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In This Issue

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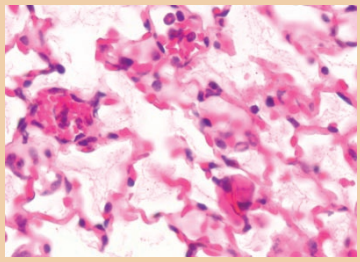
Blazing a trail to TRALI Transfusion-related acute lung injury (TRALI) is a major problem in transfusion medicine and has emerged as the leading cause of death from a blood transfusion. There is a lack of mechanistic insight into the pathogenesis of transfusion-related acute lung injury, primarily due to the absence of an in vivo model. Looney and colleagues now describe a new in vivo mouse model of transfusion-related acute lung injury (pages 1615–1623). Transfusion of an MHC I mAb into BALB/c mice produced acute lung injury with increased excess lung water, increased lung vascular and lung epithelial permeability, and decreased alveolar fluid clearance. Half of the mice died 2 hours after antibody administration. Within those 2 hours, neutrophil sequestration in the lung microvasculature occurred concomitantly with acute peripheral blood neutropenia. Depletion of neutrophils protected mice from the lung injury. While FcRγ–/– mice were resistant to lung injury, adoptive transfer of wild-type neutrophils into the FcRγ–/– animals restored susceptibility to TRALI. With their clinically relevant in vivo mouse model of TRALI, the authors therefore suggest that the mechanism of lung injury is dependent on neutrophils and their Fcγ receptors. New insights into bipolar disorder Calcium is a ubiquitous intracellular signaling molecule required for initiating and regulating a wide range of neuronal functions, including neurotransmitter release, synaptic plasticity, neurite outgrowth, and neurodegeneration. […]

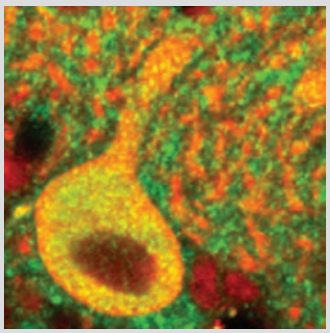
Blazing a trail to TRALI



Transfusion-related acute lung injury (TRALI) is a major problem in transfusion medicine and has emerged as the leading cause of death from a blood transfusion. There is a lack of mechanistic insight into the pathogenesis of transfusion-related acute lung injury, primarily due to the absence of an in vivo model. Looney and colleagues now describe a new in vivo mouse model of transfusion-related acute lung injury (pages 1615–1623). Transfusion of an MHC I mAb into BALB/c mice produced acute lung injury with increased excess lung water, increased lung vascular and lung epithelial permeability, and decreased alveolar fluid clearance. Half of the mice died 2 hours after antibody administration. Within those 2 hours, neutrophil sequestration in the lung microvasculature occurred concomitantly with acute peripheral blood neutropenia. Depletion of neutrophils protected mice from the lung injury. While *FcRγ*$^{-/-}$ mice were resistant to lung injury, adoptive transfer of wild-type neutrophils into the *FcRγ*$^{-/-}$ animals restored susceptibility to TRALI. With their clinically relevant in vivo mouse model of TRALI, the authors therefore suggest that the mechanism of lung injury is dependent on neutrophils and their Fcγ receptors.

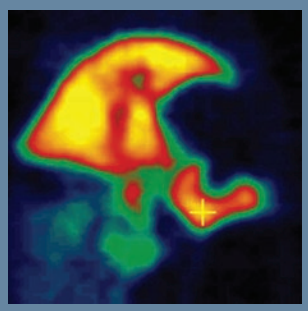
New insights into bipolar disorder

Calcium is a ubiquitous intracellular signaling molecule required for initiating and regulating a wide range of neuronal functions, including neurotransmitter release, synaptic plasticity, neurite outgrowth, and neurodegeneration. Now Schlecker and colleagues investigate the interaction between the principal intracellular calcium release channel in cells, the inositol 1,4,5-trisphosphate receptor ($InsP_3R$), and the calcium-binding protein neuronal calcium sensor-1 (NCS-1) (pages 1668–1674). NCS-1 was found to modulate the activity of the $InsP_3R$. Interaction between the 2 proteins was observed with purified proteins and in intact cells. NCS-1 dramatically increased the opening rate of the $InsP_3$-gated channel in both calcium-dependent and -independent manners. As NCS-1 has been found to be elevated in the cortex of bipolar patients, the authors show that levels of lithium used for treating bipolar patients attenuate the enhanced signaling when NCS-1 is overexpressed. These data suggest a new mechanism of action for lithium and suggest that the interaction of $InsP_3R1$ and NCS-1 is an essential component of the pathobiology of bipolar disorder.



A noninvasive method for measuring β cell mass

Diabetes results from a reduction in pancreatic β cell mass (BCM) leading to insufficient insulin secretion and hyperglycemia. Measurement of insulin secretion is currently used as a surrogate measure of BCM; however, serum insulin concentrations provide an imprecise index of BCM. Now Souza and colleagues describe a reliable noninvasive measure of BCM (pages 1506–1513). The authors exploit the finding that type 2 vesicular monoamine transporters (VMAT2) are expressed in human islet β cells, as well as in tissues of the CNS. Because the radioligand [^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) binds specifically to VMAT2 and is currently used in clinical imaging of the brain, the authors were able to use [^{11}C]DTBZ to estimate BCM in a rat model of spontaneous type 1 diabetes. In longitudinal PET studies, the authors saw a significant decline in pancreatic uptake of [^{11}C]DTBZ that preceded the loss of glycemic control in the diabetic rat. These studies suggest that PET-based quantitation of VMAT2 receptors could provide a noninvasive measurement of BCM that could be used to study pathogenesis of diabetes and to monitor therapeutic interventions.



Epimorphin: epithelial master regulator

Epithelial-mesenchymal interactions are critical for the normal morphogenesis and maintenance of epithelia in various organs including intestine, skin, mammary gland, lung, gallbladder, and liver. Epimorphin has been identified as a mesenchymal/myofibroblast molecule with putative morphogenetic effects. Wang and colleagues now describe the phenotype of epimorphin-null mice (pages 1535–1546). The authors show that epimorphin is required for the regulation of epithelia in many tissues as well as for normal spermatogenesis. In the gut, epimorphin was found to act as a negative regulator of gut epithelial proliferation, and epimorphin deficiency provided protection in an experimental model of colitis. Amelioration of colitis resulted from enhanced proliferation of the epimorphin-deficient colon epithelia. These data suggest that modulation of epimorphin expression could be used therapeutically to increase mucosal regeneration following injury to the gut in inflammatory bowel disease, ischemia, or intestinal resection.