Neurobiology

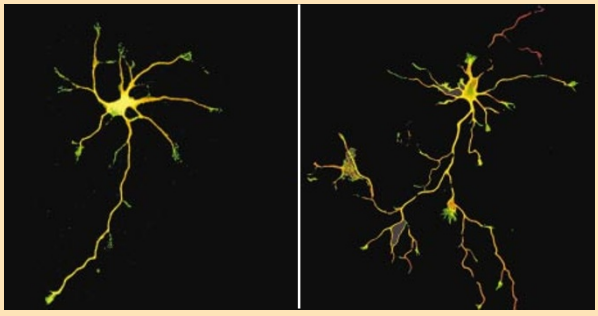
Motor proteins branch out

Molecular motors are perhaps best known for their ability to transport cargo around inside cells. To do so, these tiny vehicles move along defined intracellular 'tracks'; motor proteins of the kinesin family, for instance, move on microtubule filaments. But some kinesins have a quite separate function, at least in cultured cells: they can break down microtubules into their constituent parts. Writing in *Cell* (**114,** 229–239; 2003), Noriko Homma *et al.* show that the kinesin KIF2A has this activity *in vitro* — and they propose that this function is essential *in vivo* for the brain to develop normally.

The authors started by generating mice that lack KIF2A, and found that the animals died within a day of birth with severe brain abnormalities. Delving deeper, Homma *et al.* discovered defects in the collateral branches of neurons. During development, nerve cells extend projections — axons — to form appropriate connections in the brain. Sometimes, branches also extend outwards from the axons to form further connections. These collateral branches generally remain short until the primary axon has found its way.

But that doesn't appear to happen in KIF2A-deficient mice. The authors took neurons from the hippocampus of normal and mutant mice and cultured the cells for two days. The normal neurons (left-hand image) extended a single primary axon, with some short collateral branches. The mutant nerves, by contrast, developed abnormally long collateral branches, which rebranched several times (right-hand image).

Video analysis showed that, in wild-type neurons, any collateral branches that formed actively shrank back. But in the mutant cells the branches continued growing. So KIF2A seems to be necessary to stop the branches lengthening. How does it do this? Homma *et al.* found that the protein can depolymerize microtubules within extending neuronal protrusions, and that this activity is reduced in KIF2A-deficient cells. Moreover, when the authors studied the polymerization and depolymerization of microtubules in another type of cultured brain cell (it's difficult to do this in neurons), they found that, if KIF2A was missing, microtubules carried on growing when they reached the edge of the cell. But in the presence of KIF2A, microtubules either stopped growing or showed cycles of growth and shrinkage.



It seems, then, that microtubule growth drives the protrusion of collateral branches — possibly by pushing out the edge of the cell — and that KIF2A normally keeps this process under control by depolymerizing microtubules when they reach the edge. It remains possible that KIF2A has an indirect role: perhaps it carries microtubule-depolymerizing molecules to the edge. But the protein's *in vitro* activity would seem to argue against this.

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results[4,5] alike are enlivening discussion of canalization. Theoretically, it seems that canalization can be a by-product of the existence of genetic regulatory networks that maintain their function when any given gene is knocked out[3]. On the experimental side, the protein and molecular chaperone Hsp90 has properties that suggest it could be a central player in a general canalizing mechanism[4,5]. On page 549 of this issue, Bergman and Siegal[6] advance the discussion by showing — with both a simulation model and new analysis of data on the effects of gene knockouts in yeast — that most genes in regulatory networks have canalizing properties.

The authors first set up computer simulations of gene networks, in which each virtual gene regulates the expression of itself and every other gene. A matrix showing the regulatory relationships is the 'genotype' — the representation in the model of the set of genes relevant to the issue at hand. The traits that might be buffered (the 'phenotype') are represented by the equilibrium profile of gene expression that results from the regulatory relationships. The starting point is arbitrary, and not yet at equilibrium. A gene is then knocked out at random by setting its value in the matrix to zero, and the population is allowed to evolve.

The results were striking: the knockout populations showed, in general, much more phenotypic variation between individuals than did populations in which genes were not deleted. And simulated populations with a supply of knockout mutations evolved more rapidly to an equilibrium (optimum) phenotype than did simulated populations without such a supply. The authors propose that the knocked-out regulatory genes usually have canalizing effects on phenotypic variation that are lost when the genes are knocked out — releasing previously hidden variation. In my view, however, this in itself does not provide evidence of canalization, for an increased supply of mutations with diverse effects would be expected to accelerate evolution whether or not a regulatory network with canalizing effects existed.

On the other hand, Bergman and Siegal also analysed experimental data from a large-scale project with the yeast *Saccharomyces cerevisiae*; this project aims to delete each yeast gene in turn, and to study the effects. The genetic background of the yeasts is identical, save for the gene knockout, so here the authors were studying the effects of environmental variation on phenotype. They found that deleting a gene at random increased environmentally induced variation in the expression of other genes — again suggesting that such phenotypic variation is usually canalized.

Bergman and Siegal interpret these findings as providing support for the notion of 'evolutionary capacitance'. By this they mean that evolution is accelerated when genetic or environmental stress disturbs canalizing mechanisms. The disturbance reveals genetic and phenotypic variation that had previously been hidden, and which now becomes available to fuel an evolutionary response that would not have been possible had the canalizing mechanism not been functionally compromised.

How do these results fit with previous work? From experiments on fruitflies and thale cress[4,5] we know that trait variation increases when Hsp90 is functionally compromised, and that the function of Hsp90 can be compromised by environmental stress. From theory we know that knockout mutations in genetic regulatory networks reveal hidden genetic and phenotypic variation, and speed the approach to a new optimum. And Bergman and Siegal's analysis of yeast knockouts suggests that knocking a gene out at random in a genetically uniform background increases environmentally induced variation in the expression of other genes.

So far so good. But a crucial element in the theory is missing from the data: we do not yet have an experimental demonstration that compromising a canalizing mechanism accelerates evolution to a new optimal phenotype. We only know that the amount of genetic variation that is expressed as phenotypic variation is increased. That such