human cancer cell lines.

Moberg and colleagues started with a screen to identify *Drosophila* mutants that lead to increased cell proliferation. They identified over 23 loci, one of which they termed *archipelago* (*ago*). Within *ago*-mutant clones, the ommatidial clusters of the retina contained extra cells that seemed to arise from extra cell divisions. So the authors examined *ago*-mutant cells for increased levels of positive cell-cycle regulators, and found elevated Cyclin E protein, yet no increase in any other cyclins or in levels of *cyclin E* messenger RNA.

The Archipelago protein contains seven WD40 repeats, which are thought to be involved in protein–protein interactions, and an F-box. The F-box is a common signature in SCF (Skp1/Cullin/F-box protein) complexes, a large family of E3 ubiquitin ligases that control the selection of target proteins for ubiquitylation. So could Archipelago target Cyclin E for ubiquitin-mediated destruction? Moberg *et al.* showed that Archipelago could indeed bind Cyclin E, and that this correlates with the ability of Archipelago to down-regulate Cyclin E *in vivo*.

The WD40 repeats and F-box were also features of the proteins that were identified by the other two groups in yeast. These groups started from the assumption that the SCF complex might be involved in the turnover of cyclin E, and compared this process in wild-type yeast versus strains that were defective in components of the SCF — Cdc53, Skp1 and Cdc4. In each case, levels of cyclin E were stabilized in the SCF mutant strains.

From these initial findings, the two groups narrowed down the culprit to a protein that they called Fbw7 (Koepp *et al.*) or Cdc4 (Strohmaier *et al.*). Koepp *et al.* showed that overexpression of Fbw7 decreased the levels of cyclin E, whereas inhibition of Fbw7 increased cyclin E accumulation. Strohmaier *et al.* identified the human homologue of yeast Cdc4, and confirmed that this protein is not only part of the SCF complex, but that it can also ubiquitylate cyclin E in a phosphorylation-dependent manner. Finally, Moberg *et al.* and Strohmaier *et al.* showed that the human homologue of the protein that was identified in *Drosophila* and yeast is mutated in cell lines derived from ovarian and breast carcinomas.

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References and links

ORIGINAL RESEARCH PAPERS

Moberg, K. H. *et al.* Archipelago regulates Cyclin E levels in *Drosophila* and is mutated in human cancer cell lines. *Nature* **413**, 311–316 (2001) | Strohmaier, H. *et al.* Human F-box protein hCdc4 targets cyclin E for proteolysis and is mutated in a breast cancer cell line. *Nature* **413**, 316–322 (2001) | Koepp, D. M. *et al.* Phosphorylation-dependent ubiquitination of cyclin E by the SCF^{Fbw7} ubiquitin ligase. *Science* **294**, 173–177 (2001)