inhibited⁶⁻⁸, endocytosis no longer occurred. Furthermore, if GTP was added to dynamin rings assembled around lipids, these lipid tubes fragmented into small vesicles⁹.

Sever and colleagues³ now show that inhibition of GTP hydrolysis can, in fact, increase the rate of endocytosis, raising significant questions about the original model. But what did these authors do that was different? From their earlier work, they knew that dynamin's carboxy-terminal region contains a GTPase effector domain (GED), which is distinct from the GTPase domain (located at the amino terminus). The GED is required to stimulate dynamin's GTPase activity when it forms rings — an effect that could be due either to an increase in the rate at which GDP is exchanged for GTP, or to activation of GTP hydrolysis.

Sever *et al.* first show that the GED acts as a GTPase activating protein (GAP), both when the GTPase domain is isolated in solution and in polymerized rings of intact dynamin. Then, guided by known mutants of rasGAP (a GAP for another GTPase, Ras), they created two dynamin mutants, dyn(K694A) and dyn(R725A). These mutant proteins turned out to have defects in the assembly-dependent GAP activity. Whereas dyn(R725A) directly affects the catalytic GAP function, dyn(K694A) partially interferes with the self-assembly of dynamin.

Because mutations in the GED impair dynamin assembly — and because GEDs associate with each other — we can assume that the GED domain forms part of the contact between stacked dynamin rings (forming the spirals that wind round on themselves). Presumably, dyn(K694A) allows the dynamin spirals to form, but with impaired communication between the rings, reducing stimulation of the GTPase activity. So these new dynamin mutants should be functionally equivalent to mild GTPase mutants, and would be expected to show impaired endocytosis. It was a surprise, then, that Sever *et al.*³ obtained exactly the opposite result. Overexpression of dyn(K694A) or dyn(R725A) leads to accelerated endocytosis of a probe molecule, transferrin, indicating that GTP hydrolysis, although required to complete the fission cycle, is not rate limiting for endocytosis.

So a new concept for dynamin function emerges (Fig. 1). GDP-dynamin is recruited to the forming bud, where it assembles into rings. Dynamin's intrinsic GAP is activated on completion of a spiral around the neck of the bud, when dynamin tetramers from one end of the spiral stack onto tetramers at the other end (rather than by lateral interactions along the dynamin ring). GTP hydrolysis then sends a signal to as-yet-unidentified effectors to proceed with fission. So the GTPase domain has to

do a balancing act: too rapid GTP hydrolysis would prevent ring formation or block recruitment of the pinching machinery to the GTP-bound ring; but a complete failure of GTP hydrolysis would not activate fission.

Presumably, if the neck of the vesicle is too large this will preclude efficient lateral dynamin associations (dynamin rings do not form on templates larger than 30 nm across). One end of the spiral cannot connect up with the other, and the GTPase will not be activated. By sensing the dimensions of neck constriction dynamin acts as a checkpoint, in effect coordinating the last step of budding. Sever *et al.* predict that if dynamin forms an incomplete ring it should have low GTPase activity (to allow recruitment of the fission machinery), and that only after the rings stack should there be a dramatic increase of GTPase activity.

But the new model is not without problems. We must assume that the GTPase mutants studied previously did not just affect the rate of GTP hydrolysis, but that they also inhibited the interaction with unknown downstream effectors. We must also explain why Sever *et al.* find that endocytosis is increased. Perhaps the delay in GTP hydrolysis allows a deeper dynamin spiral to form, increasing the number of binding sites for downstream effectors or prolonging their activation. And we must find out why dynamin changes shape on binding GTP — does this change allow the fission machinery to bind, or does it allow the dynamin spirals to interact, leading to rapid GTP hydrolysis?

Although one possible conclusion is that dynamin is not the true pincher, the system could, in theory, work with dynamin alone. The pinching would have to happen after the conformational change that occurs on binding GTP, which has been assumed to cause vesicle scission. But there could be a second, more elusive, conformational change after GTP hydrolysis, before the dynamin spiral falls apart. And perhaps the GTPase defect in Sever and colleagues' mutants allows a longer spiral to assemble, which is why the fission reaction is faster. □

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Daedalus

New eyes

The human eye, as the spectacles industry shows, is astonishingly imperfect. We cannot blame evolution; our primitive ancestors must have had perfect vision for their spacious world. But then civilization invented craft-work, reading and other close-up activities. Young eyes had to adapt to very short distances. Daedalus surmises that such repeated stresses on the lens of a growing eye give rise to short-sightedness, and possibly astigmatism too.

Now almost every organ of the body is flexible enough to adapt to the demands made on it. Why does the eye alone persist in useless errors such as astigmatism? One theory blames the invention of spectacles. Once an optometrist has prescribed corrective lenses for your eyes, they are fixed in their imperfection. Any changes they might make will make your vision worse; so they have no 'motive' for improvement. Daedalus now has a remedy.

These days, he points out, children (and indeed many adults) spend most of their waking hours in front of TV, computer or games-machine video screens. So he is devising a screen which appears at optical infinity, like the 'head-up' display in a fighter cockpit. For the dwindling numbers of young book-readers, a similar infinity book-viewer should also be possible. Users of these devices should reach adult life in much better ophthalmic shape.

To correct remaining errors, Daedalus recalls a flexible spectacle lens he once invented, made of the piezoelectric polymer PVDF. It was deformed into the desired shape by a pattern of voltages applied through transparent electrodes and maintained by a small battery-powered circuit. As the wearer's eyes altered, his optometrist simply updated the voltages. Daedalus now reckons that these cunning spectacles should be set so as to under-correct the wearer's vision slightly. His eyes will therefore have an incentive to 'learn' the slight adjustment needed for sharp vision. When they have done so, the 'training glasses' will be under-corrected again, provoking further adaptation. In due course the glasses will be reduced to plane lenses. They can then be discarded, for the wearer will have perfect vision.

Thus the optimization mechanism, which our eyes must possess, will be put to good use at last. We will recover the keen vision of our distant ancestors, at least until middle age when our lenses start to harden. Even then, Daedalus's training glasses may be able to encourage a valuable extra degree of optical flexibility.

David Jones