Abstractions

LAST AUTHOR

For the past century, biologists have debated the cause of morphological differences between species. The classical view holds that the accumulation of many small changes among multiple genes is responsible. But some evidence suggests that the differences result from large, abrupt changes in the expression of developmental genes. David Stern of Princeton University in New Jersey and his colleagues have been working with naked and hairy fruitfly larvae to find out more. On page 587, they report that a number of small-effect changes in a single gene is responsible for the hairy difference between these species.

Why answer this question with naked versus hairy fruitfly larvae?

It's not clear whether being hairy or naked is evolutionarily important in fruitflies, but it's similar to the difference in hairiness between humans and chimpanzees. We study what is tractable with genetics. It helped that we already knew a lot about the developmental pathways that pattern larval fruitfly hair. We can determine the origin of mutations in closely related species but not in more distantly related ones.

How long have you been working on this?

In 2000, we were amazed to find that differences in larval hairiness mapped entirely to one gene called *shavenbaby*. We thought it would take only another six to twelve months to find what we guessed would be a single mutation in a nearby enhancer region. But we found an unexpectedly complex pattern of overlapping expression from three enhancers scattered over a long DNA stretch. As a result, seven years and five postdocs later, we still haven't identified the mutations.

What was the key to unravelling this complexity?

Having found three separate enhancers, we needed to do a recombination assay to dissect each enhancer's role in hair distribution, but couldn't figure out how to do it. We needed a marker system to keep track of the relevant recombinants. Then we remembered that, in the 1990s, Cathy Laurie produced fly strains in a closely related species with more than 100 visible genome markers. Using these markers, we generated unprecedented resolution of the evolved differences between species.

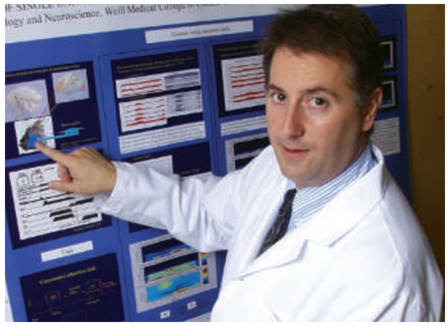
What was the biggest lesson you learned?

Think big and do the experimental work. We tried various predictive computational methods to find the enhancers, but none was accurate. When we found the first enhancer we thought we were done, then we found the second. Only a survey of the entire regulatory region provided the full story. ■

MAKING THE PAPER

Nicholas Schiff

Electrical stimulation improves brain function after severe injury.



Traumatic brain injury (TBI) is a major cause of neurological impairment for which there is no effective treatment. Some 1.4 million new cases occur each year in the United States alone, and there is little evidence that those with impaired consciousness will show any improvement after an initial 12-month period. In the most severe cases, TBI can result in a lifetime in an unconscious or partially conscious state. But this grim prognisis may be set to change.

Severe impairment resulting from TBI, including loss of alertness, communication and goal-directed behaviour, has been assumed to result from broad damage to cerebral networks. But recent brain-imaging studies in humans suggest that significant connectivity may persist in some patients in the minimally conscious state (MCS) — a condition characterized by limited or intermittent signs of perception and responses to external stimuli. This convinced Nicholas Schiff, a neurologist at the Weill Cornell Medical College in New York, that patients in the MCS might benefit from deep-brain electrical stimulation (DBS).

Schiff's interest in severe brain injury was piqued by imaging work he did in the early 1990s with patients in the vegetative state. He and Weill medical ethicist Joseph Fins teamed up with MCS expert Joseph Giacino, a neuropsychologist at the JFK Johnson Rehabilitation Institute in Edison, New Jersey, and Ali Rezai, a neurosurgeon at the Cleveland Clinic in Ohio who pioneered therapeutic DBS. The four investigated whether electrical pulses from electrodes implanted in the central thalamus (an important regulator of alertness) could recruit and activate unused but functional cerebral networks in patients in the MCS. They hoped this might improve awareness, communication and other behaviours in such patients.

This began what Schiff describes as "a ten-year process of trying to get the work approved, despite the constant presumption of others that it would never work and wouldn't be worth doing." The researchers persevered, conducting animal and imaging studies, and developing a surgical approach and an ethical framework for the procedure. This week, they report that DBS can promote significant functional improvements in a patient in the MCS, even 6 years after the initial injury (see page 600).

Their work centred on a single patient who was unable to follow commands consistently, communicate, or vocalize after severe TBI. The team implanted DBS electrodes bilaterally in the central thalamus, then used imaging and behavioural tests to follow and assess the effects of stimulation over an six-month period. The patient's alertness, awareness and motor control improved, and for the first time since his injury he was able to chew and swallow food. Most strikingly, he can now communicate through gestures, words and, at times, short sentences.

Fins stresses that this is not yet a therapy, only a first study that needs confirmation. But, he says, "it is an extraordinary development that, through a prosthetic intervention, this individual regained the ability to participate with the human community."

Schiff emphasizes that the team's collaboration was essential to their success. He describes the work as "an innovation in neurosurgery". But, he adds, it's also an innovation in how MCS patient behaviour is assessed and how doctors think about finding ethical ways to improve function in the severely injured brain. ■

FROM THE BLOGOSPHERE

Writing on Nautilus, at http://tinyurl.com/29lyfa, Monica Zoppè of the Institute of Clinical Physiology in Pisa, Italy, proposes a "female road of science".

Funding agencies distribute money on the basis of competition — an attitude, writes Zoppè, typical of males. Women, she adds, "are more inclined to collaboration... and if forced to compete do so reluctantly". The best way to grant women their share of funding (50%), she says, would be to have one channel for men, "in which male scientists set the rules and judge applications; and one for women, managed by and dedicated to female scientists".

In the online discussion, in which we invite you to participate (at the URL above), Bill Hooker writes: "I would be sorry to be trapped by my Y chromosome in the other, competitive, track — but I would not oppose the new system in the slightest. Since my hypothesis is that greater emphasis on cooperation over competition would vastly improve the infrastructure of science, such a system as Dr Zoppè proposes can only benefit me as a test of that hypothesis." ■

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