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In This Issue

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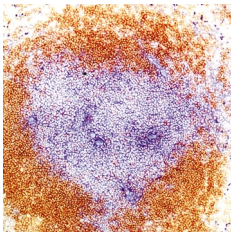
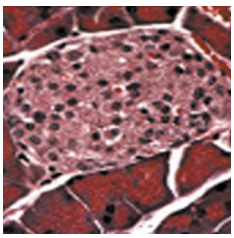
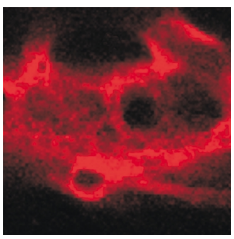
CCL21 shows T cells the way to nonlymphoid tissues. The critical function of the chemokine CCL21 in directing lymphocytes from primary to secondary lymphoid tissues is well established; however, little is known about the molecular cues responsible for lymphocyte trafficking to nonlymphoid tissues. Yang-Xin Fu and colleagues investigated the role of CCL21 in recruiting lymphocytes to a nonlymphoid organ — the lung — in a murine model of airway inflammation (pages 1495–1505). The authors found that CCL21 in lymphoid and nonlymphoid tissues is differentially regulated by lymphotoxin-dependent (LT-dependent) and -independent mechanisms, respectively. This is due to the selective regulation of the Ccl21-Ser but not the Ccl21-Leu gene by the LT and noncanonical NF-κB pathways. These findings establish an essential role for CCL21 in the recruitment of effector T cells to peripheral tissues and suggest that LT-dependent and -independent regulation of CCL21 plays a role in balancing the central and peripheral immune responses between lymphoid and nonlymphoid tissues. See figure Upregulation of Irs2 prevents diabetes. Insulin action and secretion are closely linked at the molecular level through the insulin receptor substrate-2 (Irs2) branch of the insulin/IGF signaling cascade. Mice lacking Irs2 display similarities to humans with type 2 diabetes. Morris White and colleagues evaluated the actions of β cell–specific overexpression of Irs2 on diabetes development and pancreatic β cell function in […]



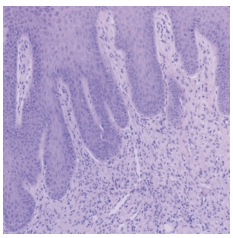
CCL21 shows T cells the way to nonlymphoid tissues. The critical function of the chemokine CCL21 in directing lymphocytes from primary to secondary lymphoid tissues is well established; however, little is known about the molecular cues responsible for lymphocyte trafficking to nonlymphoid tissues. Yang-Xin Fu and colleagues investigated the role of CCL21 in recruiting lymphocytes to a nonlymphoid organ — the lung — in a murine model of airway inflammation (pages 1495–1505). The authors found that CCL21 in lymphoid and nonlymphoid tissues is differentially regulated by lymphotoxin-dependent (LT-dependent) and -independent mechanisms, respectively. This is due to the selective regulation of the *Ccl21-Ser* but not the *Ccl21-Leu* gene by the LT and noncanonical NF-κB pathways. These findings establish an essential role for CCL21 in the recruitment of effector T cells to peripheral tissues and suggest that LT-dependent and -independent regulation of CCL21 plays a role in balancing the central and peripheral immune responses between lymphoid and nonlymphoid tissues.



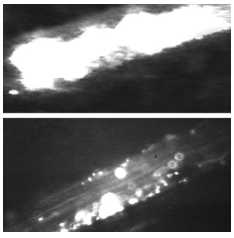
Upregulation of *Irs2* prevents diabetes. Insulin action and secretion are closely linked at the molecular level through the insulin receptor substrate-2 (Irs2) branch of the insulin/IGF signaling cascade. Mice lacking *Irs2* display similarities to humans with type 2 diabetes. Morris White and colleagues evaluated the actions of β cell–specific overexpression of *Irs2* on diabetes development and pancreatic β cell function in murine models of autoimmune diabetes and islet transplantation. The authors show that upregulation of Irs2 in pancreatic β cells promotes β cell growth, survival, and insulin secretion (pages 1521–1532). Furthermore, they demonstrate that increased expression of *Irs2* in β cells improves islet transplantation, as significantly fewer islets were required to normalize serum glucose levels. The data support a potential pharmacological role for *Irs2* or downstream factors in the treatment of β cell failure and human diabetes.



Building better barriers with hyperosmolar sucrose. During lung injury, the normally air-filled alveoli fill with fluid from the surrounding vasculature. Jahar Bhattacharya and colleagues have now described a therapeutic scheme to prevent capillary permeability and treat lung edema through the use of hyperosmolar sucrose (pages 1541–1549). The authors gave 15-minute infusions of hyperosmolar sucrose in lung venular capillaries. The barrier enhancement was sufficient to block the injurious effects of thrombin, TNF-α, and H_2O_2 in single capillaries and of intratracheal acid instillation in the whole lung. Hyperosmolar infusion augmented actin filament formation and E-cadherin expression at the endothelial cell periphery. An actin depolymerizing agent abrogated both the barrier enhancement as well the actin filament formation, suggesting a role for actin in the barrier response. Further, hyperosmolar infusion blocked TNF-α–induced P-selectin expression in an actin dependent manner. These results suggest that hyperosmolar therapy may be beneficial in lung inflammatory disease.



IL-15 antibodies to the rescue in psoriasis. Psoriasis is a chronic inflammatory disease of the skin characterized by overgrowth of epidermal cells, angiogenesis, infiltration of immune cells, and increased production of cytokines. IL-15 can trigger inflammatory cell recruitment, angiogenesis, and production of other inflammatory cytokines. To investigate the role of IL-15 in psoriasis, Janine Schuurman and colleagues generated monoclonal antibodies to IL-15 using human immunoglobulin-transgenic mice (pages 1571–1580). The 146B7 antibody did not compete with IL-15 for binding to its receptor but interfered with the assembly of the IL-15 receptor αβγ complex. 146B7 effectively blocked IL-15–induced T cell proliferation and monocyte TNF-α release. In a human psoriasis xenograft model, 146B7 reduced the severity of psoriasis, as measured by epidermal thickness, grade of parakeratosis, and numbers of inflammatory cells and cycling keratinocytes. These results support an important role for IL-15 in the pathogenesis of psoriasis.



Curious antithrombotic effects of TNF-α. It is commonly believed that TNF-α, a proinflammatory cytokine, also has strong prothrombotic effects. Denisa Wagner and colleagues have now addressed this question experimentally using intravital microscopy of thrombus formation in mice arterioles (pages 1589–1596). Treatment with doses of TNF-α, such as would occur in patients with septic conditions or related infectious disorders, actually inhibited platelet aggregation and thrombus formation in vivo. Platelets from TNF-α–treated mice had decreased fibrinogen binding and P-selectin expression and reduced platelet aggregation in response to agonists. In contrast, in vitro treatment of platelets with TNF-α did not affect their function. The antithrombotic effect of TNF-α was mediated through rapid production of NO by inducible nitric oxide synthase from cells of the vessel wall. This study points to a new inflammatory function of TNF-α in transiently inhibiting thrombosis to allow the immune response to be optimally executed.