Research Roundup

Gellular transport

Nuclear pores are plugged with a protein gel, say Steffen Frey, Ralf Richter, and Dirk Görlich (Universität Heidelberg, Germany). The researchers succeeded in forming the gel in vitro and believe that in vivo it forms a hydrophobic mesh—a mesh that can be breached only by small proteins or by the hydrophobic nuclear transport receptors (NTRs) that escort larger proteins in and out of the nucleus.

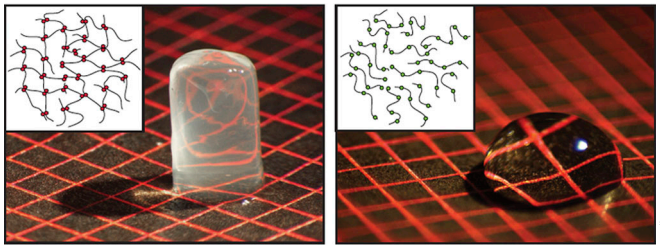
The group focused on the Phe and Gly (FG)-rich repeats present in many nuclear pore proteins. The effective concentration of the repeat proteins in the pore is close to 100 mg/ml. "At such a concentration, a gel must form," says Görlich.

But proving that in vitro was not easy. Agarose makes a gel, but only if the powder is first boiled with water to make a homogeneous solution. A similar approach does not work with FG repeats, whose hydrophobic interactions are largely unresponsive to heat. Finally, the German group found that a regime of pH changes could give a similar result: a hydrogel whose properties are comparable to those of a 0.4% agarose gel. Gel formation runs counter to some other models for nuclear pore action, which only work if repeat proteins do not significantly interact with each other.

Repeat proteins with Phe residues mutated to Ser could no longer form the in vitro gels, bind to NTRs, or rescue nucleoporin mutants. Phe-to-Tyr mutants also failed to bind NTRs but could still rescue nucleoporin mutants. Apparently, the Tyr version interacted with the mesh enough to fulfill the essential function—maintenance of a barrier—and other nucleoporins helped out by interacting with NTRs.

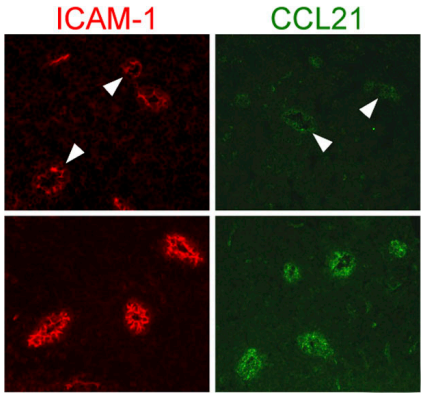
The next step, says Görlich, will be to demonstrate that the in vitro gel can act as a selective permeability barrier. How might such a solid-looking structure perform this function? One might think the multivalent interaction between gel and NTR would freeze any movement, but "it's analogous to water," says Görlich. "A protein diffuses through water even though it has bonds with water. It's just a matter of how fast the rearrangements occur." The NTRs, he says, must use their hydrophobicity to catalyze the necessary exchange. JCB

Reference: Frey, S., et al. 2006. *Science.* 314:815–817.



GÖRLICH/AAAS

Repeats from nucleoporins can form a gel (left) unless mutated (right).



EVANS/MACMILLAN

Heat (bottom)-induced increases in ICAM-1 and CCL21 increase trafficking to lymph nodes.

Fever brings in the lymphocytes

"In whatever part of the body there is a sweat, it shows that the disease is seated there," said Hippocrates. Now, Qing Chen, Sharon Evans (Roswell Park Cancer Institute, Buffalo, NY), and colleagues find that fever turns on homing molecules that direct lymphocytes into lymph nodes. The increased trafficking through lymph nodes should increase the chance of a lymphocyte encountering and being activated by its target antigen-presenting cell.

Higher temperatures are known to be beneficial for postinfection survival. Cold-blooded animals do better if they can seek out the sun when infected. Infected warm-blooded animals incur a 15% increase in metabolic cost for every 1°C rise in core temperature, suggesting that the benefit may be equally high.

The most obvious response to fever is that vasodilation (an attempt to cool down the body) increases blood flow, thus increasing the sheer number of cells that pass by high endothelial venules (HEVs), the entry gates to lymph nodes. "If anybody thinks of fever at all, they think of it in those terms," says Evans. "But we think there is an additional change besides the physics."

Evans turned up the temperature to 39.5°C, and then returned it to normal before the experiment began so that blood flow effects were eliminated. Her team found that the initial rolling interaction of lymphocytes on HEVs was unchanged, but two key downstream molecules were up-regulated. The CCL21 chemokine and ICAM-1 adhesion molecule (both on HEVs) mediate a post-rolling arrest that is required for entry through HEVs, and lumenal presentation of both was increased up to twofold by the prior increase in temperature.

IL-6 signaling is required for the heat-induced up-regulation of the trafficking and ICAM-1 but not of CCL21. It is not yet clear what turns on IL-6 or what makes the signaling so specific to HEVs.

The fever signal might be particularly useful when there is a rare antigen or when a previously localized infection spreads. So should we all suffer through our fevers rather than combat them with drugs? "I'm the biggest hypocrite," says Evans. "If I don't feel well I take a Tylenol." She says the study has important clinical implications, but for most people "if we take a Tylenol it's not going to be the deciding factor." JCB

Reference: Chen, Q., et al. 2006. *Nat. Immunol.* doi:10.1038/ni1406.