Because *nat*-mutant cells had problems adhering to each other, Trinh and Stainier again inspected their architecture. Some cell-junctional components such as atypical protein kinase C and zonula occludens-1 were missing, and the cells were disorganized. So cell adhesion to fibronectin somehow influences the formation and/or integrity of junctions in myocardial precursors. Cell attachment to fibronectin is also required for the myocardial epithelia to mature, as none of the cell-shape changes that are associated with this process occurred in *nat* mutants.

Fibronectin, therefore, seems to be required for getting myocardial precursor cells together as polarized epithelia and choreographing their movement to the midline. The authors propose that this goes beyond the more traditional role of fibronectin as a substrate for cell migration.

Katrin Bussell

References and links

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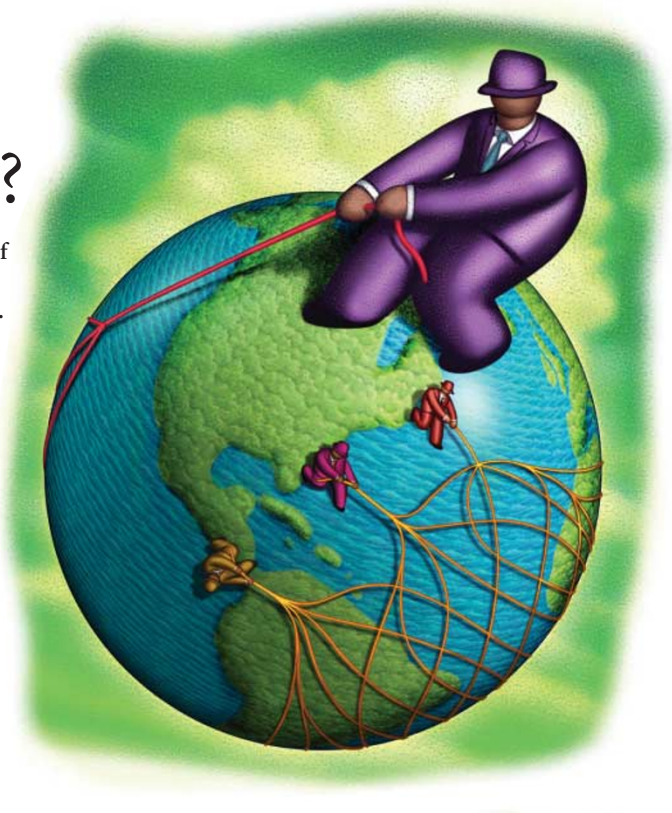
CELL CYCLE

The APC: a control freak?



Waves of ubiquitin-dependent degradation of key cellular regulators are required to help drive the cell cycle through its various phases. In *Nature*, two complementary papers by Bashir *et al.* and Wei *et al.* now show that the anaphase-promoting complex/cyclosome (APC/C), a well-known regulator of mitosis, in complex with the activator subunit CDH1 (APC/C^{CDH1}), is also required in late G1 phase to control the activity of its fellow ubiquitin-ligase complex SCF^{SKP2} (the SKP1/CUL1/F-box protein complex that contains the specific substrate-targeting F-box protein SKP2).

As components of an SCF ligase ($SCF^{SKP2–CKS1}$), SKP2 and its cofactor CKS1 regulate the degradation of the cyclin-dependent-kinase inhibitors p27 and p21. These, in turn, regulate the onset of S phase. SKP2 is an oncoprotein that is often overexpressed in human cancers and the two groups set out to clarify how SKP2 is regulated.

Both studies showed that the amount of SKP2 fluctuates during the cell cycle, being at its lowest during G1 phase. Bashir *et al.* also showed that CKS1 follows a similar pattern of abundance, and downregulation of both SKP2 and CKS1 is prevented by treatment with a proteasome inhibitor.

Overexpression of the APC/C subunit CDH1 by Bashir *et al.*, in conjunction with SKP2 and CKS1 overexpression, caused a considerable destabilization of SKP2 and CKS1, but this was not the case when the alternative APC/C activator subunit CDC20 was overexpressed. Similarly, Wei *et al.* showed that overexpression of CDH1 reduces the amount of SKP2, but that this SKP2 downregulation can be attenuated by proteasome inhibitors.

Short interfering RNAs (siRNAs) were then used in both studies to deplete the levels of CDH1 and SKP2 in synchronized cells. Wei *et al.* showed that *CDH1*-depleted cells contained an increased amount of SKP2, which led to attenuated p27 accumulation and accelerated entry into S phase. This accelerated cell-cycle progression in *CDH1*-siRNA-treated cells was abrogated by the simultaneous addition of *SKP2* siRNA. Similar results were obtained by Bashir *et al.* — so SKP2 must be an essential APC/C^{CDH1} target. In addition, when CDH1 is silenced, CKS1 is also stabilized in both cycling G1 cells and in cells withdrawing from the cell cycle.

Both groups also showed, using SKP2 mutants, that SKP2 interacts with CDH1 through its amino terminus, which contains a destruction-box (D-box) motif, and that APC/C^{CDH1} polyubiquitylates SKP2 in a D-box-dependent manner. Bashir *et al.* also noted that expression of a stable SKP2 mutant (at levels identical to the endogenous SKP2 protein) caused accelerated S-phase entry in these cells. But, wild-type SKP2 expressed at physiological levels was regulated by proteolysis and unable to speed up entry into S phase. Therefore, SKP2 destruction must be an essential event in cell-cycle control.

So, these studies show that, apart from its role in the control of mitosis, the APC/C complex is also important for preventing the unscheduled degradation of $SCF^{SKP2–CKS1}$ substrates during G1 phase and the consequent premature entry into S phase that could cause genetic instability. Indeed, Wei *et al.* suggest that APC/C^{CDH1} might have tumour-suppressor activity through its inhibition of SKP2, high concentrations of which correlate with the destabilization of p27 in human cancers.

Lesley Cunliffe

References and links

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