

Tough antigens trigger immunity

The harder a protein is to chop up, say Delamarre and colleagues on [page 2049](#), the more vigorous an immune response it will trigger. This suggests that the most durable antigens—or those attached to degradation-resistant carrier proteins—might make the best vaccines.

The correlation between stability and immunogenicity may seem counterintuitive, given that the very products of lysosomal degradation—antigenic peptides or epitopes—bind to class II MHC molecules for presentation to CD4⁺ T cells. And many (but not all) in vitro studies show that blocking lysosomal function in vitro inhibits antigen presentation.

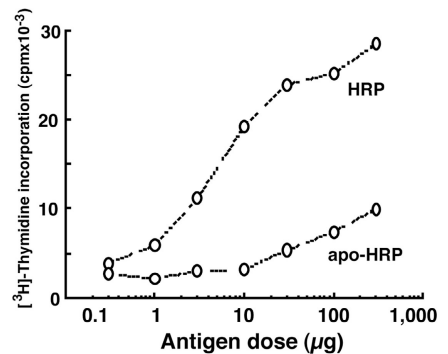
To determine which kind of antigen elicits the strongest immune response, Delamarre et al. stuck identical T or B cell epitopes into lysosomal degradation-resistant and degradation-sensitive ver-

sions of the same protein. Mice immunized with the more durable versions of the proteins generated more robust T cell and antibody responses than those immunized with the more degradable forms. Stabilizing the degradation-prone antigens using aldehyde fixation boosted their immunogenicity.

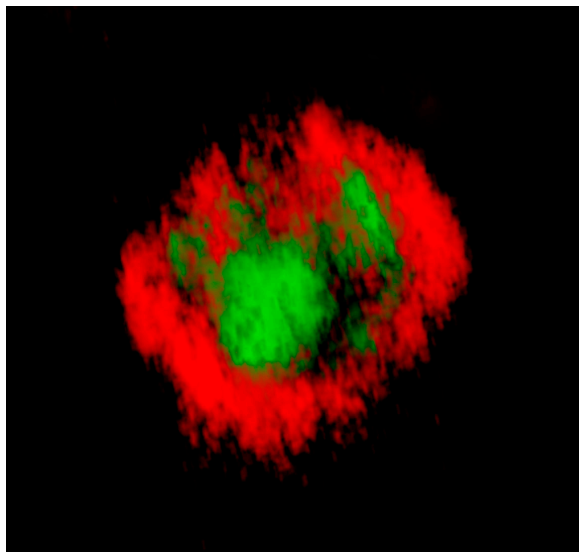
Antigen-presenting cells did not simply have a bigger appetite for the more stable form of the protein, as both forms were taken up equally well by dendritic cells (DCs). Rather, the more stable antigens were better retained in DCs as they transited from peripheral sites of antigen capture to lymph nodes, where they present their antigenic cargo to T cells.

This group previously showed that DCs express a paucity of proteases compared with macrophages, allowing them to degrade internalized proteins more

slowly and thus retain them longer—perhaps explaining why DCs are so good at disseminating antigens and initiating immunity. Thus, both the nature of a protein and the cell type it ends up in help determine how immune provoking that protein will be. [JEM](#)



Protease-resistant proteins (HRP) induce more robust T cell proliferation than their degradation-sensitive counterparts (apo-HRP).



LFA-1 (red) molecules surround central TCRs (green) in a live synapse.

Desperately seeking synapses

Signaling between a T cell and an antigen-presenting cell (APC) is orchestrated through a bull's eye-like structure known as the immunological synapse. But no one had ever spotted these structures in vivo, causing many to wonder whether they are immunology's equivalent of the Loch Ness monster. Synapse devotees can now rest easy, thanks to Barcia et al., who provide the first in vivo glimpse of these elusive cellular structures on [page 2095](#).

When first described, immunological synapses—their centers rich with T cell receptor (TCR)-MHC/peptide complexes and their outer rings with stabilizing integrins and adhesion molecules—provided a satisfying spatial model of how T cells get activated and signal to target APCs. But although these structures formed readily when T cells bumped into artificial lipid bilayers or cultured APCs, they have proven difficult to capture in real-life settings—in part due to limitations of live imaging and the touch-and-go nature of T cell-APC interactions.

Barcia et al. used a well-characterized model of viral brain infection in rats to help them pinpoint when and where to look for cytotoxic T cells engaging infected brain cells. The use of a nonreplicating virus—which infected brain cells but did not destroy

them—also aided the synapse hunt. Three-dimensional reconstructions of confocal images revealed both the polarization of phosphorylated signaling kinases toward the T cell-APC contact site (an early sign of T cell activation) and—voilà!—the characteristic bull's-eye structure of the synapse.

