Signal transduction
Actin, cofilin and cognition
Jody Rosenblatt and Timothy J. Mitchison

Patients with Williams syndrome, a multi-gene deletion syndrome, suffer from mild mental retardation and vascular disease. They also have defects in visuo-spatial cognition — a failure to integrate parts into a whole — that are linked to deletion of the gene that codes for LIM-kinase 1 (LIMK-1)¹. Consistent with this cognitive defect, large amounts of LIMK-1 are expressed in neurons², yet its molecular targets have remained elusive until now. On pages 805 and 809 of this issue, however, Arber et al.³ and Yang et al.⁴ report that LIMK-1 phosphorylates cofilin, an essential protein that is required for turnover of actin filaments.

During cell movements such as neuron outgrowth or leukocyte chemotaxis, actin filaments must be organized into a dense, dynamic meshwork. This forms at the leading edge of a cell, where actin polymerization drives forward movement, and it usually takes the form of thin sheets (lamellipodia) or spikes (filopodia). Cell movement is a dynamic process; and actin at the leading edge of the cell must be continuously depolymerized and then repolymerized to produce this movement⁵. Actin depolymerization limits the length of lamellipodia and enables the actin subunits to be recycled for further rounds of polymerization.

There is mounting evidence that the key enzyme required for actin depolymerization is cofilin. In vivo, cofilin has been shown to be essential for cytokinesis⁶, endocytosis⁷ and other cell processes that require rapid turnover of actin filaments⁸. In vitro, cofilin binds to both actin monomers and polymers, and promotes the disassembly of actin filaments. Cofilin is regulated by phosphorylation of the serine residue at position 3, which inhibits its actin-binding and depolymerization activities. Stimuli that induce the production of lamellipodia relieve this inhibition by causing the rapid dephosphorylation of cofilin⁹.

Arber et al.³ and Yang et al.⁴ now provide evidence that LIMK-1 phosphorylates (and therefore inactivates) cofilin. Both groups labelled mammalian cells with radioactive inorganic phosphate, and found that isolated LIMK-1 associates with only one phosphoprotein — cofilin. Moreover, LIMK-1, but not an inactive form of the enzyme, can phosphorylate recombinant cofilin. These findings account for the observations that overexpression of LIMK-1 leads to accumulation of excess actin filaments, whereas overexpression of a dominant-negative LIMK-1 (a mutant form that disrupts the wild-type activity) inhibits the accumulation of actin filaments.

For cells to move, signals from their peripheries must be relayed to proteins such as LIMK-1 and cofilin. What factors relay these signals? Arber et al.⁴ and Yang et al.⁴ show that the small GTPase Rac may be important in regulating the activity of LIMK-1. Rac regulates the actin reorganization that is required to form lamellipodia¹⁰, yet few of its protein targets have been identified. The authors found that Rac-dependent formation of lamellipodia is blocked by dominant-negative forms of LIMK-1, suggesting that LIMK-1 acts downstream in the Rac pathway. Moreover, dominant-negative Rac leads to decreased phosphorylation of cofilin, whereas activated Rac modestly increases phosphorylation. These results indicate that Rac activates LIMK-1 which, in turn, phosphorylates — and inactivates — cofilin (Fig. 1, overleaf).

To induce the formation of lamellipodia, Rac must do more than simply inactivate cofilin — it must also induce the polymerization of actin. One possible mechanism involves Rac-induced increases in the levels of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P₂), which is thought to cause filament uncapping¹¹. Removal of a capping protein from the end of an actin filament could then allow the polymerization of actin to resume. Actin also needs to be depolymerized for the formation of lamellipodia, so we might expect that the Rac pathway only transiently inactivates cofilin. Indeed, Yang et al.⁴ find no net change in cofilin phosphorylation when endogenous (not overexpressed) Rac is activated. Transient inactivation of cofilin at the leading edge could allow nearby actin filaments to grow. Additionally, cofilin phosphorylation may induce the release of recently depolymerized actin monomers. Continuous cycles of cofilin phosphorylation...
and dephosphorylation would allow both cofilin and actin to be recycled for further rounds of depolymerization and polymerization, respectively. Clearly, further work is needed to sort out the role of cofilin phosphorylation in actin dynamics, and to clarify the temporal and spatial regulation of actin depolymerization in cells.

