Meet the family

From an evolutionary perspective, *Mycobacterium tuberculosis* and its close relatives are so similar that they seem to have separated from a common ancestor only 20,000–35,000 years ago. What happened before this separation? A 2005 paper by Cristina Gutierrez *et al.* has redrawn the evolutionary tree of this family, linking it to African mycobacterial strains (*PLoS Pathog.* **1**, e5).

Using genetic data, the authors found that human tubercle bacilli from East Africa are the living representative of an ancient progenitor species, perhaps as old as three million years, from which *M. tuberculosis* and its relatives evolved. Gutierrez and her colleagues also detected evidence of horizontal gene transfer that seemed to have occurred in the pool of ancient bacteria before the origin of *M. tuberculosis*. This observation is remarkable, as recombination between *M. tuberculosis* and its close relatives does not seem to have occurred since their separation.

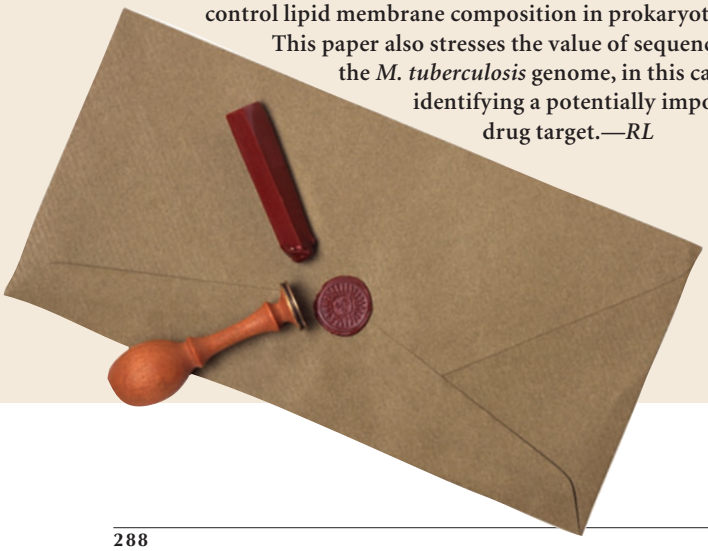
These findings challenge the idea that tuberculosis originated relatively recently, substantially pushing back its potential birth. It is therefore possible that early hominids may have already experienced the nasty effects of the disease.—*JCL*

The envelope, please

Mycobacterium tuberculosis contains diverse lipids in its cell envelope, all with nonredundant roles in virulence or in persistence of infection. But the intracellular factors that control this membrane composition have been unclear. In 2005, Hideki Makinoshima and Michael Glickman (*Nature* 436, 406–409) identified a gene for a novel, site-two protease (S2P) homolog (*Rv2869c*) that is not only responsible for determining lipid composition, but is also important for cell growth and persistence *in vivo*.

The authors identified the gene by panning the *M. tuberculosis* genome for S2P homologs that harbored signature motifs of this protein family. They then deleted the gene and showed that its absence altered the growth of the mutant bacteria *in vitro*, while changing the lipid composition of the cell envelope. Given the direct role that cell envelope lipids play in pathogenesis, the authors then tested growth and persistence of bacteria lacking *Rv2869c* in a mouse model of tuberculosis, showing reductions in both phenomena.

This is the first time that an SP2 family member is shown to control lipid membrane composition in prokaryotes. This paper also stresses the value of sequencing the *M. tuberculosis* genome, in this case identifying a potentially important drug target.—*RL*



Kamikaze bacilli

In tuberculosis, bacteria persist in the host despite an intense immune response. This response is particularly strong in granulomas—structures that contain immune cells and that form in response to infection. A prevailing explanation for bacterial persistence was that *M. tuberculosis* avoids the immune response by reinfecting the host outside granulomas. In 2004, Christine Cosma *et al.* made the surprising observation that mycobacteria do not avoid, but instead traffic into, granulomas upon reinfection (*Nat. Immunol.* **5**, 828–835).

