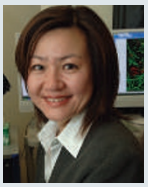
Abstractions



FIRST AUTHOR

Alzheimer's disease typically starts with lapses in memory and culminates in full-blown dementia. Using mice that had suffered considerable neuronal loss to model the disease, Li-Huei Tsai's group at the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology, Cambridge, and the Howard Hughes Medical Institute in Chevy Chase, Maryland, shows that an environment with lots of toys improves access to memories that seemed to have been lost. In looking for the mechanism responsible, Tsai and colleagues found that the enriched environment did not increase the number of neurons in the brain, but rather spurred existing neurons to make more connections with other neurons. The change was brought about by specific modifications to the histones — the proteins that help package DNA into chromatin. Tsai tells *Nature* about the roots of neuronal enrichment.

What made this study possible?

We have a mouse model that develops very severe neuronal loss coupled with deficits in learning and memory. By the time patients with Alzheimer's disease present with clinical symptoms, they already show severe loss. So, to a certain extent, this model mimics the human disease in progress. Also, the symptoms can be induced at specific times by turning on the expression of a transgene in the mice.

What was your most important finding?

We knew that Alzheimer's patients eventually lose long-term memory — they cannot remember their own names or the names of their spouses. We gave our mice a task to learn and waited several weeks for the memory to be consolidated. When we then turned on expression of the transgene for a prolonged period of time, the mice could no longer recall the memory. But when we put the mice in an enriched environment or used drugs to induce histone modifications, the memory came back.

Does that mean that memories are not lost?

This is still an open question in patients. But this study strongly suggests that some memories are not lost, just cannot be accessed. It is possible that by inducing a rewiring of the brain and increasing connectivity, memories can be retrieved once again.

How did you move from biochemistry to neuroscience?

When I was doing my postdoctoral work in a cell-cycle lab, I discovered CDK5, a cyclin dependent kinase highly expressed in postmitotic neurons. That was my foray into neurobiology. In the end it worked out well. ■

MAKING THE PAPER

Tarjei Mikkelsen

Marsupial genome reveals the treasure hidden in junk DNA.

In the past few years, the pace of publishing genomes has been fast and furious. Researchers have sequenced our pets (dogs), our food (cows and chickens), our closest relatives (chimps) and of course the most popular laboratory animals. So why should the genome of the opossum, an obscure marsupial, grab attention?

The divergence of marsupial and placental mammals represents a key time point in evolution — one that was missing from the comparative genomics map until now, explains Tarjei Mikkelsen, doctoral student at the Broad Institute in Cambridge, Massachusetts. Through the efforts of his 60 collaborators, this addition to the evolutionary timeline provides the power to distinguish which genome changes are specific to placental mammals.

When comparing two species' genomes from one evolutionary group, researchers need a third genome from outside that group to measure them against. But before now, if comparing say, mouse and human, both placental mammals, then the next closest outside genome would be chicken, which diverged from mammals about 310 million years ago. But that split is too long ago to trust whether your comparison is catching true differences or just shared sequences that have become unrecognizable over time.

Conversely, if you were to compare humans and chimps (both primates), and use the mouse genome as the outlier, the mouse and primate groups, which diverged from each other in the past 100 million years, would be too close in time to pick up small changes. Marsupials diverged from placental mammals about 180 million years ago, which in evolutionary time is about halfway between the aforementioned divergence events. "Before, even if something was conserved from chickens to humans, we may not have recognized it. The opossum is distant enough to have striking differences, yet close enough to ensure we did not accidentally miss any similarities," says Mikkelsen.

The team has used the opossum data to boost the biological importance of conserved non-coding elements (CNEs) — DNA that doesn't give rise to proteins — in mammalian genomes. Using the opossum as the measuring stick, the authors discovered that one-fifth of CNEs is an invention of placental mammals' evolution.

In addition, the opossum sequence allowed the team to classify a larger fraction of relatively recent CNEs as originating from transposons, so-called junk DNA. These pieces of DNA were once thought to be merely selfish bits, replicating and inserting themselves into genomes, but current thinking has them transforming the regulatory sequences of mammalian genes. The finding throws more weight behind the idea that "evolution is recycling", says Mikkelsen. "It's much easier to repurpose old parts from junk DNA, than to invent new ones from scratch."

Mikkelsen has worked previously on the human, chimp and dog genome projects. "When I started seven years ago on the human genome, we knew very little about how genomes were organized — it was a big, uncharted text file made up of four letters," says Mikkelsen. What makes us human is not written down in that code per se, it's the journey from ancient organisms to us that matters: what did we keep, what did we change and how does it work differently in us? That story can only be told by collecting other genomes, and now Mikkelsen and colleagues can check off the marsupial. ■

FROM THE BLOGOSPHERE

YouTube has revolutionized the Web, with video content from the serious to the mundane. Can science co-opt this latest grassroots craze in an attempt to reach the researchers of tomorrow? On Nautilus, the Nature Publishing Group blog for past, present and future authors, a group of biological-science professors from the National University of Singapore make the intriguing suggestion of outreach via YouTube (http://blogs.nature.com/nautilus/2007/04/science_outreach_by_online_vid.html).

YouTube is a free website containing more than 70 million video clips. It's viewed monthly by around 20 million people. Videos can be tagged with key words by the user who uploads them, and hyperlinked to other websites, such as authenticated science information sites. Hence, argue the professors, YouTube is an ideal venue for scientists to contribute expert opinions and persuasive videos to an audience "that primarily consists of impressionable 12- to 17-year-olds". They provide a link in their Nautilus post to a dramatic example: a video documenting deforestation within Lore Lindu National Park in Sulawesi, Indonesia. ■

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