IN BRIEF

THERAPEUTICS

Targeted killing of virally infected cells by radiolabeled antibodies to viral proteins

Dadachova, E. *et al. PLoS Med.* **3**, e427 (2006)

A proof of principle study recently published in *PLos Medicine* has demonstrated the effectiveness of radioimmunotherapy in targeting HIV-infected cells. Antibodies specific for the HIV-1 envelope glycoproteins gp120 and gp41 were labelled with either radioactive bismuth (^{213}Bi) or radioactive rhenium (^{188}Re). ACH-2 cells and HIV-infected peripheral blood mononuclear cells (PBMCs) were both selectively killed by radioisotope treatment *in vitro*. The treatment was also shown to be effective *in vivo* — in a SCID (severe combined immunodeficient) mouse model, >99% of the HIV-infected human PBMCs in the spleen were eliminated by gp41-specific antibodies labelled with ^{213}Bi or ^{188}Re. The authors suggest that the major clinical use for HIV-targeting radioimmunotherapy could be as an adjunct to highly active antiretroviral therapy regimens.

BACTERIAL PATHOGENESIS

Salmonella typhimurium disseminates within its host by manipulating the motility of infected cells

Worley, M. J. *et al. Proc. Natl Acad. Sci USA* 09 Nov 2006 (doi:10.1073/pnas.0604054103)

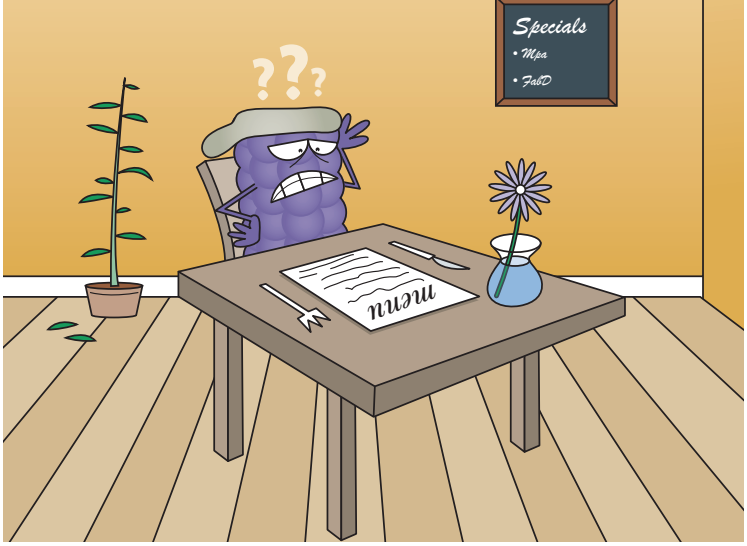
Salmonella enterica serovar Typhimurium (*S. typhimurium*) is thought to be able to cross the intestinal barrier within CD18$^+$ phagocytic cells. Phagocytes infected with *S. typhimurium* have been found to enter the bloodstream as quickly as 15 minutes after the organism has been ingested. What is responsible for the remarkable speed of this extraintestinal dissemination? Micah Worley and colleagues have been investigating this phenomenon, and specifically the role of SrfH, an *S. typhimurium* type III-secreted effector. CD18$^+$ phagocytes were infected with wild-type *S. typhimurium* and an *srfH* mutant, and their ability to undergo chemotaxis was observed using a Boyden chamber. The results showed that SrfH stimulates phagocyte migration, and further work in a mouse model established that *in vivo*, SrfH accelerates the entry of *S. typhimurium* into the bloodstream.

PARASITOLOGY

Anopheles and *Plasmodium*: from laboratory models to natural systems in the field

Cohuet, A. *et al. EMBO Rep.* 10 Nov 2006 (doi:10.1038/sj.embor.7400831)

Interrupting the transmission of *Plasmodium falciparum* from human to human is a potential malaria-control strategy. The survival of the parasite to the oocyst stage within the vector is one of the stages that could potentially be targeted in malaria control, as shown by previous gene-silencing studies using the rodent malaria parasite *Plasmodium berghei*, which highlighted a strong positive or negative role for three *Anopheles gambiae* genes, *CTL4*, *CTLMA2* and *LRIM1*. Now, Cohuet *et al.* report the results of the first gene-silencing studies using sympatric natural *P. falciparum* isolates and *A. gambiae* mosquitoes to look at the effects of these genes under near-natural conditions in Cameroon. The results showed that, in contrast with the results obtained previously using the *P. berghei* model, silencing of *CTL4*, *CTLMA2* and *LRIM1* had no effect on parasite development. This emphasizes the importance of studying the natural interactions between *P. falciparum* and *A. gambiae* as a follow up to laboratory work using model systems.



BACTERIAL PHYSIOLOGY

But what does it eat?

Studies of prokaryotic proteasomes are still in their infancy; little is known about the substrates that they degrade or the cofactors required for their function. Scientists from the United States and India now combine their expertise to identify the first putative endogenous substrates of the proteasome of *Mycobacterium tuberculosis*.

Eukaryotic and prokaryotic proteasomes consist of a barrel-shaped 20S core particle composed of two inner-catalytic β-subunit rings and two outer α-subunit rings that block the entry of substrates into the proteasome. In eukaryotes, the 20S core particle is flanked by one or two 19S regulatory caps, which include AAA+ ATPase proteins. The regulatory

HIV

Breaching the barrier

New research in *Nature Medicine* indicates that the systemic immune activation that is characteristic of chronic HIV infection could be caused by the translocation of microorganisms through a breach in the integrity of the mucosal barrier in the gut.

HIV replicates preferentially in mucosal tissues such as the gut, as these areas are rich in CD4$^+$ T cells that express the CCR5 co-receptor. It was recently determined that the most marked depletion of CD4$^+$ CCR5$^+$ T cells in HIV infection occurs in the gut during acute infection. This led to the hypothesis that this breach in the integrity of the mucosal immune system, perhaps in combination with damage to the intestinal epithelium, could allow the translocation of microorganisms from the intestinal lumen, leading to the systemic immune activation seen during chronic HIV infection. Brenchley *et al.* now present experimental evidence to support this hypothesis.

The levels of lipopolysaccharide (LPS) in plasma can be used to quantify the extent of microbial translocation. The authors found that the plasma levels of LPS were significantly higher in HIV-infected than in uninfected individuals. To determine the main source of LPS, a simian immunodeficiency virus (SIV) infection model was used and SIV-infected macaques were treated with antibiotics for two weeks. The antibiotic treatment decimated the faecal bacterial load, which correlated with a significant decrease in plasma LPS, indicating that the source of the plasma LPS is likely to be microorganisms from the gastrointestinal tract.

Does this LPS have an immunostimulatory effect *in vivo*? Assessment of the levels of two plasma proteins known to be induced by LPS provided evidence that it does, as the levels of both proteins were higher in HIV-infected than uninfected individuals. Additionally, elevated plasma LPS levels showed a positive