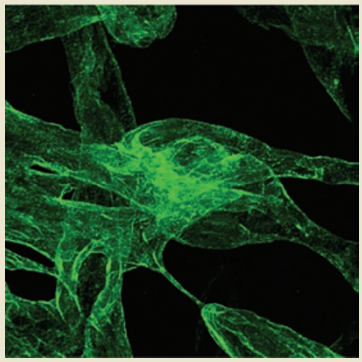
Boosting lymphogenesis



The frequent spread of certain cancers to lymph nodes often necessitates surgery or radiation therapy that damages the lymphatic system and can cause lymphedema, a condition of localized fluid retention that often increases susceptibility to infections. Using a mouse model, Tammela *et al*. have shown that the administration of adenoviral vectors encoding vascular endothelial growth factor-C (VEGF-C) to sites where lymph nodes and lymph vessels have been excised ensured formation of mature lymphatic vessels and incorporation of lymph node transplants into existing lymphatic vasculature. The VEGF-C gene therapy not only enhanced lymphatic drainage but also restored normal lymphatic vascular anatomy. As lymph nodes can prevent systemic dissemination of metastases, the ability to transfer lymph nodes that reconstitute a functional network of lymphatic vessels in adult tissues is of particular importance in cancer follow-up therapy. Accordingly, mice with VEGF-C–treated lymph nodes were more effective in trapping tumor cells than control lymph vessel transplants. (*Nat. Med.* advance online publication, doi: 10.1038/nm1689, 2 December 2007) *PH*

Truncated *Bt* toxins

Understanding how the toxins released by digestion of the crystalline (Cry) proteins of *Bacillus thuringiensis* (*Bt*) in susceptible insects disrupt the intestinal lining is key to designing new insecticides and countering the emergence of resistance. Soberón *et al*. provide compelling evidence that, for both the tobacco hornworm (*Manduca sexta*) and the pink bollworm (*Pectinophora gossypiella*), cadherin receptors mediate toxicity of Cry1A toxins by facilitating removal of an N-terminal α-helix. Whereas native Cry1A toxins require cadherin to form toxin oligomers that punch holes in the midgut membrane, truncated variants lacking the N-terminal 56 amino acids oligomerized without cadherin. *P. gossypiella* and *M. sexta* larvae, with mutant or silenced cadherin, respectively, were more susceptible to the truncated variants than their wild-type counterparts. The modified toxins may thus provide a valuable addition to the growing arsenal of insecticides for combating pest resistance to currently used *Bt* toxins. (*Science*, published online, doi: 10.1126/science.1146453, 1 November 2007) *PH*

Short-circuiting quorum sensing

New avenues for controlling bacterial infections are desperately needed, as supervirulent and antibiotic-resistant strains of *Staphylococcus aureus* are appearing in hospitals and in the community. Knocking out virulence factors might provide one such avenue, but their redundancy in some bacteria means that targeting one will not quell an infection. Now Park and colleagues have produced antibodies against a regulator of virulence factors (autoinducing peptide (AIP)-4), which controls the expression of virulence factors by quorum sensing and its principle regulator, the accessory gene regulator (agr). Monoclonal antibodies (mAbs) raised in mice against a synthetic hapten designed to mimic the structure of AIP-4 alter virulence factor expression in *S. aureus* and inhibited *S. aureus*–induced apoptosis in cultured mammalian cells. One of the mAbs (AP4-24H11) provided mice protection in two *in vivo* assays—a subcutaneous infection model and passive immunization with lethal challenge of *S. aureus*. By measuring both protein and RNA levels of factors regulated by AIP-4 and other accessory regulators, the researchers showed that AP4-24H11 interfered specifically with the agr quorum-sensing system. These results show that mAb-based interference of AIP-4 signaling is a viable approach for inhibiting production of virulence factors, opening up a new avenue for antibacterial treatments. (*Chem. Biol.* **14**, 1119–1127, 2007) *LD*

Crossover immunity to HIV

Human endogenous retroviruses (HERVs) are evolutionary relics ubiquitous in the human genome and generally quiescent. Infection and integration into the human genome of HIV, however, can reactivate HERV sequences. Nixon and colleagues now show that in a cohort of HIV-positive patients, HERV activation correlated with a low HIV plasma viral load, suggesting that the immune response to activated HERV may control HIV as well. Looking at the response of peripheral blood mononuclear cells both to epitopes that are unique to HERVs and those that are shared between the two viruses, they found that T cells from HIV-positive patients reacted to both HERV and HIV epitopes, whereas T cells from HIV-negative (low risk) patients and hepatitis C patients did not. They further characterized HERV-positive $CD8^+$ T cells (the subset involved in killing virally infected cells) in a smaller cohort of infected individuals. They found that the cells resembled those that effectively control viral infections in that they bear surface markers of terminally differentiated cells and were able to lyse infected cells. In contrast, HIV-positive $CD8^+$ T cells tend to be less mature and hence less effective in controlling virus. As the large number of HIV variants in HIV-positive patients has confounded vaccine design, HERV-specific immunity might offer a new avenue for controlling HIV infection. (*PLOS Pathog.* **3**, e165, 2007) *LD*

ES cells model fragile X

Human embryonic stem (ES) cells provide a unique opportunity to model genetic disease. ES cells generated from an affected embryo could be propagated indefinitely in culture and differentiated to relevant lineages to explore early mechanisms of pathogenesis. Benvenisty and colleagues have used this approach to study the origins of fragile X syndrome, a disorder linked to inactivation of the fragile X mental retardation 1 (FMR1) protein and expansion of a CGG triplet in the 5′UTR of the *FMR1* gene. The triplet expansion alone is not sufficient to cause fragile X syndrome; this region of the gene must also carry abnormal epigenetic marks such as hypermethylation. To investigate the acquisition of these epigenetic marks, the authors generated an ES cell line from a fragile X blastocyst, identified through preimplantation genetic diagnosis. In undifferentiated ES cells, *FMR1* was transcribed and translated, and its promoter region was unmethylated. Upon differentiation, however, expression of *FMR1* decreased and changes occurred first in histone modifications and then in DNA methylation, suggesting that silencing of *FMR1* is developmentally regulated. (*Cell Stem Cell* **1**, 568–577, 2007) *KA*

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