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p27 destruction: Cks1 pulls the trigger

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Recent work has discovered the role of the cyclin-dependent kinase (CDK)-binding protein Cks1 in degrading the CDK inhibitor p27^{Kip1}. This process is essential for DNA replication and is aberrantly enhanced in cancer. Surprisingly, new work indicates that this function of Cks1 is independent of CDKs and links Cks1 with the Skp2 subunit of the SCF ubiquitin ligase.

The cell's ability to self-reproduce is a fundamental feature of life, essential for species continuation and embryonic development, as well as tissue renewal in adult organisms, including humans. Cellular self-reproduction reflects the workings of the cell division cycle machinery, whose two major driving forces, the activi-

ties of cyclin-dependent kinases (CDKs) and ubiquitin-mediated, proteasome-dependent proteolysis, are carefully orchestrated at multiple levels. Failure to control the cell cycle adequately can lead to diverse life-threatening diseases such as cancer.

This aspect has motivated the rapid pace of discovery in this dynamic field of cell

biology. Given the impressive progress of cell cycle research over the past decade or so, it is surprising that a group of essential, phylogenetically conserved cell cycle regulators known as the Cks/Suc1 proteins have not been linked with a specific molecular function for some 15 years. The work of two research teams^{1,2} using different approaches has recently converged to reveal an unexpected role for Cks1, one of the two mammalian Cks orthologues. Cks1 seems to be an essential accessory factor for SCF^{Skp2}, the ubiquitin ligase that targets the p27^{Kip1} CDK inhibitor for proteasome-dependent destruction, thereby allowing CDK activity to drive cells into S phase. This discovery is intriguing from several points of view and it has important implications for biomedicine.

In the first report, Ganoth *et al.*¹ identified Cks1 as the missing factor that complemented the otherwise inefficient ubiquitinylation of p27^{Kip1}. This was done by reconstituting the SCF^{Skp2} complex purified from insect cells using baculovirus expression vectors complemented with factors biochemically

Stung by WASP

Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) are disorders resulting in variable immunodeficiency. The protein mutated in these diseases, WASP, is expressed in cells of a haematopoietic lineage and is known to regulate the actin cytoskeleton by linking signalling via Rho-family GTPases and activation of the Arp2/3 complex, which promotes actin nucleation and crosslinking.

A recent paper in *Nature Genetics* by Devriendt and colleagues (*Nature Genetics* **27**, 313–317; 2001) describes a third disorder arising from a defect in WASP: X-linked severe congenital neutropenia (XLN). Linkage analysis of a family whose male members displayed immunodeficiency and neutropenia revealed the presence of a single base-pair mutation (resulting in an L270P substitution) in WASP. This finding was surprising because both WAS and XLT patients have normal neutrophil counts, and, although no WASP was detectable in an XLT cell line, WASP was present in almost normal amounts in XLN lines.

WASP activity is regulated by an intramolecular interaction between its GBD and VCA domains. Binding of Cdc42 to WASP disrupts this interaction and allows WASP to interact with and activate the Arp2/3 complex. L270 (green residue in figure) is located within an α helix that is part of the hydrophobic centre of the GBD–VCA globular domain (which is shown in the figure). Thus, it seemed likely that a kink introduced by the substitution of a proline residue in the mutated WASP would relieve the autoinhibition, effectively producing a constitutively active molecule. In agreement with this idea, when this mutation was introduced into different constructs encompassing the autoinhibitory domains, the stability of the proteins was decreased because the domain was now unfolded.

In addition, the affinity of these proteins for Cdc42 was enhanced because the GBD domain was no longer buried. Finally, a construct containing the mutation and both domains was much more effective at stimulating the activity of the Arp2/3 complex *in vitro*, such that the addition of Cdc42 elicited no further stimulation.

The question now to be addressed is: how does constitutive activation of WASP result in neutropenia? Devriendt and colleagues propose that the constitutively activated WASP prevents normal signalling via Cdc42 and leads to higher cellular levels of F-actin. Because actin filaments and the cytoskeleton are involved in many aspects of T cell activation, shape and motility, this might be the basis for the different effects of WAS and XLT on the one hand, and XLN on the other. Thus, WASP joins the small cohort of proteins in which different disorders can be ascribed to activating and inactivating mutations.

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