Building the immunological bull’s eye

After an antigen-presenting cell meets a T cell, a bull’s eye–shaped immunological synapse is formed, with T cell receptors (TCRs) and their antigen clustered in the center, surrounded by a ring of adhesion molecules that holds the cells together. According to Yoshihisa Kaizuka, Adam Douglass, Ronald Vale (University of California, San Francisco, CA), and colleagues, TCRs and adhesion molecules separate early during synapse formation. They might be further segregated by differential interactions with the T cell’s actin cytoskeleton.

The movements of the T cell receptor were previously described, but little was known about the movements of adhesion molecules. Direct imaging of T cells in contact with a flat lipid bilayer containing the right ligands showed that TCRs and adhesion molecules initially clustered at the perimeter of the contact zone. Each formed their own microdomains in an actin-dependent process. “This early segregation is probably due to different protein–protein interactions that cause these microdomains to coalesce,” Vale says.

The microdomains were then driven inward by retrograde actin flow. The TCRs traveled farther, to the actin-depleted center of the synapse. Adhesion clusters remained in the actin-rich outer portion, unable to travel further inward. They might be stalled by the dense packing of TCRs already in the center or by their own instability in the absence of actin. Neither set traveled as fast as actin itself, probably because they repeatedly slipped off and reattached to the actin conveyor beneath them.

Reference: Kaizuka, Y., et al. 2007. Proc. Natl. Acad. Sci. USA. doi:10.1073/pnas.0710258105.

trNA’s Los is a gain after damage

Shutting down nuclear export of unspliced tRNA keeps cells in G1 during DNA repair, say Ata Ghavidel and colleagues (University of Toronto, Canada). The authors found that DNA damage caused the nuclear accumulation of tRNAs containing unspliced introns, which are removed in the cytoplasm. This accumulation required the damage-induced signaling molecule Rad53 and correlated with the retention of the main tRNA export receptor, Los1, in the cytoplasm.

Without their exporter, tRNAs were stuck in the nucleus, causing cell cycle arrest in G1 and giving the cell time to repair damage before DNA synthesis. Deleting Rad53 prevented the nuclear tRNA build-up, and damaged cells exited G1 prematurely. Deleting Los1 in these cells restored the G1 arrest.

The G1 stall was not due to decreased cytoplasmic tRNA, which remained in large excess due to its long turnover time. Instead, the stall stemmed from the surplus of nuclear tRNA, which somehow enhanced translation of a stress response factor called Gcn4—a protein that promotes repair and slows the synthesis of G1 cyclins.

“This process couples the nuclear sensing of DNA damage to cytoplasmic protein synthesis,” Ghavidel says. “It was an entirely unanticipated mechanism, since tRNA export has traditionally been viewed as constitutive.” JCB Reference: Ghavidel, A., et al. 2007. Cell. 131:915–926.

Lipid + Alzheimer’s plaque = problem

Lipids rapidly dissolve Alzheimer’s disease plaques into toxic protofibrils, according to Joost Schymkowitz, Frederic Rousseau (Vrije Universiteit Brussel, Belgium), and colleagues.

Insoluble amyloid plaques of the Aβ protein are found throughout the Alzheimer’s brain but are thought to be largely inert. By contrast, oligomeric protofibrils—the intermediate between soluble Aβ and insoluble amyloid—are known to be neurotoxic. But once they make plaques, protofibrils were not thought to escape back into toxic form.

Because disturbed lipid metabolism has been implicated in Alzheimer’s development, the authors tested the effects of lipids on plaque solubility. When subjected to a variety of naturally occurring lipids, plaques released large amounts of protofibrils that were toxic to neurons in culture. Injecting a mixture of lipids and amyloids into the mouse brain caused memory deficits not seen with either alone. “If the brain harbors a lot of aggregates, it can be a significant reservoir of toxic material,” Rousseau says, which may contribute to worsening Alzheimer’s disease.

As a silver lining, Rousseau notes, the discovery may make anti-protofibril antibody production much easier, because abundant quantities of protofibrils can be kept in solution for long periods. JCB Reference: Martins, I.C., et al. 2007. EMBO J. doi:10.1038/sj.emboj.7601953.