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In This Issue

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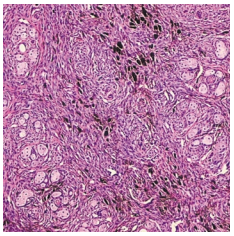
IFN-α battle plan: attack the host. High dose cytokine therapy is used for cancer treatment, but little is known regarding the targets of these drugs or the intracellular signaling pathways they activate in vivo. William Carson and colleagues show (pages 170–180) that the cytokine IFN-α, which activates transcription factors belonging to the signal transducer and activator of transcription (STAT) family, exerts its antitumor actions primarily via its ability to stimulate immune effectors in the host rather than through a direct effect on malignant cells. Using a mouse model of malignant melanoma, the authors demonstrate that STAT1 signaling within the host, and not within the tumor cells, mediates the antitumor effects of IFN-α therapy. These investigations may ultimately permit the identification of phenotypic characteristics that correlate with patient responsiveness to IFN-α.Neph1 as the gatekeeper in the kidney. Recent studies have identified a central role for the podocyte slit diaphragm as a size-selective barrier for plasma macromolecules in the kidney, and extensive progress has been made in identifying key proteins contributing to the structure and function of this filter. Sumant Chugh and colleagues now show (pages 209–221) that Neph1 is localized to the slit diaphragm and is directly involved in determining permeability through interactions with resident anchoring proteins ZO-1 and nephrin. Antibody-induced disruption of the Neph1-Nephrin interaction in vivo resulted in complement- […]



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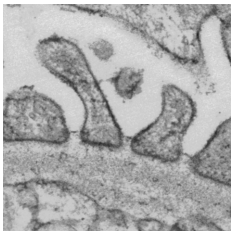
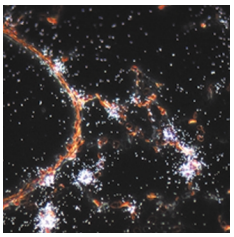
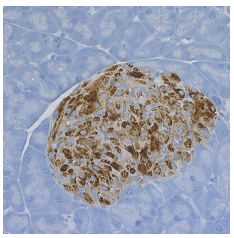


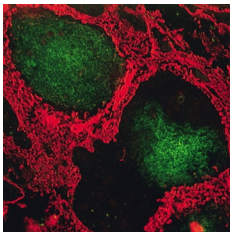
Neph1 as the gatekeeper in the kidney. Recent studies have identified a central role for the podocyte slit diaphragm as a size-selective barrier for plasma macromolecules in the kidney, and extensive progress has been made in identifying key proteins contributing to the structure and function of this filter. Sumant Chugh and colleagues now show (pages 209–221) that Neph1 is localized to the slit diaphragm and is directly involved in determining permeability through interactions with resident anchoring proteins ZO-1 and nephrin. Antibody-induced disruption of the Neph1-Nephrin interaction in vivo resulted in complement- and leukocyte-independent proteinuria. This study points to new possibilities for studying the pathogenesis of proteinuria.



Speeding surfactant production with KGF. Pulmonary surfactant lowers the surface tension at the air/liquid interface in the lung and prevents alveolar instability and small airway closure. Produced by type II alveolar epithelial cells, surfactant is composed predominantly of phospholipids. Understanding the regulation of lipid synthesis is important for developing new therapeutic strategies for increasing endogenous surfactant production. In order to characterize this system, Robert Mason and colleagues identified culture conditions that stimulate lipogenesis in type II cells (pages 244–255). Keratinocyte growth factor (KGF) increased synthesis of surfactant phospholipids, especially disaturated phosphatidylcholine and phosphatidylglycerol, and was found to regulate the expression of key transcription factors, lipogenic enzymes, and transport proteins responsible for lipogenesis. This data may stimulate further work on the regulation of surfactant phospholipid biosynthesis.



Akt acts out. The serine/threonine kinase Akt/PKB has three mammalian isoforms: Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ). The three isoforms show broad tissue distribution, with the Akt2 isoform predominating in insulin-responsive tissues. Robert Garofalo and colleagues have now generated Akt2 knockout mice (page 197–208) that show similar growth retardation to that previously reported in the Akt1 KO mice. The Akt2 KO mice exhibit impaired glucose metabolism, pancreatic β cell failure, and lipoatrophy, which were not previously reported in mice lacking Akt1. The authors conclude that both Akt1 and Akt2 play a role in regulation of growth, but only Akt2 regulates glucose metabolism and adipose mass. In addition, Akt2 is critical for the adaptive response of pancreatic β cells to insulin resistance and hyperglycemia.



Antibodies regulating myasthenia gravis. Specific regulatory T (T_{reg}) cells play a major role in keeping T cells from responding to self antigens. Sylvia Cohen-Kaminsky and colleagues now suggest (pages 265–274) that one type of T_{reg} cell, T cell receptor (TCR) peptide-specific regulatory CD4 T cells, may play a key role in the control of the autoimmune disease myasthenia gravis (MG). The authors explore the occurrence, reactivity, and regulatory role of anti-TCR antibodies against a T cell population expressing the Vβ5.1 TCR gene, which is responsible for the production of pathogenic antiacetylcholine receptor autoantibodies in patients with early-onset MG. High levels of anti-Vβ5.1 IgG antibodies in HLA-DR3$^+$ MG patients were present, providing evidence for their spontaneous increase in the absence of prior TCR vaccination. These data suggest that there is a natural regulatory process involving B cells directed to TCR determinants, which may be boosted by TCR peptide vaccines for treatment of MG.