Imaging the immune response

You can learn a lot from a picture. Case in point, a new report from Kamal Khanna, Jeffrey McNamara, and Leo Lefrançois (University of Connecticut, Farmington, CT) images T cells as they prepare to fight infection.

To examine the cell dynamics of an immune response, the researchers used laser scanning microscopy to take 3D snapshots of T cells in the spleen during infection. The authors infected mice with *Listeria monocytogenes* that expressed a well-studied antigen, ovalbumin. They then examined the animals’ spleens at different times, staining for T cells (of the CD8+ T cell subtype) that could recognize and kill cells expressing ovalbumin antigens.

Immune responses can be initiated in the spleen, which is subdivided into compartments containing different kinds of immune cells; upon infection, the authors saw increased movements of T cells between certain compartments. Initiation of the immune response in the spleen appeared to take place within the lymphocyte-containing white pulp, at the border between B cell–rich areas and a T cell–rich area known as PALS. What is so special about this zone that drives the immune response will have to be addressed in future studies.

Later during infection, T cells moved between the white pulp and red blood cell–rich red pulp areas of the spleen via structures called bridging channels. Only once they made it to the red pulp did the T cells have access to the circulation and travel to the rest of the body to fight infection.

After infection was resolved, memory T cells (those that had seen the antigen) were found in both the red pulp and B cell areas of the spleen.

"For a CD8+ T cell, it was rather bizarre to find them in the B cell areas," says Lefrançois. "We're still trying to understand the functional significance.

Reference: Khanna, K.M., et al. 2007. Science. 318:116–120.

Tumors’ accomplices in invasion

Tumors that escape from their original site are associated with a poor prognosis for cancer patients. New research by Antoine Karnoub, Robert Weinberg (Whitehead Institute, Cambridge, MA), and colleagues suggests that the ability to escape may be acquired through the tumor’s interactions with normal tissues.

A growing tumor is considered by its surrounding normal tissue to be a bit like a wound. As also occurs during the wound response, tumors recruit mesenchymal stem cells (MSCs)—which are meant to help with repair—from the bone marrow. Karnoub et al. hypothesized that these MSCs, rather than being helpful, may instead advance disease. To investigate this idea, they injected human breast cancer cells, either alone or along with human MSCs, into mice and then looked for metastases in the animals’ lungs.

When MSCs were mixed with tumors, several cancer cell lines were more metastatic. This behavior was reversible; MSC-induced metastases purified from one animal and then injected without MSCs into new animals were no more metastatic than the original primary tumors. MSCs thus seem to teach cancer cells tricks that are not intrinsic to the cancer itself.

Some of these tricks might be learned from MSC-derived chemokines. The MSCs provided two lines of breast cancer cells with the chemokine CCL5, which caused the tumor cells to become more motile and invasive. MSCs had to contact cancer cells to make CCL5, but it is not known what interactions are important. And not every cancer line stimulated CCL5 production. “I liken it to a key-and-lock situation,” says Karnoub. “The cancer has the key, but what lock it fits to release CCL5 from MSCs is a mystery.”

Karnoub is also interested in how cancer cells cause long-term changes in MSC behavior. “The MSCs remembered having been in contact with tumor cells; even three days or more after their initial exposure, they were still making CCL5. There’s a two-way communication going on there.”

Reference: Karnoub, A., et al. 2007. Nature. 449:557–565.
Localized mRNA is the norm

Location, location, location. It’s critical for real estate, proteins, and—according to work by Eric Lécuyer, Henry Krause, and colleagues (University of Toronto, Canada)—mRNAs, too.

Several localized mRNAs have been previously studied, but just how many transcripts are localized in the cell, and in what patterns, is unknown. Lécuyer et al. approached this problem by optimizing fluorescence in situ hybridization (FISH) in a global analysis of developmentally expressed mRNAs. They found that 71% of the mRNAs in early fly embryos showed specific patterns of subcellular localization.

In several cases, they found new examples of mRNAs that colocalized with their protein products. Less energy is probably required to transport a few copies of an mRNA than to move around many more copies of the protein. And the proteins will be created where they are needed and possibly prevented from straying where they are not wanted.

“We need to revise the textbook image of proteins being made in a centralized location near the nucleus, then trafficking to their ultimate locations,” says Krause. “Our work shows that the mRNAs are an intelligent actor, not just a dumb vehicle for creating proteins.” With their new database, the group can now further investigate how and why mRNAs are localized.

Reference: Lécuyer, E., et al. 2007. Cell. 131:174–187.

Cholesterol and Alzheimer’s

Alzheimer’s disease (AD) presents in early- and late-onset forms that share the same neuronal pathology but have different genetic causes. A new study by Qiang Liu, Guojun Bu (Washington University, St. Louis, MO), and colleagues now suggests that both AD forms are linked to a cholesterol pathway.

Cholesterol was already linked to late-onset AD. The best-known risk factor for this disease is a specific form of apolipoprotein E (apoE), which delivers lipids such as cholesterol to neurons. But early-onset AD stems from mutations in genes encoding amyloid precursor protein (APP) or its cleaving enzymes, which result in the accumulation of disease-associated Aβ amyloids. How these disparate pathways both lead to AD was not known.

In addition to Aβ, APP cleavage also produces the APP intracellular domain (AICD) peptide. Liu et al. now show that AICD blocks the apoE pathway, thereby lowering cholesterol levels in the brain. AICD blocked the lipid’s import into neurons by reducing the expression of the apoE receptor, LRP1.

In AD, APP processing gone awry might cause AICD to accumulate, thus depriving neurons of cholesterol. Both early and late forms of AD may therefore stem at least in part from faulty, cholesterol-deprived neurons.

“We now have a better idea of APP’s function in the brain,” says Bu. “It could be linked to disease through both Aβ-dependent and -independent mechanisms.”

Reference: Liu, Q., et al. 2007. Neuron. 56:66–78.

Structure of the meiotic spindle

The meiotic spindle is made up of shorter microtubules than previously believed, suggest results from Ge Yang, Gaudenz Danuser (Scripps Research Institute, La Jolla, CA), Ben Houghtaling, Tarun Kapoor (Rockefeller University, New York, NY), and colleagues. Current models of the spindle, as a bipolar array of overlapping filaments extending from opposite spindle poles, will require revision.

To get a closer look at the architecture of the meiotic spindle, Yang et al. incorporated labeled tubulin subunits into the spindle in a cell-free system. By refining their fluorescent speckle microscopy techniques, the authors were able for the first time to track individual tubulin subunits (seen as speckles) in a single tubulin polymer.

The authors identified pairs of speckles representing subunits on the same filament. Speckle separation supplied them with the minimum length of that filament. They then fitted a mathematical model to these observed lengths to predict overall filament lengths: most filaments were only ~40% of the total spindle length. The short filaments were also scattered throughout the spindle. The researchers now propose that the spindle is a tiled array of overlapping short filaments.

The group next examined how spindle-associated proteins might control filament and spindle size. By inhibiting microtubule motor proteins, they found that dynein–dynactin limited individual fiber lengths and thus overall spindle length. Kinesin 5 activity limited the overlap between fibers by sliding them apart. “Our work suggests the spindle is a self-organizing system, whose stability and functional characteristics are built on these kind of local interactions,” says Kapoor.

Reference: Yang, G., et al. 2007. Nat. Cell Biol. doi:10.1038/ncb1643.