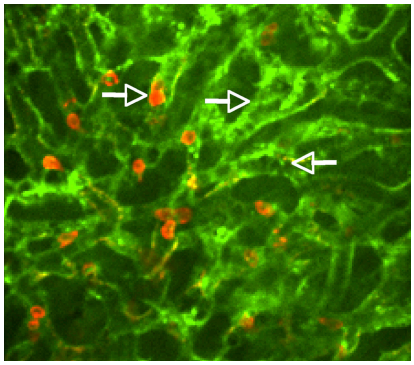
Text by Hema Bashyam; hbashyam@rockefeller.edu
and Caitlin Sedwick; csedwick@gmail.com



Neutrophils (red) adhere to an adhesion molecule called SHAP (green) in liver blood capillaries (arrows).

Flushing out neutrophils

Activated neutrophils that infiltrate the liver during severe sepsis lodge themselves in the liver's tiniest blood vessels and cause organ damage. On page 915, McDonald et al. examine how neutrophils burrow into the liver and suggest a way to pry them out.

Neutrophil recruitment in response to sepsis-triggering bacterial toxins such as LPS unfolds in several stages. In most places in the body, adhesion molecules called selectins initially snare neutrophils and help them tether to and roll along blood vessel walls. The cells subsequently adhere more firmly through integrins. But because neutrophils do not seem to need these molecules to stick to the blood capillaries in the liver, researchers suspected that the narrowness of these vessels instead physically traps the neutrophils.

McDonald et al. now provide evidence against this entrapment model by showing that neutrophils are snagged by a different adhesion molecule, hyaluronan (HA), which they found at high levels in liver vessels. When mice were injected with LPS, neutrophil adhesion levels increased 14 fold, although HA levels did not change. The increased adhesiveness may be due to an HA-associated protein called SHAP, which increases HA's affinity for its neutrophil cell surface ligand, CD44. SHAP levels on the liver's capillary walls were increased by LPS treatments.

Disrupting the interaction between CD44 and HA might potentially reverse sepsis; injecting LPS-treated mice with an anti-CD44 antibody rapidly detached neutrophils from the liver capillary walls and decreased liver damage. JEM

A safer poxvirus vaccine

The smallpox virus has been eradicated thanks to widespread vaccinations with the vaccinia virus. But because live vaccinia virus is used, some vaccine recipients, particularly those who are immune compromised, have experienced fatal infections. Xu et al. (page 981) now offer up an alternative that might side-step the pitfalls of the old vaccine.

Killed vaccinia virus does not induce antibodies against proteins that trigger smallpox, forcing researchers to look for alternative strategies. Xu et al. considered designing vaccines that target virulence proteins that mute the immune response. They reasoned that a vaccine that did not include the entire virus would be safer, while antibodies against virulence proteins, known as immune response modifiers (IRMs), would prevent disease even if they did not neutralize the virus.

The group now identifies an IRM that is the major target of protective antibodies in a mouse model of smallpox. This IRM prevents the antiviral cytokine interferon-α from activating its receptor on immune cells. Deletion of the IRM from the mousepox virus, the group found, caused a 10^7-fold decrease in its virulence and prevented lethality.

Mice that were injected with the IRM alone were protected against a later challenge with the wild-type virus. The IRM, the type I interferon binding protein, is well-conserved among poxviruses that infect mice and men, so the hope is that the recombinant IRM protein might be an effective poxvirus vaccine for humans as well. JEM

Vγ segments are selected based on their proximity to the J segment during the rearrangement of the γδ TCR in fetal stage.

A matter of (V segment) choice

T cell receptor genes are created by stitching together three gene segments—V, D, and J—in different arrangements. But how each set of T cells selects its segments is not clear. Xiong et al. (page 929) now find that, for a set of fetal T cell γδ chains, the appeal of a V segment lies in its location relative to the chosen J segment.

In the fetal stage, γδ T cells prefer to use Vγ3 or Vγ4 gene segments, whereas T cells in the adult thymus instead use Vγ2 or Vγ5. Because Vγ3 and Vγ4 are closer to the J segments, Xiong et al. wondered whether V segment selection is dictated simply by their position. Closer V segments are used preferentially in fetal immunoglobulin genes as well, but in that case, proximity correlated with greater transcription and histone acetylation.

To test their new idea, the group engineered mice in which the γ locus was altered to replace the Vγ3 segment with a Vγ2 segment. The fetal γδ T cells in these mice now included the new Vγ2 segment in preference to the more distant Vγ2 segment. They only included more distant gene segments if closer segments were deleted. How the nearby segments shut out their more remote neighbors is not yet known.

The accessibility of the V segments seemed to be equal across the board in fetal cells, as Xiong et al. found that transcription rates didn't predict which segments were used. But in adult γδ T cells, the unused segments had lower levels of transcription. Perhaps the gene segments used during the fetal stage become inaccessible during adulthood, leaving only more distant choices. JEM