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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 neurons[2], 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 movement[5]. 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 cytokinesis[6], endocytosis[7] and other cell processes that require rapid turnover of actin filaments[8]. *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 cofilin[9].

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.* and Yang *et al.* 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 lamellipodia[10], yet few of its protein targets have been identified. The authors[3,4] 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 ($PtdIns(4,5)P_2$), which is thought to cause filament uncapping[11]. 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 phosphoryla-

100 YEARS AGO

All persons who interest themselves in the progress of celestial mechanics, but can only follow it in a general way, must feel surprised at the number of times demonstrations of the stability of the solar system have been made. Lagrange was the first to establish it, Poisson then gave a new proof; afterwards other demonstrations came, and others will still come. Were the old demonstrations insufficient, or are the new ones unnecessary? The astonishment of these persons would doubtless be increased if they were told that perhaps some day a mathematician would show by rigorous reasoning that the planetary system is unstable. ... It can be shown, in certain particular cases, that the elements of the orbit of one planet will return an infinite number of times to very nearly the initial elements, and that is also probably true in the general case; but it does not suffice. It should be shown that these elements will not only regain their original values, but that they will never deviate much from them. This last demonstration has never been given in a definite manner, and it is even probable that the proposition is not strictly true. – M. H. Poincaré.

From *Nature* 23 June 1898.

50 YEARS AGO

The French Association of Scientific Workers is organising an International Holiday Centre at Morzine (Haute-Savoie) during July 15–September 1. Morzine, without being a fashionable holiday resort, is one of the beauty spots of the French Alps. It lies to the south of Thonon at a height of about 1,000 metres; and around it are ranges rising to about 2,500 metres. So far as hotels are concerned, the French Association of Scientific Workers can secure accommodation at 800 and 700 francs a day (including service and taxes). It has also secured some good camping sites, and is trying to make arrangements for a canteen. Bookings can only be made for whole weeks (from Monday morning to Sunday night) and for a minimum of two weeks; registration fee, 500 francs each person. Applications should be made as soon as possible to the Association des Travailleurs Scientifiques, Maison de l'Université Française, 47 Boulevard St. Michel, Paris 5.

From *Nature* 26 June 1948.

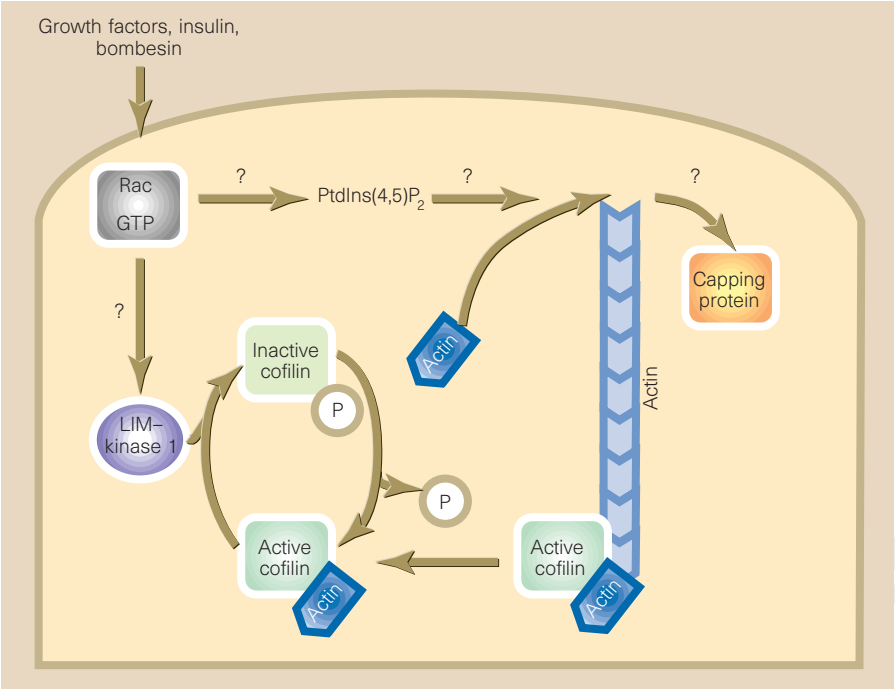

Figure 1 **Model for Rac-induced changes in actin dynamics to form a lamellipodium, based on the findings of Arber *et al.*[3] and Yang *et al.*[4]. When Rac is stimulated by growth factors, it activates LIM-kinase 1 (LIMK-1) which, in turn, phosphorylates cofilin. This may inhibit localized disassembly of actin filaments and help to release cofilin from the actin monomers. Rac-mediated stimulation of actin polymerization may occur through uncapping or increased nucleation of actin filaments. Both of these mechanisms may occur through production of phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$) by phosphatidylinositol phosphate 5-kinase. The intermediates that activate phosphatidylinositol phosphate 5-kinase and LIMK-1, and the factor that stimulates dephosphorylation of cofilin, are unknown.**

tion 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, as opposed to other processes that require actin dynamics? 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[12].

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. □

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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 pop-crazed 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