The formation of synapses preceded viral clearance, suggesting that these ordered structures might indeed be necessary for T cell activation and subsequent elimination of infected cells. Formal proof of this, however, awaits the development of inhibitors or genetic mutations that selectively interfere with synapse formation. At least now we can rest assured that synapses really are more than just visually pleasing in vitro phenomena. [JEM](#)

Complement complicates pregnancies

During pregnancy, growth of new blood vessels into the placenta is required to nourish the developing fetus. On [page 2165](#), Girardi et al. show that activation of the complement cascade blunts placental development by triggering the production of a potent angiogenesis inhibitor. Monitoring levels of complement activation in pregnant women might thus be useful in predicting pregnancy complications.

This group had previously shown that inhibition of complement activation prevented pregnancy loss in an antibody-dependent mouse model of miscarriage. But they understood neither what triggered complement activation nor how complement interfered with normal fetal development.

Girardi and colleagues now solve half the mystery in a model of spontaneous miscarriage. Complement activation, they show, triggers the production of a decoy receptor—soluble vascular endothelial growth factor receptor-1 (sVEGFR-1)—that sops up the

vessel-building protein VEGF, which is needed to establish the placental blood supply. Blocking complement activation inhibited the production of sVEGFR-1 and restored normal fetal development. The in vivo cellular source of sVEGFR-1 was not

identified, but monocytes are a good candidate, as these cells produced sVEGFR-1 in vitro when stimulated with complement.

During pregnancy, excessive inflammation—and the resulting complement activation—may create conditions unfavorable for the pregnancy to proceed. [JEM](#)



Complement activation causes embryo loss (asterisks) in mouse uteri.

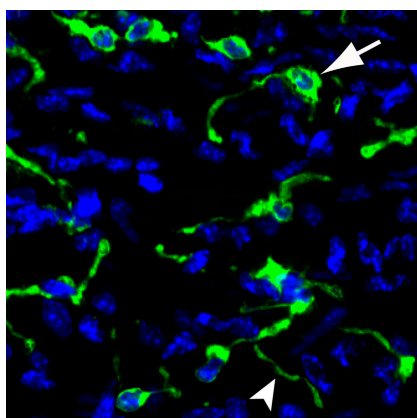
Can DCs forecast atherosclerosis?

Atherosclerotic lesions are initiated mostly at vessel branch points and curvatures, where blood flow is irregular and inflammatory gene expression is high. Circulating blood cells—including macrophages, T cells, and dendritic cells (DCs)—accumulate in these areas at steady state, creating a scaffold on which the lesion is built. On [page 2073](#), Jongstra-Bilen et al. suggest that it is DC build-up that most portends future lesion development.

Although many cell types have been shown to congregate in lesion-prone regions of vessels, few studies have analyzed the relative abundance of these cell types in lesion-prone and lesion-resistant regions. Nor have they compared the cellular composition in atherosclerosis-susceptible and -resistant strains of mice.

Jongstra-Bilen and colleagues now show that, in normal mice, DCs (but not T cells) were 100 times more abundant in lesion-prone areas of the aorta than in resistant areas. But these cells were found only in the innermost vessel layer (the intima). In the outermost layer (the adventitia), the cellular composition (mostly macrophages and T cells) was comparable in lesion-prone and -resistant regions.

These strategically located DCs were more plentiful in atherosclerosis-prone mice than in resistant mice, suggesting that a preponderance of intimal DCs might predispose them toward atherosclerosis. The authors speculate that the DCs, which are adept at gobbling up macromolecules, might take up oxidized lipoproteins. Lipid-laden macrophages are important building blocks of atherosclerotic plaques—but perhaps these cells get in on the act only after lipid-stuffed DCs set the foundation. [JEM](#)



Dendritic cells (green) are abundant in atherosclerosis-prone vessel regions.

Sympathy for t-PA

Tissue plasminogen activator (t-PA), a protease released by vascular endothelial cells, keeps blood flowing freely by busting up clots. But t-PA is also produced by sympathetic nerve endings where, according to Schaefer et al. on [page 2191](#), it enhances the release of norepinephrine (NE), which can cause the heart to beat erratically.

The clot-busting power of t-PA—which works by cleaving the proenzyme plasminogen into the active plasmin that then breaks down the clot protein fibrin—is often used to dissolve clots in patients who have had heart attacks or strokes. But treatment with recombinant t-PA has been associated with erratic heartbeats (or arrhythmias)—a common cause of death post-heart attack.

The team now shows that the production of t-PA causes sympathetic nerve endings in the heart to release NE. And NE, which constricts vessels and increases heart rate, is known to trigger arrhythmias. Indeed, mice lacking t-PA produced lower levels of NE and were less likely to develop arrhythmias after ischemic heart injury.

t-PA did not need to cleave plasminogen to induce NE release, but this activity did involve both Ca^{2+} -dependent exocytosis and carrier-dependent transport of NE from nerve endings. Exactly how this process gets started remains obscure, in part because plasminogen is thus far the only known t-PA substrate.

Sympathetic nerve endings, which are abundant in vessel walls and heart tissue, may produce t-PA to magnify fibrin breakdown in response to injury. But the secondary release of NE might then contribute to the arrhythmia often associated with therapeutic t-PA. [JEM](#)