# HIGHLIGHTS



CELL CYCLE

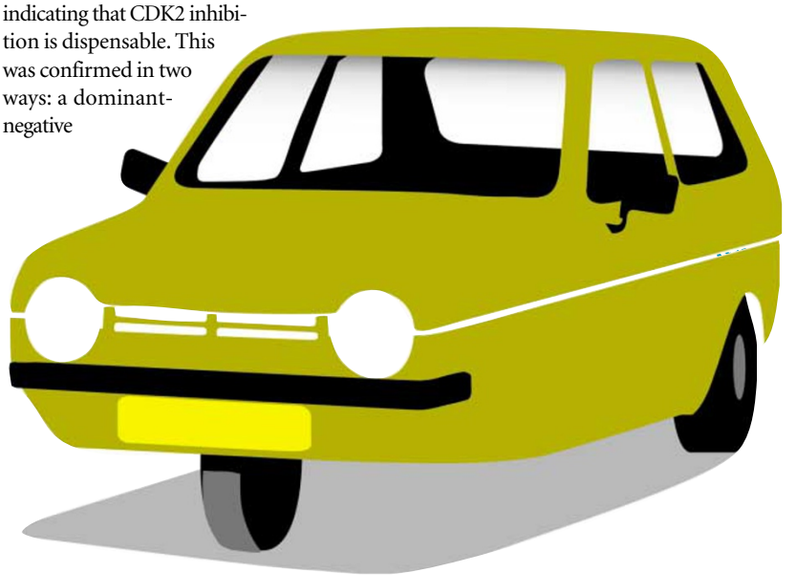
## Three-wheel drive

Ever heard of a three-wheeled car? Although this might sound strange, cars can be driven with what would first appear to be a key component missing. And, surprisingly, the same is also true of cells. Osamu Tetsu and Frank McCormick report in *Cancer Cell* that cells can continue to cycle in the absence of CDK2.

The authors were investigating the mechanism of action of mitogen-activated protein kinase kinase (MEK) inhibitors, such as U0126 and PD 184352, in colon cancer cells, and discovered that they cause G1 arrest. This was due to reduced levels of various proteins — cyclins D1 and D3, cyclin-dependent kinase (CDK) 4 and the CDK inhibitor WAF1 — that ultimately decrease the activity of CDK4–cyclin-D complexes.

CDK2–cyclin-E complexes are also thought to be required for the G1–S transition, but CDK2 protein levels remain stable as cells arrest in G1. However, the kinase activity might be inhibited by redistribution of the CDK inhibitor KIP1 from CDK4 to CDK2 complexes. By immunoprecipitating CDKs and looking for the associated proteins, the authors showed that the association between CDK2 and KIP1 does increase following MEK inhibition, and this corresponded with a decrease in CDK2 kinase activity.

So, is it more important to inhibit CDK4 or CDK2 for this G1 arrest? Overexpressing KIP1, which predominantly inhibits CDK2, does not cause growth arrest in colon cancer cells, indicating that CDK2 inhibition is dispensable. This was confirmed in two ways: a dominant-negative



CDK2 did not cause cell-cycle arrest, and the arrest induced by U0126 was not rescued by KIP1 antisense, which restored CDK2 activity. Interestingly, a specific CDK4 inhibitor could induce cell-cycle arrest in cultured cells, indicating that CDK4 inhibition was sufficient for this.

Not only is CDK2 inhibition not required for arrest, but cells seem to proliferate happily in its absence. Decreasing CDK2 levels and activity by either antisense treatment or RNA interference in colon cancer cells, as well as in $RB^+$ and $RB^-$ cervical cancer and osteosarcoma cells, failed to induce a growth arrest. This also occurred in the presence of CDK4 inhibitors, so proliferation without CDK2 does not depend on CDK4, despite the fact that CDK4 can phosphorylate key sites in RB — normally phosphorylated by CDK2 — that are important for the G1–S transition.

As well as questioning the requirement for CDK2 in cancer-cell proliferation, this study also has an important impact on the development of CDK2 inhibitors, which are progressing through the clinical trial system at present. We should certainly re-think their use, in light of these results.

*Emma Greenwood*

### References and links

**ORIGINAL RESEARCH PAPER** Tetsu, O. & McCormick, F. Proliferation of cancer cells despite CDK2 inhibition. *Cancer Cell* **3**, 233–245 (2003)

**WEB SITE**
Frank McCormick's lab:
http://cc.ucsf.edu/mccormick/