Another exciting aspect of this work comes from studies on patients with Williams syndrome, who have only one copy of the LIMK-1 gene. Given that LIMK-1 regulates the turnover of actin filaments, why should people with Williams syndrome have defects in visuo-spatial cognition? Perhaps neurons require high levels of LIMK-1 to finely regulate the turnover of actin filaments during axonal guidance. The PC12 neuronal cells containing dominant-negative LIMK-1 studied by Arber et al may provide a clue as to what neurons with decreased levels of LIMK-1 look like. Although neuron outgrowth still occurred, the neurites contained dramatically fewer filopodia — finger-like projections that are thought to sense in which direction axons should grow. If this is true, a decrease in LIMK-1 could account for the abnormally clustered and aligned neurons seen in the brains of patients with Williams syndrome.

To show that a decrease in LIMK-1 leads to abnormal neuronal wiring, we need to study people who lack a copy of the LIMK-1 gene (and not contiguous genes), as well as mouse knockout models. Future work will also need to address whether the visuo-spatial cognitive defect in people with Williams syndrome results exclusively from phosphorylation of cofilin by LIMK-1, or whether other substrates for LIMK-1 exist.

Jody Rosenblatt is in the Department of Biochemistry, University of California at San Francisco, 513 Parnassus Avenue, San Francisco, California 94143, USA.
e-mail: jody@gl.ucsf.edu

Timothy J. Mitchison is in the Department of Cell Biology, Harvard Medical School, Room C517, 240 Longwood Avenue, Boston, Massachusetts 02115, USA.
e-mail: Timothy_Mitchison@hms.harvard.edu


**Daedalus**

**Muffled furnace**

Noise is one of the major nuisances of modern life. Yet the usual sound-absorbing materials are purely passive, and can never damp it out completely. Daedalus now proposes an active absorber, inspired by the observation in a chemical textbook that the carbon monoxide flame “gives a curious impression of silence”. Carbon monoxide, he notes, burns with a reduction in the number of gas molecules. If, like most gas reactions, the burning speeds up with pressure, then a sonic pressure-peak will deplete the gas of molecules at an enhanced rate, and damp itself out. Conversely, when the pressure is low, the depletion slows down. So the flame absorbs the sound. Furthermore, certain flames are extremely sensitive to sound. They were used as acoustic detectors in pre-microphone days. Even a weak sound changed their combustion regime very visibly.

So Daedalus is inventing quiet flame technology. He is devising nozzles and flame-surrounds that optimize this sound-damping effect. He hopes to perfect a gas burner whose nonlinear reaction regime overreacts to sound, and thus absorbs it perfectly. A street lamp that absorbed traffic noise would be welcome on busy roads; victims of aircraft noise or popcorn neighbours would love a gas fire that gave out quiet as well as heat.

Even so, nobody would want to keep a fire burning on a hot day, merely to keep the noise down. So Daedalus is taking the argument further. When iron rusts, for example, gas molecules are completely absorbed into a solid. DREADCO’s chemists are now studying the oxidation of iron alloys, as well as yellow phosphorus, aluminium amalgam and even lithium (which absorbs nitrogen as well). They are seeking pressure-sensitive reaction regimes with strong nonlinearity, or even a pressure threshold. Their goal is a surface that rusts or tarnishes with total absorption of sound. Ideally it should change colour during the reaction. When fully reacted, it could be regenerated, perhaps by reduction with hydrogen.

This novel decor will be very expensive at first, and will be aimed at acoustics laboratories and recording studios. Gradually it should spread to the more opulent homes, offices and public buildings. A personal version in earmuff form would be widely welcomed; not only for the quiet in which it wrapped the wearer, but for the pleasing warmth released by its slow sonic oxidation.

David Jones