IN BRIEF

VIRAL IMMUNITY

Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection

Teijaro, J. R. *et al. Cell* **146**, 980–991 (2011)

This study shows that pulmonary endothelial cells can negatively regulate both immune cell infiltration and cytokine production during influenza virus infection. In wild-type mice infected with a lethal strain of influenza virus, administration of sphingosine-1-phosphate receptor 1 ($S1P_1$) agonists suppressed virus-induced cytokine storms and led to increased survival. $S1P_1$ was found to be expressed by both lymphocytes and endothelial cells in the lungs. However, $S1P_1$ agonists also suppressed the virus-induced cytokine storm and immunopathology in lymphocyte-deficient mice, suggesting that their effects were mediated via the pulmonary endothelium. In support of this, pulmonary endothelial cells purified from virus-infected mice showed decreased chemokine production when the mice had received $S1P_1$ agonists. The authors suggest that targeting pulmonary endothelial cells could be a useful strategy for preventing virus-induced immunopathology during influenza virus infection.

VACCINES

Live attenuated malaria vaccine designed to protect through hepatic $CD8^+$ T cell immunity

Epstein, J. E. *et al. Science* 8 Sep 2011 (doi:10.1126/science.1211548)

The malaria parasite *Plasmodium falciparum* goes through an immunogenic sporozoite stage in the liver before entering the blood and infecting erythrocytes. A recent clinical study evaluated the safety and efficacy of a newly developed malaria vaccine that consists of irradiated *P. falciparum* sporozoites (PfSPZ vaccine). Intradermal or subcutaneous administration of metabolically active, non-proliferating sporozoites was shown to be well tolerated, and the vaccinated volunteers exhibited no parasite transmission to the blood. Although sporozoites have been previously shown to induce interferon-γ-producing $CD8^+$ T cells in the liver, the vaccinated volunteers showed weak $CD8^+$ T cell and antibody responses. However, further studies in non-human primates and mice indicated that the low vaccine immunogenicity may be related to the administration route, as intravenous vaccination resulted in increased protective immune responses as compared with subcutaneous vaccination.

SIGNALLING

E3 ubiquitin ligase CHIP facilitates Toll-like receptor signaling by recruiting and polyubiquitinating Src and atypical PKCζ

Yang, M. *et al. J. Exp. Med.* 12 Sep 2011 (doi:10.1084/jem.20102667)

Carboxyl terminus of HSP70-interacting protein (CHIP) is a chaperone-dependent E3 ubiquitin ligase that is involved in protein quality control. Here, Yang *et al.* describe a role for CHIP in promoting Toll-like receptor (TLR) signalling. CHIP was found to be widely expressed by immune cells, and small interfering RNA-mediated knockdown of *Chip* in macrophages and dendritic cells inhibited their activation in response to agonists of TLR2, TLR4, TLR7 and TLR9 (although CHIP was not required for TLR3 signalling). Further experiments showed that CHIP associates with the activated TLR signalling complex and can directly bind and recruit SRC and protein kinase Cζ (PKCζ), resulting in downstream activation of IRAK1, TBK1, IRF3 and IRF7. CHIP-mediated enhancement of TLR signalling did not occur in the presence of ubiquitylation-resistant forms of SRC and PKCζ, indicating that the E3 ligase activity of CHIP is required for the activation of these kinases. Finally, the authors showed that CHIP is essential for dendritic cell maturation in response to TLR4 or TLR9 agonists.