MACROPHAGES

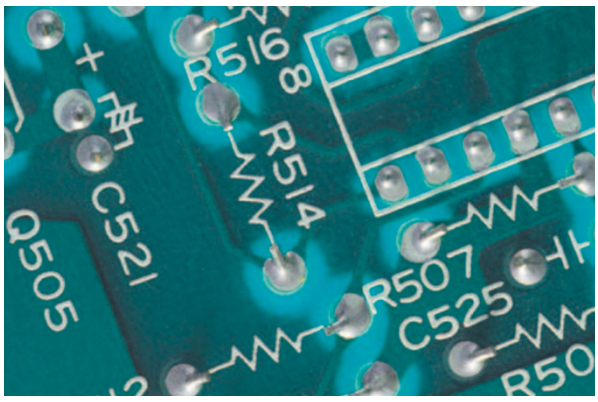
Regulatory circuit in the lungs

Given that the air we breathe is contaminated with infectious agents and particulate matter, it is vital that our alveolar macrophages are not in a constant state of activation as this would cause collateral damage and compromise lung function. Indeed, alveolar macrophages are normally kept in check by the presence of active transforming growth factor-β (TGFβ), which is bound by $\alpha_v\beta_6$-integrin on the surface of alveolar epithelial cells (AECs). But how do alveolar macrophages overcome this tonic inhibition to mount responses when the need arises? In their study published in *Immunity*, Takabayshi *et al.* show that exposure of alveolar macrophages to microbial products releases the macrophages from their close association with AECs and suppresses the expression of $\alpha_v\beta_6$-integrin by AECs, thereby removing TGFβ-mediated inhibition of alveolar macrophages.

To understand the immune response to an infectious assault in the lungs, the authors first assessed the effects of microbial products that stimulate Toll-like receptors (TLRs) on the expression of $\alpha_v\beta_6$-integrin by AECs. They showed that intratracheal administration of a TLR9 ligand, immunostimulatory oligodeoxynucleotide (ISS-ODN; also known as CpG DNA), led to a reduction in $\alpha_v\beta_6$-integrin expression by AECs. All other TLR ligands tested had a similar effect. This decrease in $\alpha_v\beta_6$-integrin expression was associated with downregulation of TGFβ-mediated signalling in the alveolar macrophages, as indicated by decreased phosphorylation of the TGFβ-mediated-signalling molecules SMAD2 and SMAD3. Moreover, alveolar macrophages (but not peritoneal macrophages) isolated from mice pretreated with ISS-ODN were more responsive to subsequent stimulation with lipopolysaccharide *in vitro* compared with cells from untreated mice, indicating that exposure to microbial products releases alveolar macrophages from tonic inhibition by TGFβ.

> “exposure to microbial products releases alveolar macrophages from tonic inhibition by TGFβ”

Next, the authors explored the mechanisms behind this effect. They showed that cell–cell contact between alveolar macrophages and AECs was required for TGFβ-mediated inhibition. They also showed that TLR signalling in the alveolar macrophages rapidly induced actin polymerization, which disrupted this cell–cell contact and led to the subsequent decrease in $\alpha_v\beta_6$-integrin expression and increase in macrophage activation.



The authors then asked whether tonic inhibition of alveolar macrophages could be restored after clearance of the infectious threat by the activated alveolar macrophages, to avoid subsequent damage to surrounding tissues. Consistent with this, a few days after delivery of ISS-ODN, the authors observed an upregulation of expression of matrix metalloproteinase 9 (MMP9), which was shown to reactivate latent TGFβ and reset the inhibitory system. Expression of MMP9 by alveolar macrophages was probably induced by interferon-γ (IFNγ), because IFNγ-receptor-deficient mice showed prolonged suppression of $\alpha_v\beta_6$-integrin expression and TGFβ-mediated signalling following exposure to ISS-ODN.

This study provides evidence of a new, organ-specific mechanism of macrophage activation, which allows quick adaptation to infectious insults and minimizes potential damage to surrounding tissue.

Lucy Bird

ORIGINAL RESEARCH PAPER Takabayshi, K. *et al.* Induction of a homeostatic circuit in lung tissue by microbial compounds. *Immunity* **24**, 475–487 (2006)
FURTHER READING Lambrecht, B. N. Alveolar macrophage in the driver's seat. *Immunity* **24**, 366–368 (2006)