Endogenous lung injury inducer

Acute respiratory distress syndrome (ARDS) is a pathological hallmark of potentially lethal diseases, including SARS and H5N1 avian influenza. In *Cell*, Penninger and colleagues find that endogenous oxidized phospholipids activate a Toll-like receptor 4 (TLR4)-dependent injurious pathway common to ARDS. Mice lacking TLR4 or its signaling components TRIF, TRAF6 or IRF3 are resistant to acid aspiration–induced lung injury, an experimental model of human ARDS. Present in the bronchiolar lavage fluid of mice treated with inactivated H5N1 or subjected to acid aspiration, surfactant phospholipids oxidized by reactive oxygen species induce TLR4-dependent production of interleukin 6 (IL-6) and acute lung injury. The detection of abundant oxidized phospholipids in lung samples from humans with SARS or H5N1 infection indicates that efforts to target these detrimental endogenous mediators might hold broad therapeutic utility. ***CB***

***Cell* 133, 235–249 (2008)**

Anti-inflammatory antibodies

Intravenous immunoglobulin is commonly administered to lessen inflammatory episodes in patients with autoimmune disease. In *Science*, Ravetch and colleagues elucidate the molecular structure of the carbohydrate moiety that confers anti-inflammatory properties onto the immunoglobulin G (IgG) molecules. N-linked 2,6-sialylated but not 2,3-sialylated Fc fragments protect mice from serum-induced autoantibody arthritis in the K/BxN mouse model. A recombinant IgG1 fragment glycosylated *in vitro* by sequential β1,4-galactosylation and 2,6-sialylation also confers protection against inflammation. Marginal zone macrophages show 'preferential' binding of the 2,6-sialylated Fc molecules. The authors hypothesize that these macrophages express a specific lectin receptor that binds these inhibitory IgG1 molecules to dampen inflammation. The identity of that putative lectin receptor remains unknown. *LAD*

Science **320**, 373–376 (2008)

Anaphylaxis and basophils

The classical pathway of anaphylaxis, a severe allergic reaction commonly triggered by exposure to allergens, is associated with IgE and the release of histamine by mast cells. In *Immunity*, Karasuyama and colleagues find that basophils can mediate an alternative pathway involving allergen-specific IgG and the release of platelet-activating factor rather than histamine. Basophils efficiently bind allergen-IgG1 complexes and release platelet-activating factor, which is associated with morphological changes in human umbilical vein endothelial cells consistent with increased vascular permeability. Depletion of basophils but not of macrophages, neutrophils or natural killer cells ameliorates IgG1-mediated anaphylaxis and 'rescues' mast cell–deficient mice from anaphylactic death. These data demonstrate the physiological importance of this alternative pathway of severe allergic responses in addition to the well known classical pathway. ***DCB***

***Immunity* 28, 5814–589 (2008)**

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Secondary killer infections

Bacterial infections often follow influenza infection and are responsible for much of the morbidity and mortality associated with influenza. In *Nature Medicine*, Sun and Metzger show that interferon-γ (IFN-γ) induced by the viral infection dampens the antibacterial responses of lung tissue. IFN-γ-treated alveolar macrophages have lower phagocytic capacity and thus are less able to clear bacteria from infected lung tissues. *In vitro* treatment of alveolar macrophages with IFN-γ leads to down-regulation of the scavenger receptor MARCO, which has been associated before with complement-independent pneumococcal phagocytosis. Mice lacking either IFN-γ or its receptor show enhanced survival after secondary bacterial infection upon influenza virus exposure. Notably, neutralization of IFN-γ in virus-infected wild-type mice results in lower mortality. These findings indicate therapeutic intervention strategies for enhancing innate immunity and limiting the lethality of secondary bacterial infections. *LAD*

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Cytokine-regulated balance

Regulation of T helper cell differentiation occurs via coordinated activities of specific transcription factors and cytokines. In *Nature*, Littman and colleagues analyze how TGF-β can regulate both the differentiation of regulatory T cells (T_{reg} cells) and interleukin 17-producing T helper cells (T_H-17 cells). TGF-β induces co-expression of transcription factors Foxp3 and RORγt in 10% of lamina propria $CD4^+$ T cells, and fate-mapping experiments indicate that approximately 25% T_H-17 cells had previously expressed Foxp3 at some point in their development. High TGF-β concentrations or forced-expression of Foxp3 block RORγt-dependent gene expression; in contrast, proinflammatory cytokines IL-6 or IL-21 in the presence of low TGF-β induce IL-17 expression. Foxp3 antagonizes RORγt via physical interaction and IL-16 and/or IL-21 relieve that inhibition possibly by a post-translational effect on either RORγt or Foxp3. Such plasticity may be particularly important in the lamina propria of the gut where $Foxp3^+$ regulatory T cells and $ROR\gamma t^+$ T_H-17 cells co-exist. ***DCB***

***Nature* (26 March 2008) doi:10.1038/nature06878**

Aspirin targets TRAFs

Aspirin suppresses inflammation by triggering the generation of lipoxin eicosanoid mediators, which activate SOCS2. In the *Journal of Experimental Medicine*, Aliberti and colleagues further our understanding of the anti-inflammatory effects of aspirin. In mouse dendritic cells, lipoxin A4 induces the interaction of SOCS2 with the adaptors TRAF2 and TRAF6; these interactions result in ubiquitination and proteasome-dependent degradation of TRAF2 and TRAF6. Overexpression of TRAF6 but not of TRAF2 effectively 'overrides' the anti-inflammatory effects of lipoxin A4 in a macrophage cell line. Proteasome inhibitor treatment prevents SOCS2-mediated suppression of inflammation in mice infected with *Toxoplasma gondii* and abolishes aspirin-induced suppression of lipopolysaccharide-induced cytokine release by dendritic cells. The molecular principles underlying the specificity of SOCS2 for TRAF2 and TRAF6 and the physiological importance of SOCS2-induced TRAF2 destruction remain to be elucidated. *CB*

J. Exp. Med. (14 April 2008) doi:10.1084/jem.20072416