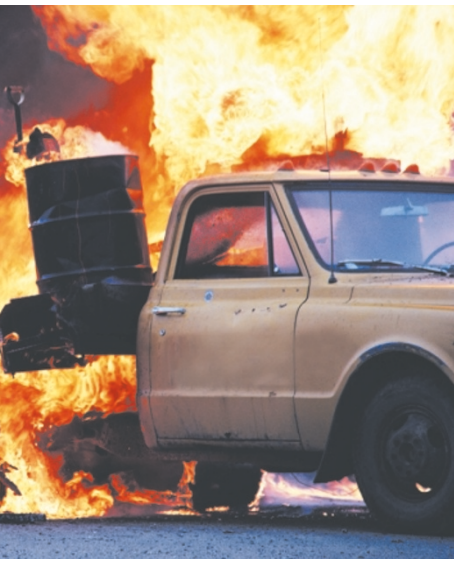

processing signal located upstream of the termination codon (as is found in 1.2% of expressed sequence tags from *S. cerevisiae*), or the nonstop mRNAs might be created when 3′-end formation takes place upstream of the normal termination after RNA polymerase pausing, when ribosomes pause at rare codons or normal termination codons, or 3′–5′ decay is initiated on ribosome-bound mRNA. Nonstop decay is also initiated after manipulations that increase read-through of termination codons, as occurs after administration of aminoglycoside antibiotics.

Simon Frantz

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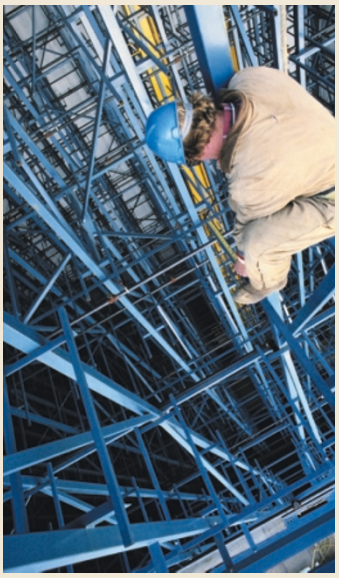

CELL CYCLE

Daughter control

Controlling cytokinesis so that two identical daughter cells are formed from mitosis is one of the many crucial steps in the cell-cycle pathway. And despite intense study, the mechanisms involved in this process are still unknown. But enter a new player, report Fujikawa and colleagues in *Proceedings of the National Academy of Sciences*. They have found that Vav3 is regulated in a cell-cycle-dependent manner and could be involved in cytokinesis regulation.

The Vav family are guanine nucleotide exchange factors for Rho-family GTPases. Although the three members of the Vav family (Vav1–3) are highly similar (50–70% homology at the amino-acid level) and share certain domains, recent studies had shown that Vav3 might regulate RhoGTPases in a different manner to Vav1 and Vav2.

The exact function of Vav3 is unknown, but *in vitro* studies had shown that Vav3 was a specific activator for RhoA — which is known to be involved in cytokinesis — so Fujikawa and colleagues wanted to see if Vav3 also had a role in this process. Analysis of the expression and intracellular distribution of Vav3 in HeLa cells showed that levels of the protein rapidly increased during mitosis — Vav3 could be detected after the disappearance of the nuclear membrane (during the transition from prophase to prometaphase) and then slowly decreased throughout anaphase towards the onset of cytokinesis. RNase protection assays confirmed this expression pattern and showed it differed from that of its family members — *Vav3* messenger RNA levels were upregulated during mitosis, whereas levels of *Vav2* mRNA did not change (Vav1 was not studied as it is not expressed in HeLa cells).

The importance of this regulation became apparent as the enforced expression (by transfection of full-length cDNA constructs in HeLa cells) of *Vav3*, but not *Vav1* or *Vav2*, disrupted cell division and led to the production of multinucleated cells, which indicates a block in cytokinesis. This effect seems likely to involve the activation of endogenous RhoA, as production of these multinucleated cells could be stopped by coexpression of Vav3 with a dominant-negative mutant of RhoA, but coexpression with mutants of other Rho-family members, such as Rac1 or Cdc42, had no effect.

Further characterization of Vav3 showed both differences and similarities to the other Vav proteins. The authors were surprised to find that deletions of the amino-terminal region of Vav3 did not affect the ability to produce multinucleated cells, as similar deletions in Vav1 and Vav2 had affected their activity. However, like Vav1, the activity of Vav3 is regulated by phosphorylation of a conserved tyrosine residue at position 173 (174 in Vav1), as a Y173F substitution completely abolished the ability to induce multinucleated cells.

So, the authors conclude that Vav3 could be an upstream regulator of RhoA during cytokinesis. This not only provides a new target for studies in cytokinesis control but, given the cell-cycle-dependent expression pattern of Vav3, also identifies a new mode of regulation among the Vav proteins.

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CELL SIGNALLING

The MIDAS touch

Although integrins bind to a structurally diverse range of ligands, most of these ligands contain the sequence Arg–Gly–Asp (RGD). The structural basis for this cation-dependent interaction has been unclear, but now, in *Science*, Arnaout and colleagues report the crystal structure of the extracellular segment of integrin αVβ3 in complex with an RGD ligand.

Integrins are composed of an α and β subunit — both type I membrane proteins with large extracellular domains — and fall into two classes depending on the presence or absence of an αA domain. Studies on the structure of αA have previously shown that a metal-ion-dependent adhesion site (MIDAS) at the ligand-binding interface is required for ligand interactions with αA-containing integrins. In αVβ3, which lacks αA, Arnaout and co-workers found that ligand binding is mediated by an αA-like βA domain in β3. Surprisingly, βA acquires two cations on complex formation — one in MIDAS and another in a ligand-associated metal-binding site (LIMBS). They propose that LIMBS, which does not directly contact RGD, stabilizes the ligand-binding surface.

The authors found that RGD binds at the major interface between αV and β3, and induces both tertiary and quaternary structural changes, which probably represent "a minimalist view" of the changes in integrins that are required for cell signalling. Although the ligand used here was synthetic, its RGD motif is almost conformationally identical to that present in a known natural ligand, which indicates that this structure can be used to understand integrin interactions with other RGD-containing ligands.

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