Making room for new memories

Joe Tsien (Princeton University, Princeton, NJ) and colleagues have suggested that the creation of new neurons in the hippocampus may allow old memories to be wiped clean, thus making way for the new.

New neurons were thought to form new memories, because widespread adult neurogenesis correlates with song learning in songbirds. But adult primate neurogenesis involves far fewer cells. The new neurons last only a few weeks, during which a memory is transferred from short-term storage in the hippocampus to long-term storage in the cortex.

Tsien found he had a tool for testing the possible link between memory and neurogenesis when he made mice that lacked Presenilin-1 (PS1) in their forebrains. PS1 helps cleave amyloid precursor protein (APP) and Notch, and alterations in PS1 activity are associated with Alzheimer’s disease (AD). Mutant mice lacking forebrain PS1 were normal in appearance, behavior, learning, and nerve conduction.

When Tsien put the mice in an enriched environment (with new toys every day), the normal increase in neurogenesis was reduced in mutants relative to that seen in wild-type mice. But the enrichment still allowed both wild-type and mutant mice to better remember a task that was taught after enrichment. Thus enrichment with lowered neurogenesis still increases subsequent memory abilities, suggesting that the level of neurogenesis is not correlated with levels of learning.

Next, Tsien changed the order of activities: learning came first, then enrichment, and then testing. The enrichment procedure still increased memory retention. But enrichment with lowered neurogenesis (in the mutant mouse) increased memory retention to an even greater extent.

The mutant mouse may still show improvement after enrichment because, based on Tsien’s previous experiments, the relevant changes occur in the cortex. But enrichment also brings new memories into the hippocampus. In the wild-type mouse these new memories may interfere with the old, test-associated memory, and thus reduce the success in the later test. Tsien believes that the interference arises from hippocampal neurogenesis, which helps obliterate the old memories by making random connections to old memory neurons.

With less neurogenesis the mutant mouse can retain a memory more successfully in the short term. But this might not work forever. “These animals spend their entire lives in cages,” says Tsien. “The system really never has a chance to process a lot of memories. In a more natural situation you might show a problem.”

Tsien plans to look for such a problem by challenging the mice with multiple, overlapping tasks.

If proven, the new theory would have widespread implications. Those searching for memory drugs would now face the fact that the hippocampus, where new memories are first processed, has a far more limited storage capacity than the cortex. “Eventually the hippocampus may run the risk of overcrowding with memories,” says Tsien. The opposite problem of premature memory obliteration may arise if excessive neurogenesis occurs as a result of either AD or the addition of a neural stem cell transplant.

Reference: Feng, R., et al. 2001. Neuron. 32: 911–926.

Romeo and Leishmania

By faking its own death, Leishmania can gain access to macrophages. Once in the macrophage, say Marcello André Barcinski (Universidade de São Paulo and Instituto Nacional de Câncer, Rio de Janeiro, Brazil) and colleagues, the fake death signal then suppresses the host’s ability to kill the invading parasite.

Leishmania makes the fake death signal by exposing phosphatidylserine (PS) on its surface. Exposed PS is also seen on apoptotic cells, where it induces engulfment by macrophages, and reduces inflammation by prompting production of TGF-β. The same two activities are seen with Leishmania, although the parasite also induces both an increase in IL-10 production (which distracts the immune system by shifting it away from cell-mediated immunity) and a reduction in NO production. The latter change favors parasite survival, as NO is one of the main mechanisms by which macrophages kill Leishmania.

Reference: de Freitas Balanco, J.M., et al. 2001. Carr. Biol. 11:1870–1873.