IN THE NEWS

TB hotspots

Multi-drug-resistant tuberculosis (MDR-TB) is a growing concern in geographical hotspots across the globe, according to a new report from the World Health Organization (WHO). The study, released in the run-up to World TB Day on 24 March, which looked at 77 countries and ~68,000 patients worldwide, identified high rates of MDR-TB — up to 14% in new patients — in Eastern Europe and Central Asia. Treatment for non-drug-resistant TB is cheap and effective — about \$10 for a 6-month course of drugs — whereas it costs about \$1,000 to treat MDR-TB. If left untreated, MDR-TB is a death sentence.

MDR-TB goes hand in hand with high rates of HIV infection — worldwide, TB accounts for one-third of all deaths due to AIDS (*TB Alert*, UK). According to Paul Nunn of the WHO, "We are obviously concerned that ... HIV will cause increased transmission of multi-drug-resistant tuberculosis" (*Reuters*).

In May of this year, the European Union opens its borders to three of the top ten geographical hotspots (Estonia, Latvia and Lithuania), and according to Andrew Murrison, the UK Shadow Health Minister, there are "concerns that the public's health will be seriously under threat" (*BBC News*). However, Mario Raviglione, director of WHO's Stop TB department, said, "It is in the interest of every country to support a rapid scale-up of TB control if we are to overcome MDR-TB. Passport control will not halt resistance; investment in global TB prevention will" (WHO).

Elaine Bell

INNATE IMMUNITY

ST2 promotes TOLerance

ST2 is a member of the TIR domain-containing superfamily of Toll-like receptors (TLRs) and interleukin-1 receptors (IL-1Rs), but in contrast to most other members of this family, signalling through ST2 does not induce pro-inflammatory cytokine production. Instead, the orphan receptor ST2 has been implicated in T helper 2-cell responses. Now, a report in *Nature Immunology* shows that ST2 mediates endotoxin tolerance — the reduced production of cytokines after re-exposure to the bacterial cell-wall component lipopolysaccharide (LPS) — and reveals the molecular mechanisms involved.

Previous studies showed that prior exposure to a soluble form of ST2 can suppress pro-inflammatory cytokine production by LPS-stimulated macrophages. Brint and colleagues investigated this inhibitory effect and showed that ST2-deficient macrophages produced higher levels of cytokines than wild-type macrophages after stimulation with LPS and

various other ligands of TIR domain-containing family members — with the exception of poly I:C (a ligand for TLR3). This indicated that ST2 is a negative regulator of the function of several TIR domain-containing family members, which the authors confirmed by examining the effect of ST2 overexpression on several cell lines.

Next, the authors investigated the mechanism of action by examining downstream components in the signalling pathways. Signal transduction through most TIR domain-containing family members is mediated by the adaptor Myd88; TLR4 additionally recruits the adaptor Mal (also known as Tirap) and the adaptor Trif, whereas TLR3 only interacts with Trif. Using a cell line transfected with a nuclear factor- κ B reporter gene, the authors showed that ST2 inhibited signalling through IL-1RI when either Myd88 or Mal was co-expressed, but not when Trif or the downstream signalling molecule IL-1R-associated kinase (Irak) was co-expressed. These results

show that ST2 acts upstream of Irak and interacts with Myd88 and Mal, which the authors verified by 'pulling down' these adaptors with the TIR domain of ST2. In addition, they indicate that the failure of ST2 to inhibit activation through TLR3 is probably due to a lack of interaction with its adaptor Trif.

The authors also demonstrated that ST2 expression is upregulated on macrophages after exposure to

IMMUNE EVASION

Virus 2 — dendritic cell 0

By suppressing the very cells that induce and promote effective antiviral immune responses, viruses can evade detection and persist in the host. As key mediators of effective immune responses, dendritic cells (DCs) are targeted by several viruses that cause persistent infection and generalized immune suppression. Now, a report in *The Journal of Clinical Investigation* describes two mechanisms by which lymphocytic choriomeningitis virus (LCMV) disables DCs, inhibiting both their development and T-cell stimulatory capacity.

Inoculation of mice with wild-type LCMV causes an acute infection characterized by the clonal expansion of cytotoxic

T lymphocytes that clear the virus. However, the virus variant LCMV clone 13 (LCMV Cl 13) causes a persistent infection and host immunosuppression, characterized by defective T-cell and antibody responses. To explore the mechanisms behind this immunosuppression, the authors studied the phenotype and function of DCs infected with these two viruses.

First, they showed that *in vivo* infection with LCMV Cl 13, but not wild-type virus, markedly inhibits the cell-surface expression of MHC class I and II molecules and the co-stimulatory molecules CD40, CD80 and CD86 by DCs, indicating impaired DC maturation. As a result, DCs from

LCMV Cl 13-infected mice were unable to stimulate T-cell proliferation in a mixed lymphocyte reaction.

As well as viral inhibition of DC function, they demonstrated that DC development was also disrupted by infection with LCMV Cl 13. The development and differentiation of haematopoietic progenitors into myeloid and lymphoid DCs can be induced by *in vivo* administration of the stimulatory cytokine Flt3 ligand (Flt3L) or by *in vitro* treatment with granulocyte-macrophage colony-stimulating factor (GM-CSF). However, these cytokines did not induce marked expansion of DC populations when administered to mice infected with LCMV Cl 13, or to *in vitro* cultures of LCMV Cl 13-infected bone-marrow cells. This interference in DC development was shown to involve type 1