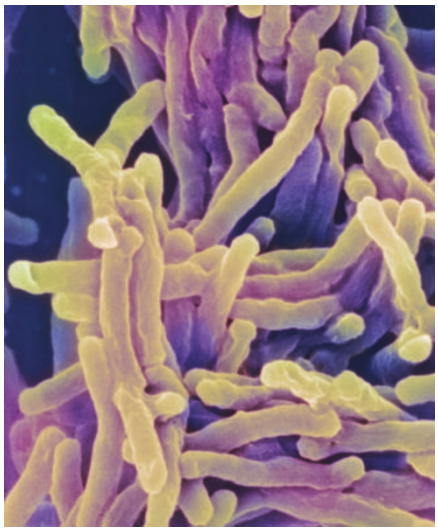

CAMR/A. B. DOWSETT/SPL

Figure 1 **Agent of tuberculosis: the tubercle bacillus, *Mycobacterium tuberculosis*.**

*sst1* (for 'supersusceptibility to tuberculosis 1') that the authors previously mapped[7] to chromosome 1. Now, Pan *et al.* have generated a mouse strain in which the *sst1* locus from the C3HeB/FeJ mice has been replaced with the same region from C57BL/6J mice, which are resistant to TB. The authors used this 'congenic' strain to study the contribution of *sst1* to the pathogenesis of TB.

Pan *et al.* first show that the acquisition of resistance in the congenic strain is associated with an increased capacity of bone-marrow-derived macrophages to restrict intracellular replication of *M. tuberculosis*. Interestingly, resistance is also linked to the induction of apoptosis (a strictly regulated form of cell suicide) in macrophages following infection. Macrophages in susceptible mice, by contrast, die by necrosis — an uncontrolled process that may be less likely to restrict bacterial spread.

Scrutiny of the *sst1* chromosomal region for candidate genes that are expressed in macrophages then led the authors to a gene that they call *Ipr1* (for 'intracellular pathogen resistance 1'). *Ipr1* is expressed in resistant macrophages and is induced upon *M. tuberculosis* infection, but is absent from susceptible cells. The authors' gene hunt was complicated by the fact that the *sst1* locus includes part of a 'homogeneously staining region' — a large, unstable region of repeated DNA that contains several rearranged copies of *Ipr1*-related sequences. This may explain the susceptibility of C3HeB/FeJ mice: the instability in this region may have decapitated the regulatory sequences of the *Ipr1* gene, preventing it from being expressed.

Pan *et al.* went on to validate their findings by showing that reintroducing full-length *Ipr1* into C3HeB/FeJ mice could partially suppress the replication of *M. tuberculosis* in the lungs *in vivo*, and in macrophages infected *in vitro*. A particularly exciting finding is that *Ipr1* expression in such genetically altered C3HeB/FeJ macrophages could also restrict the replication of another bacterium, *Listeria monocytogenes* — suggesting a general role for *Ipr1* in innate macrophage defences against intracellular infections.

So what exactly does *Ipr1* do? The gene encodes a protein known as Ifi75, which contains several sequence motifs that indicate that it is localized to the cell nucleus and has a role in regulating gene expression. In support of that idea, Ifi75 is a relative of the human protein SP110 (ref. 8) — a proposed regulator of gene transcription. Like *Ipr1*, SP110 is regulated by interferons, signalling molecules involved in immunity. SP110 also interacts with certain viral proteins, including proteins from hepatitis C virus and Epstein–Barr virus[9]. All of this places *Ipr1* at the interface of host–pathogen interactions, possibly participating in transcriptional activation in macrophages in response to intracellular pathogens. (See also the supplementary information in ref. 3.)

It will be interesting to see how the presence of products from bacteria as different as *Listeria* and *Mycobacterium* can activate *Ipr1*, and what other host proteins may be involved in this signalling. Other questions are: which genes are in turn activated by *Ipr1*, and how do they contribute to the resistance of macrophages to bacterial replication in general, and to the induction of apoptosis in particular? Might this response involve the activation of 'inflammatory' or 'apoptotic' caspase enzymes? And does this pathway run parallel to, or intersect with, other pathogen-sensing pathways, such as those triggered by extracellular pathogens through the so-called Toll-like receptors or other proteins, including those of the NBS-LRR (nucleotide-binding site leucine-rich repeat) or NOD (nucleotide oligomerization domain) families[10]?

Suffice it to say that, once again, careful genetic studies in the laboratory mouse have delivered an unexpected gift. More exciting biology in an area of immense interest for global health is sure to follow. ■

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### 100 YEARS AGO

***A Study of Recent Earthquakes.*** **A subject attractive to the general reader… is an account of signs which have given warning of a coming earthquake. Underground sounds have been heard, springs have varied in their flow, horses, birds, dogs, and even human beings have been restless for some time before great earthquakes. In his reference to the Riviera earthquake in 1887, Mr. Davison remarks that as premonitions were noted at 130 different places within the central area, "there can be little doubt that they were caused by microseismic movements for the most part insensible to man." In these days of psychical research we think that the author has lost an opportunity for romantic speculation… It is pointed out that the area over which earthquake sounds are heard is variable in different countries. One reason for this is that the limits of audibility vary with different races. From illustrations given it would appear that for certain sounds the Anglo-Saxon ear is more acute than that of the Neapolitan, and very much more than that of the Japanese.**
**From *Nature* 6 April 1905.**

### 50 YEARS AGO

**A new instrument called the 'maser' (microwave amplification by stimulated emission of radiation) has been invented by Prof. C. H. Townes, of the Physics Department, Columbia University, for which the claim is made that it enables time to be measured with an accuracy of one part in $10^{11}$. The 'clock' used is an ammonia molecule which radiates an electric dipole spectrum as a set of lines of about 6 mm. wavelength and, as used in the instrument, maintains its frequency to the above order of magnitude. This would be sufficient to enable it to measure variation in the rate of rotation of the earth… the instrument consists of a molecular beam of ammonia molecules which are excited in an electric field and then pass into a tuned cavity-resonator, where they induce each other to radiate by negative absorption… It seems that the method of use is to extract by means of wave-guides the radiation emitted by two 'masers', tuned to different but adjacent frequencies by the ammonia spectrum. When mixed, the beat frequency can then be counted electronically. The 'maser' is also claimed by its inventor to be very effective as an amplifier.**
**From *Nature* 9 April 1955.**