is curtailed; but is it also required to maintain the tumours once they have formed? Switching off c-Myc, 14 days after its induction, resulted in a reversal of the tumorigenic process: β-cells exited the cell cycle, E-cadherin was re-expressed and cells re-established cell–cell contacts, and endothelial cells and β-cells apoptosed. Even mice that had expressed c-Myc for 8 weeks, with extensive tumours that had invaded into lymph nodes, made a full recovery following c-Myc deactivation.

These results challenge the paradigm that carcinogenesis is a multistep process that requires many mutations, and indicate that, instead, it can be driven by deregulated expression of a single growth-deregulating oncogene, provided apoptosis is suppressed. If this is found to be true for other commonly mutated oncogenes, new cancer therapeutics should aim to inhibit these few crucial molecular targets.

Emma Greenwood,
Associate Editor, Nature Reviews Cancer

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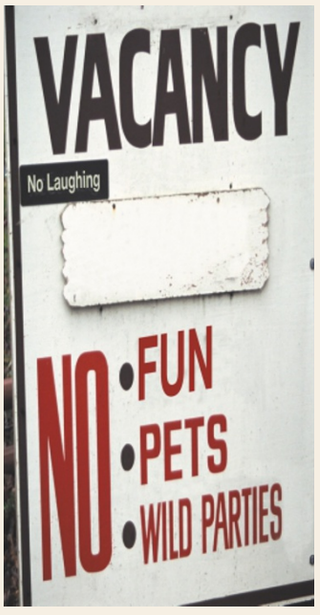

UBIQUITYLATION

A supporting role

Thousands of chemical modifications — such as ubiquitylation — occur after proteins have been synthesized. One function of ubiquitylation is to target proteins for degradation by the 26S proteasome. SCF (Skp1–Cullin–F-box protein) and SCF-like complexes are the largest family of ubiquitin-dependent ligases — or E3s — that mediate one step of ubiquitylation, and Pavletich and colleagues now describe the 3.2-Å crystal structure of the Cul1–Rbx1–Skp1–F-box^{Skp2} SCF complex in *Nature*.

E3s act at the last step of a process that involves ubiquitin-activating (E1) and ubiquitin-conjugating (E2) enzymes. They have an important role in conferring specificity on the ubiquitylation pathway, as they bind to both an E2 and a protein substrate to mediate the transfer of ubiquitin between them.

Pavletich and co-workers found that the Cul1–Rbx1–Skp1–F-box^{Skp2} SCF complex has an elongated structure, with Rbx1 (a RING finger protein that is an essential component of SCF) and Skp1–F-box^{Skp2} — the protein substrate-recognition complex — located at opposite ends of the complex. They showed that this arrangement is organized by Cul1 — an elongated protein with a long stalk (amino-terminal helical region or NTD) and a carboxy-terminal globular domain (CTD). Cul1 acts as a scaffold, making contacts with all of the other SCF subunits.

The authors found that the Cul1 NTD is made up of three cullin-repeat motifs, which form a long arc shape, and that the amino-terminal tip of the first repeat binds Skp1–F-box^{Skp2}. They also established that the Cul1 CTD binds Rbx1 through an intermolecular β-sheet to form the region that recruits E2s.

Pavletich and colleageus observed no flexible linkages in the Cul1–Rbx1–Skp1–F-box^{Skp2} complex, so they made a Cul1-mutant construct to test the importance of this rigid architecture. In this mutant, the NTD–CTD interface was disrupted and these domains were connected by a flexible linker. Although this construct could still bind to its protein substrate in the presence of the necessary substrate-recognition proteins, and could polymerize ubiquitin independently of substrate, the authors found that it could not ubiquitylate its substrate *in vitro*. They took this to indicate that the rigidity of the Cul1 scaffold, and of the entire SCF, is important for E3 activity.

The SCF structure was used by the authors to make a model of an SCF–E2 complex, which showed that the protein substrate and the E2 would be located on one side of the SCF complex. This architecture led them to propose that Cul1 evolved its long stalk to keep the substrate binding and catalytic activities separate, and to accommodate substrates of different sizes that have varying spaces between their prospective ubiquitylation site and their SCF-binding motif.

They further speculate that this type of E3 might facilitate the transfer of ubiquitin by positioning the protein substrate in a way that optimizes its presentation to the E2. Although the extent to which this positioning occurs is unclear, they propose that, as no sequence or structural motif has yet been identified for a ubiquitylation site, the spatial constraints that are imposed by E3s might have an important role in determining this specificity.

Rachel Smallridge

References and links

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