The authors labeled *Mycobacterium marinum*, a frog and zebrafish pathogen that triggers the formation of granulomas and shares virulence determinants with *M. tuberculosis*, and followed the fluorescent bacteria inside reinfected animals. They saw that host mononuclear cells rapidly transported mycobacteria into granulomas, without affecting bacterial survival. The bacilli even made it into the so-called caseum, a necrotic, secluded space within granulomas.

What are the molecular mechanisms whereby mycobacteria are transported to granulomas? How does the pathogen survive the immune response in those structures? Are the results from frogs and zebrafish indicative of what happens in humans? These are some of the questions raised by this intriguing observation.—*JCL*

Big problem, small trials

A top priority of the tuberculosis community is the development of new drugs against the disease, a point repeatedly made throughout this issue. A 2006 paper by William Burman *et al.* on the results of a clinical trial of moxifloxacin illustrates how difficult it will be to succeed in this endeavor (*Am. J. Respir. Crit. Care Med.* 174, 331–338).

The authors evaluated the efficacy of moxifloxacin, a fluoroquinolone, against tuberculosis in humans, administering it in combination with isoniazid, rifampin and pyrazinamide. As endpoint, they used a surrogate marker of the sterilizing activity of the treatment—sputum culture status at two months. Disappointingly, they did not find differences between experimental and control groups, although they saw increased activity of moxifloxacin at earlier time points.

The true disappointment, however, is that using a surrogate marker of sterilizing activity is a big limitation of this and other anti-tuberculosis drug trials. The best marker of sterilizing activity is patient relapse, but comparing relapse requires very large sample sizes. It is therefore nearly impossible to study relapse rates when testing new drugs in all the different doses and combinations that are needed for a definitive result. So, above and beyond the efficacy data, the study of Berman and colleagues highlights the need for larger numbers of subjects in tuberculosis clinical trials.—*JCL*

Highlights written by Eva Chmielnicki, Alison Farrell, Randy Levinson, Juan Carlos López and Lavanya Reddy.

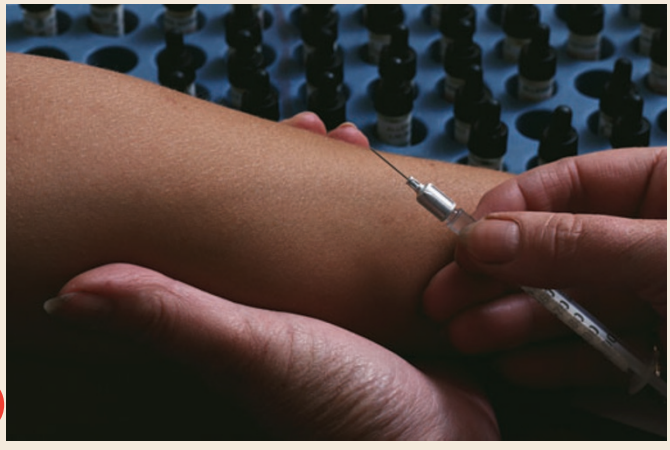
Vaccination gets one boost…

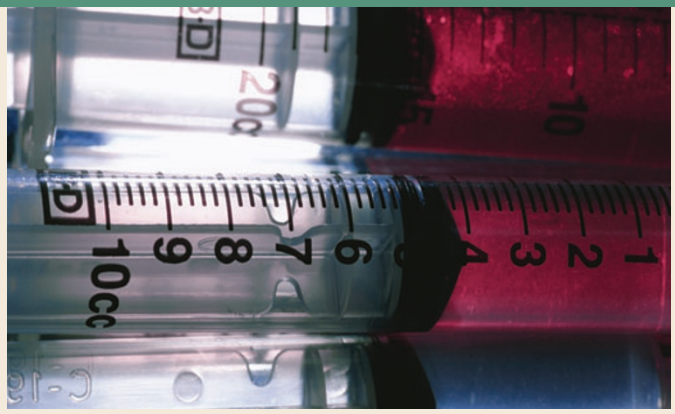
A commonly used childhood tuberculosis vaccine gets a boost—and may be rendered useful for adult exposure to the bug, according to a 2004 study published in *Nature Medicine* (**10**, 1240-1244).

