TCRs alive on the periphery

Keeping T cell receptors (TCRs) away from the center of the immunological synapse boosts stimulatory signals, based on work from Kaspar Mossman, Gabriele Campi, Jay Groves (University of California, Berkeley, CA), and Michael Dustin [New York University, New York, NY].

The immunological synapse—the cell-cell junction between a T cell and antigen-presenting cell (APC)—looks like a bull’s eye, with a central cluster of TCRs and their bound antigen–MHC ligands surrounded by a ring of adhesion molecules and their ligands. Active TCR clusters form at the periphery but then move toward the center, where they stop signaling.

To determine whether this change of locale is necessary for TCR shutdown, the group blocked the inward transport. They first replaced the APC with a supported lipid bilayer containing antigen–MHC and an adhesion ligand. They then etched chromium barriers onto the substrate to form variously patterned corrals within which MHC-bound TCRs would be trapped.

K

TCRs that were stuck in peripheral corrals signaled longer, as measured by their phosphorylation status and ability to elevate cytoplasmic calcium levels. “It’s not just a matter of timing,” says Dustin. “Location of the TCR clusters is important.” It is not clear whether the periphery is a particularly good environment to sustain signaling, the center is a particularly good environment to kill signaling, or both.

Positive feedback from dynamic actin in the periphery or negative feedback from centrally located inhibitors, perhaps phosphatases, might be involved.

The group artificially prevented TCR transport, but certain APCs, such as dendritic cells, might have that innate ability. Compared with B cells, dendritic cells are much more potent T cell activators. “So,” Dustin wonders, “do they have their own version of these barriers?” Perhaps yes, as at least one report suggested that dendritic cells cause T cells to cluster TCRs in multiple peripheral foci rather than at the typical bull’s eye of a B cell.

Reference: Mossman, K.D., et al. 2005. Science. 310:1191–1193.

Less p53 for life

New findings from Johannes Bauer, Stephen Helfand (Brown University, Providence, RI), and colleagues show that flies lacking neuronal p53 activity live longer.

Hyperactivation of p53, which kills DNA-damaged cells, reduces tumor incidence in mammals but also shortens their life span. These earlier findings suggested that reducing p53 activity might increase life span. Helfand’s group found that this did not pan out for flies lacking all p53—they died earlier than normal, probably because of the requirement for p53 in developmental apoptosis. But if the authors blocked p53 activity only in neurons, the flies lived longer healthy lives and were also more resistant to DNA-damaging agents.

Loss of p53 only in the fat body or muscle tissue did not extend life span. “Maybe,” says Helfand, “the nervous system is the weak link. If it goes [via p53-mediated apoptosis, for example], the rest of the body goes.” The group does not yet know whether neurons survive longer in the p53 mutants due to less apoptosis, but they provide evidence that traditional caspase-dependent apoptosis is probably not affected. The involvement of caspase-independent apoptosis has not been ruled out.

Another possibility is that the neuronal tinkering causes systemic effects, perhaps via the neuroendocrine system. Indeed, calorie restriction also increases life span in flies, and p53 inhibition seems to lie in this pathway, since both together did not have an additive effect. Calorie restriction has unwanted side effects, however, including reduced fertility and activity levels. Since p53-inhibited flies did not suffer from these problems, the authors have shown that the downstream effects of calorie restriction can be teased apart.

Female (left) and male (right) flies lacking (black lines) neuronal p53 live significantly longer.

The p53-inhibited flies might also be expected to have many tumors, but since adult flies are primarily post-mitotic, they are not cancer prone. If only mature human neurons, which are also post-mitotic, were smart enough to rid themselves of p53, perhaps we could all live longer. Says the cautious Helfand, “a judicious decrease in p53 activity might be advantageous.”

Reference: Bauer, J.H., et al. 2005. Curr. Biol. 15:2063–2068.