IN THE NEWS

Vaccines in the news…again

Good news this month for worried parents, as *The Guardian* explained: 'a baby's immune system could safely cope with as many as 10,000 vaccines…and is not at risk from the current practice of giving combinations such as measles, mumps and rubella together' according to an article in the journal *Pediatrics*. The *New York Times* reported: 'Parents who are worried about the increasing number of recommended vaccines may take comfort in knowing that children are exposed to fewer antigens in vaccines today than in the past'.

However, it might take some time for this news to filter through. According to *The Independent*, 'so many parents are shunning the controversial MMR vaccine that protection against childhood diseases has plunged to dangerously low levels'. A spokesman for the Royal College of Surgeons said that 'We are in very real danger of losing babies unless parents look at the medical evidence and are no longer scared by the press' (*The Independent*). The UK government's goal for MMR take-up is 95%, but national rates have now fallen to around 84%.

Meanwhile, the Global Alliance for Vaccines and Immunizations (GAVI), the public–private partnership that promotes vaccine uptake in developing countries, has been accused by the charity Save the Children Fund 'of encouraging poor countries to buy expensive new vaccinations… which they will not be able to afford once the GAVI subsidy runs out in five year's time' (*The Guardian*). GAVI is also accused of 'being in bed with the pharmaceutical industry' (*The Guardian*) because representatives of vaccine companies sit on its board.

Elaine Bell

INNATE IMMUNITY

MIF keeps macrophages on guard

The innate immune response to bacteria is essential for survival but the systemic release of inflammatory mediators results in the life-threatening septic-shock reaction. Now, reporting in *Nature*, Thierry Roger and co-workers show that a cytokine associated with endotoxic shock, macrophage migration inhibitory factor (MIF), regulates the innate response to Gram-negative bacteria.

MIF-deficient mice are resistant to endotoxic shock but the molecular mechanism behind this resistance has been unknown. Macrophages are the main source of MIF and produce high basal levels of it. To invesigate the effects of MIF on innate responses, mouse macrophages were stably transfected with a plasmid encoding an antisense *Mif* mRNA. These macrophages had impaired production of the inflammatory cytokines tumour necrosis factor α and interleukin 6 in response to lipopolysaccharide (LPS) and Gram-negative bacteria, but their responses to Gram-positive bacteria were unaffected.

Why does inhibition of MIF selectively affect responses to Gram-negative bacteria? LPS and Gram-negative bacteria are recognized by a receptor complex consisting of a signalling subunit (Toll-like receptor 4, TLR4) and two accessory proteins (MD2 and CD14). The levels of CD14 and MD2 in *Mif*-antisense macrophages are normal and the LPS-binding capacity of the macrophages is unaffected, but TLR4 production is markedly reduced. By contrast, levels of TLR2, a component of the receptors for fungi and Gram-positive bacteria, are normal. In agreement with a key role for MIF in responses to Gram-negative bacteria, macrophages from MIF-deficient mice had defective responses to Gram-negative but not Gram-positive bacteria.

How, then, does MIF modulate TLR4 production? Transfection of MIF-deficient macrophages with a *Tlr4*-promoter–luciferase reporter construct showed that the *Tlr4* promoter is only 40% as active as when MIF is present. This indicates that MIF regulates TLR4 at the level of transcription. The transcription factor PU.1 is important for *TLR4* expression in myeloid cells, and basal PU.1-DNA-binding activity is impaired in MIF-deficient macrophages.

Together, these results indicate that, through PU.1, MIF causes optimal *TRL4* expression and hence optimal LPS responses in macrophages. MIF might, therefore, be a useful, specific target for preventing endotoxic shock in cases of Gram-negative sepsis.

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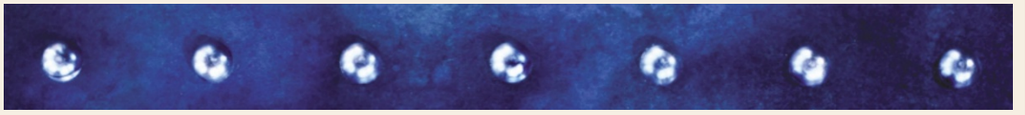
References and links

ORIGINAL RESEARCH PAPER Roger, T. *et al*. MIF regulates innate immune responses through modulation of Toll-like receptor 4. *Nature* **414**, 920–924 (2001)

FURTHER READING Medzhitov, R. Toll-like receptors in innate and adaptive immunity. *Nature Rev. Immunol*. **1**, 135–146 (2001) | Calandra, T. *et al.* Protection from septic shock by neutralization of macrophage migration inhibitory factor. *Nature Med*. **6**, 164–170 (2000)



MUCOSAL IMMUNOLOGY

Follicular line up

In the 1st of January issue of *The Journal of Immunology*, Hamada and co-workers describe a novel lymphoid component of the mouse intestinal mucosa — 200 B-cell clusters all in a row.

The gut-associated lymphoid tissue (GALT) is complex, consisting of scattered effector lymphocytes and organised 'inductive' sites — namely the Peyer's patches and mesenteric lymph nodes. The development of these organs requires subtly different signals; for example, mice transgenic for a lymphotoxin-β receptor-Ig (LTβR-Ig) fusion protein, which blocks LTβ signalling, have mesenteric lymph nodes but no Peyer's patches. This and many other transgenic and 'knockout' mouse strains have been crucial for dissecting GALT function.

In certain species — including human, rat and rabbit — microscopic, isolated lymphoid follicles (ILFs) have also been described in the intestinal mucosa, but little is known of their development or function. By immunohistochemical analysis the authors discovered 100–200 ILFs aligned along the antimesenteric wall of the mouse small intestine. ILFs resemble the follicular units that make up Peyer's patches in that they contain a germinal centre, IgM- and IgA-positive B cells, and M cells in the overlying epithelium. But, unlike Peyer's patches, they are not associated with defined T-cell areas.

Despite the structural similarities, ILFs and Peyer's patches seem to be developmentally distinct. Peyer's patches are evident at birth, but Hamada and colleagues found that ILFs do not appear until 7 days after birth or later, depending on the mouse strain. Furthermore, mice treated transplacentally with LTβR-Ig fusion protein (T-LTβR-Ig) lack Peyer's patches but have normal numbers of ILF.

As ILFs bear all the hallmarks of inductive sites it will be important to determine their precise role in gut immunity. As the authors point out, it might also be necessary to re-examine past investigations into the role of Peyer's patches that made use of mice (such as T-LTβR-Ig mice) that lack Peyer's patches but do have ILFs.

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References and links

ORIGINAL RESEARCH PAPER Hamada, H. *et al*. Identification of multiple isolated lymphoid follicles on the antimesenteric wall of the mouse small intestine. *J. Immunol.* **168**, 57–64 (2002)