BCG (bacilli Calmette-Guérin) is a weakened strain of *Mycobacterium bovis,* a cousin of the bacterium that causes tuberculosis. Children receive BGC vaccinations to reduce their chances of coming down with tuberculosis. Unfortunately, however, BCG is not effective at reducing the incidence of tuberculosis in adulthood.

To increase the effectiveness of BCG in adults, Helen McShane and colleagues attempted a heterologous prime-boost immunization schedule in a phase 1 trial in humans. In the study, volunteers received a BCG priming injection followed later by a boost of vaccinia virus genetically modified to express mycobacterial antigen 85A. People who received the prime-boost immunizations showed a substantial increase in antigen-specific T cell responses to *M. tuberculosis* antigens compared with individuals that received BCG alone.

Further studies must determine whether the prime-boost immunizations used in this work could be effective in reducing the incidence of tuberculosis in adults in countries where tuberculosis is widespread.—*EC*





…and then another

With the increasing spread of tuberculosis infection worldwide and the escalating incidence of multidrug-resistant *Mycobacterium tuberculosis* strains, the need for an effective vaccine has never been more urgent. Stefan Kaufmann and colleagues are trying to develop just that by improving upon an existing vaccine (*J. Clin. Invest.* **115**, 2472–2479, 2005).

The commonly used BCG vaccine confers virtually no protection against tuberculosis in adults. One reason for the weak effect may be that the vaccine does not strongly stimulate a $CD8^+$ T-cell response, which may be necessary for optimal immunity against the pathogen. Like *M. tuberculosis*, BCG is taken up by antigen-presenting cells (APCs) into phagosomes, processed through the major histocompatibility complex (MHC) type II pathway and presented to $CD4^+$ T cells. To enhance presentation to and activation of $CD8^+$ T cells, Grode *et al.* modified BCG by deleting urease C and introducing listeriolysin, thereby promoting release of the mycobacterium into the cytosol, and increasing processing through the MHC type I antigen-presenting pathway. Because release into the cytoplasm also triggers apoptosis of the infected APC, the recombinant BCG may also boost cross-priming of both $CD4^+$ and $CD8^+$ T cells.

The modified BCG showed better protection in mice against infection with two different strains of *M. tuberculosis*, including a multidrug-resistant strain, when compared with BCG. The improved vaccine is currently being tested clinically.—*AF*

An inside job

Many of the contributions highlighted in this issue concern discoveries about the biology of *M. tuberculosis* and its ability to cause disease. But what about host susceptibility factors? In a 2005 paper, Pedro Flores-Villanueva *et al.* identified a polymorphism in the promoter of the gene encoding monocyte chemoattractant protein 1 (*MCP-1*) that increases susceptibility to tuberculosis in people (*J. Exp. Med.* **202**, 1649–1658).

Studying two separate cohorts in Mexico and Korea, the authors identified a polymorphism at position –2518 of *MCP1* that was overrepresented in patients with tuberculosis; carriers of the *AG* and *GG* alleles were ~2–7 times more likely to develop the disease than carriers of the *AA* genotype. Moreover, in response to *M. tuberculosis*, monocytes from *GG* carriers produced more MCP-1 and less interleukin (IL)-12p40 than monocytes from *AA* carriers.

Flores-Villanueva and his colleagues propose that the effect of the *GG* genotype can be accounted for by the increased production of MCP-1, which then downregulates the antibacterial activity of the IL-12–IL-23–interferon-γ axis, thereby increasing the likelihood that infected individuals will progress to disease.—*JCL*

XDR-TB emerges

In 2006, Neel Gandhi and his colleagues stressed the urgency of finding a new approach to treating tuberculosis, particularly in HIV-infected individuals (*Lancet* **368**, 1575–1580). Writing about a cohort in sub-Saharan Africa, the authors reported that extensively drug-resistant (XDR) *Mycobacterium tuberculosis*, a strain that does not respond to any of the common TB treatments, kills patients with HIV within 16 days of diagnosis. As individuals with HIV are particularly susceptible to infection, this could have serious consequences for this group of patients. In addition, the emergence of a XDR strain of the tubercle bacillus has the potential to become a health threat for the general population.—*LR*