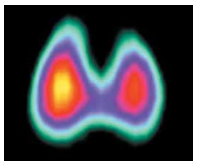
Vessel delivery

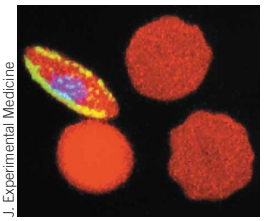
The endothelial cells that line the blood vessel are not all the same—they express different proteins depending on the type of tissue they are associated with. These tissue-specific proteins, particularly those on the surface and accessible to the bloodstream, would be ideal targets for drug delivery—if researchers could only find them. In the 10 June *Nature*, Phil Oh *et al.* apply a battery of techniques to identify and visualize such proteins: The investigators cap off their studies by destroying lung tumors in mice with a radiolabeled antibody against one of their new targets.


Nature

Oh *et al.* first enriched for their targets by isolating endothelial cell membranes and caveolae, small invaginations of the cell surface that have transport and signaling functions. Starting with this material, they pulled out proteins using mass spectrometry, bioinformatic analyses and other techniques, and they pinpointed cell-surface proteins by structural analyses. They emerged with a battery of candidates specific for endothelial cells in the lung or lung tumors.

The authors next focused their attention on two candidates, the lung-specific protein aminopeptidase-P and the tumor-specific protein annexin A1. Radiolabeled antibodies to these proteins rapidly homed to the lungs (shown here) and lung tumors in mice. To their surprise, the investigators found that the annexin A1 antibody also destroyed tumors and prolonged the lifespan of mice after a single injection. Annexin A1, they found, labels the blood vessels of human tumors, including those of prostate, liver and breast, but not normal tissues. In addition to pinpointing Annexin A1 as a promising antitumor target, the approach offers an opportunity to tailor treatments to specific tissues for a variety of diseases.

Building blocks


J. Experimental Medicine

Two years after the completion of the genomic sequence for the malaria parasite *Plasmodium falciparum*, and months after the completion of the sequence of a related parasite, *Cryptosporidium parvum*, Gabriele Pradel *et al.* have traced the arc from genome sequence to biological discovery. In the 7 June *Journal of Experimental Medicine* the researchers emerge with candidate targets for a transmission-blocking malaria vaccine. The idea behind such a vaccine is to harness human antibodies to block the development of *P. falciparum* in mosquitoes and prevent transmission.

The investigators began by mining the genomes of *P. falciparum* and *C. parvum* for genes common to both that encode potential extracellular adhesive proteins. They zeroed in on three genes whose sequences suggested they encoded particularly sticky proteins. All of the proteins expressed from these genes were found on the plasma membrane of mature gametocytes, present in mosquitoes that have just taken a human blood meal (shown here; parasite proteins in green, erythrocytes in red and DNA in blue).

To begin to assess function, the investigators knocked out two of the genes in *P. falciparum*. Unexpectedly, they detected defects in events a full seven days after mosquito feeding, during maturation of the sporozoite stage. The sporozoites did not make it to the salivary glands of mosquitoes, suggesting that blocking these proteins could prevent malaria transmission.

Written by Charlotte Schubert

Will to survive

Just a few mutations here and there can give a virus an extra advantage in its struggle against the host immune system. Most documented instances of viral 'escape' occur in response to antibodies and other selective pressures of the adaptive immune system. In the June issue of *Immunity*, Anthony French *et al.* show how a virus can also escape from 'first-line' defenses of the innate immune system.

French *et al.* examined cytomegalovirus (CMV), which can cause disease in immunocompromised individuals. Using a mouse model, the investigators zeroed in on the interaction of a CMV protein expressed on the surface of infected cells, m157, with a host membrane protein, Ly49H. The interaction benefits the host, as it prods natural killer cells to destroy virus-infected cells. But the researchers report that the virus can mutate and escape this interaction in immunocompromised mice.

Mice lacking T cells could fend off early viral replication, but later in infection, the virus ran roughshod over natural killer cells and took over the animal. This rampant replication, the authors found, was caused by the loss of m157 expression. The investigators speculate that viral evasion of the innate immune system might underlie the severe viral infections that afflict immunocompromised individuals.

Dueling with double-stranded RNA

Viruses make themselves known to host cells in several ways, chief among them the presence of double-stranded RNA (dsRNA). Despite this knowledge, tracking down the molecular sensors that recognize intracellular dsRNA has been no easy task. In the 1 July *Nature Immunology*, Mitsutoshi Yoneyama *et al.* pin down just such a molecule. They identify an RNA helicase that recognizes viral dsRNA and alerts the host cell to the presence of viruses. The molecule is a member of the DexD/H box RNA helicase family of proteins, which unwind dsRNA in processes ranging from RNA interference to mRNA splicing. The newly identified helicase appears to work through a dsRNA-induced conformational change that results in activation of the transcription factors NF-κB and IRF-3. These transcription factors in turn induce antiviral activities, including type I interferon production.

Squeezing the fruit

The contribution of different portions of fat to various obesity-associated disorders such as diabetes remains a contested topic—and the 'apples' often come up with the heavier disease burden. In the 1 June *Journal of Clinical Investigation*, Soren Nielsen *et al.* examine one reason invoked for this burden: that one type of abdominal fat, visceral fat, increases the load of free fatty acids (FFAs) released directly into the portal vein, exposing the liver to high FFA concentrations that could contribute to insulin resistance.

The investigators, using labeled FFAs and mathematical modeling, traced the path of FFAs in human subjects. They found that visceral fat indeed delivered FFAs to the liver and the amount of FFAs delivered increased along with the amount of visceral fat. But visceral fat contributed less than some researchers had predicted: between 10 and 50 percent, varying greatly among individual patients.

Abdominal fat comes in two flavors. In addition to visceral fat, which predominates in men, there is subcutaneous fat. In half of 'apple' women, visceral fat predominates over subcutaneous fat. These women may be at particular risk: the investigators found that in women, increases in visceral fat prompted steeper increases in FFA release into the liver than in men.