trolling the magnitude of the transcriptional response. Second, $SCF^{SKP2}$ may be responsible for the removal of E2F-1 after completion of S phase, thereby resetting the balance for the next cell cycle.

At present, there is no evidence that association of E2F-1 with SKP2 requires phosphorylation of E2F-1, unlike other interactions between substrates and F-box proteins. Instead, the timing of E2F-1 ubiquitination seems to depend on the timing of expression of SKP2. If so, this is the first example of an SCF-dependent process that is phosphorylation independent. However, it is conceivable that SKP2 can interact with E2F-1 only after E2F-1 has been displaced from DNA, an event mediated by cyclin A–CDK2. Thus, the timing of ubiquitination could still be phosphorylation dependent, albeit indirectly so.

SKP2 is itself cell-cycle-regulated at the transcriptional level, so perhaps E2F-1 might have a hand in its own destruction by regulating transcription of *SKP2*, much as mitotic cyclins set up their own destruction by activating the anaphase-promoting complex. This idea remains to be tested. Note that although one of SKP2's substrates is E2F-1, it must have other substrates too because its role in E2F-1 regulation cannot explain its requirement in the G1-to-S-phase transition.

F-box proteins are a versatile set of tools that can be used by the cell to perform its many tasks. Transcriptional control is particularly well suited to the form of regulation offered by the diversity of F-box proteins. These proteins may play a part in controlling multiple transcriptional pathways in addition to that involving E2F-1. For example, the β-TrCP/slimb protein has been implicated in activation of the transcription factor NF-κB/Dorsal through destruction of the regulator $I\kappa B\alpha$[10–12], in inactivation of the β-catenin pathways through constitutive turnover of β-catenin in the absence of signalling through Wnt[10,13], and in control of the Hedgehog pathway through an unknown mechanism (Fig. 1)[13]. In addition, three F-box proteins in budding yeast (Cdc4, Grr1 and Met30) may be involved in controlling metabolic transcriptional programs as well as cell-cycle functions (Fig. 1)[8].

A theme that has emerged is that F-box proteins can target multiple proteins that frequently bear no obvious relationship to one another. Matching targets and pathways with an ever-growing number of F-box proteins will be a challenge for the future. □

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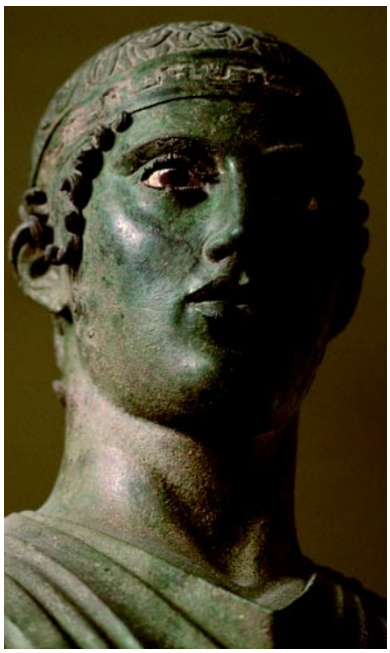
# The strain of copper on the brain

Transmissible spongiform encephalopathies (TSEs), such as scrapie in sheep and Creutzfeld–Jakob disease (CJD) in humans, occur as numerous different strains in each species. The existence of these stable variants of the disease is one of the main unresolved issues for Stanley Prusiner's prion hypothesis, or 'protein-only hypothesis', of TSEs. This hypothesis proposes that the infectious agent in TSEs is a rogue form ($Prp^{Sc}$) of a cell's normal prion protein ($Prp^{C}$), possibly along with a putative non-nucleic-acid cofactor.

Strains are a problem for Prusiner's hypothesis because, assuming that each strain represents a different conformational version of the prion protein, it is unclear how the protein can adopt, under physiological conditions, as many different conformations as there are strains of TSEs. Elsewhere in this issue (*Nature Cell Biology* **1,** 55–59; 1999), John Wadsworth and colleagues report an intriguing link between metal-ion occupancy of the prion protein and its biochemical strain characteristics.

Recent research has focused on the copper-binding capabilities of the amino-terminal domain of $Prp^{C}$ as a clue to understanding the protein's normal cellular function. Wadsworth and colleagues look instead at metal-ion occupancy in $Prp^{Sc}$



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isolated from two biochemically distinct strains of sporadic CJD. They use metal-chelating agents to disrupt binding of $Prp^{Sc}$ to $Cu^{2+}$ and $Zn^{2+}$; this treatment slightly alters the electrophoretic mobility of the cleavage products of $Prp^{Sc}$ after limited proteolysis of the prion protein using proteinase K — one of the biochemical indicators of strain in TSEs.

It would be tempting to claim that this observation points to a molecular explanation of TSE strains, with metal-ion occupancy determining strain specificity, but this would be premature. For a start, Wadsworth and colleagues found that the effect on $Prp^{Sc}$ biochemistry of altering metal-ion occupancy extends to only two of the four biochemically defined strains of CJD, and so does not seem to offer a general explanation for strain variation. It also remains to be shown whether or not these altered strain characteristics can be transmitted experimentally to animals in inocula pretreated with chelators. But this provocative link between the copper-binding capabilities of prion protein and strain variations in $Prp^{Sc}$ points research in a new direction.

**HARRIET COLES**

  