contracts during cell division). Strikingly, formin inactivation had extremely selective effects on the cables, with no apparent effect on the patches[4,5]. The patches are enriched in Arp2/3 complexes and their regulators, and cells deleted for the *ARP3* gene lacked detectable patches but retained formin-dependent cables[4]. There seems, therefore, to be a separate actin nucleator for cables — one exciting possibility is that the formins themselves either nucleate actin polymerization or regulate other factors that can do so. Alternatively, formins may simply promote the assembly of actin filaments (nucleated by some other factor) into cables.

Overexpression of formins promoted the assembly of supernumerary actin structures[4,5]. Similar to actin cables, the formin-induced filaments were coated with tropomyosin. The association of tropomyosin with cables may explain why the actin filaments in cables are not branched, as it was recently shown that tropomyosin blocks the binding of Arp2/3 complexes to the sides of actin filaments[14]. Alternatively, it is possible that the localization of most of the Arp2/3 complexes (and their activators) to the patches leaves few complexes available to form branches on the filaments generated (or assembled) by formins, allowing tropomyosin to coat the Arp2/3-free filaments. How yeast cells generate such distinct actin structures so close to each other remains a fascinating question.

Studies on formins in yeast have postulated separate roles in cell polarity, spindle orientation, and cytokinesis. Can the discovery that formins mediate actin cable assembly now provide insight into those defects that accompany partial loss of formin function? Cell polarity in yeast depends on properly oriented actin cables[15], and spindle orientation depends on components delivered into the bud by myosin-mediated transport along cables[16,17]. In addition, the cytokinetic ring may be a specialized version of an actin cable, also requiring formin function (this issue will be interesting to clarify in the future). It is conceivable, therefore, that all of the known functions of formins in yeast, and perhaps also in other cells, may boil down to the proper assembly of parallel bundles of actin filaments, which then indirectly affect various other structures, including the microtubule cytoskeleton. But it is possible that life is not that simple. One recent study suggested that formins might be involved in the polarization of actin patches in yeast, independent of cables[18]. In addition, studies on cytokinesis in yeast have suggested that the function of formins may go beyond the function of the cytokinetic actin ring[9]. Regardless of whether formins do or do not have additional functions, the new studies represent a major step towards understanding how actin cables form. Given the evolutionary conservation of formins across species, the insights gained from yeast will undoubtedly impact studies of parallel actin bundles in animal cells as well. □

Daniel J. Lew is in the Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA
e-mail: daniel.lew@duke.edu

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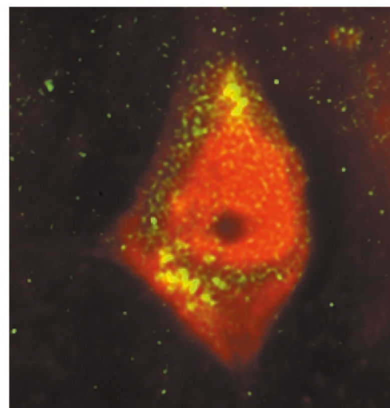
Hip, Hip, Hippi!

Huntington disease (HD) is caused by mutations in the *huntingtin* gene. Mutant Huntingtin protein (Htt) with expanded polyglutamine repeats forms aggregates in diseased brains. It has been suggested that the selective loss of neurons from the brain striatum of patients with HD is caused by apoptotic death. But how does mutant Htt activate the apoptotic pathway? Don Nicholson and colleagues now propose an attractive model on p.95 of this issue. The key is in the regulation of the interaction of Htt with its partner Hip-1. Nicholson and colleagues identify another partner for Hip-1, Hippi. The picture shows immunostaining of Hippi (yellow) in cortical pyramidal neurons (red) of the mouse brain. They show that the interaction between Hip-1 and Htt on the one hand, and between Hip-1 and Hippi on the other, are mutually exclusive, and that Hip-1/Hippi complexes can activate caspases, the effector enzymes of apoptosis.

In the normal brain, Hip-1 interacts with Htt. But the affinity of Hip-1 for mutant Htt is much lower than its affinity for wild-type Htt. So in diseased brains, levels of the Hip-1/Hippi complex are relatively higher than the levels of the Hip-1/Htt complex. In addition, the authors also demonstrate that the proenzyme procaspase-8 is recruited to Hip-1/Hippi complexes. Interestingly, previous studies have shown that active caspase-8 localizes to aggregates of mutant Htt, and that overexpression of mutant Htt induces apoptosis in a caspase-8-dependent manner.



N. NICHOLSON

Nicholson and colleagues now show that Hip-1 and Hippi cooperate to induce apoptosis in a caspase-8-dependent manner when transfected into primary neurons. So the model suggests that Hip-1 and Hippi induce dimerization, and thus activation, of procaspase-8, thereby initiating the apoptotic cascade.

VALERIE FERRIER

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