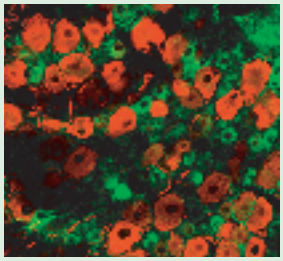
Sensing inflammatory pain

PARs are a subfamily of G protein–coupled receptors that share a unique mechanism of activation and are known to play important roles in the response to tissue inflammation. TRPA1 is a member of the transient receptor potential (TRP) family of cation channels that has been reported to be activated by icilin, a chemical that induces a cooling sensation, and by temperatures of 17°C or less and thus is proposed to be the painful cold receptor. Here, Dai and colleagues, using morphological and electrophysiological analyses, show a functional interaction of these two inflammation-related molecules in primary rat sensory neurons (pages 1979–1987). A PAR2-activating peptide increased the TRPA1 currents evoked by allyl isothiocyanate (AITC) or cinnamaldehyde in HEK293 cells expressing TRPA1 as well as in primary sensory neurons. This potentiation was inhibited by phospholipase C inhibitors; however, its downstream PKC activation was not involved in the AITC- or cinnamaldehyde-activated TRPA1 currents. This potentiation mechanism is different from that in TRPV1 currents. These findings reveal a novel mechanism through which mediators of tissue inflammation might trigger the sensation of pain by TRPA1 activation.

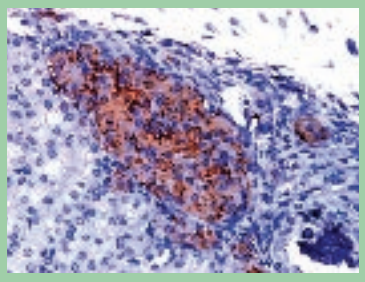


Generating and incorporating cardiac progenitors

The article by Cohen and colleagues addresses a fundamental question in the cardiac stem cell field: What are the molecular pathways required for expansion and development of cardiac stem cells? The authors have delineated a novel and essential pathway for expansion of recently identified Isl-1–positive cardiac progenitor cells (pages 1794–1804). These cells contribute to the right ventricle and outflow tract of the developing heart and are a marker of the anterior heart field. Wnt signaling through activation of FGF10 expression was required for expansion of murine Isl-1 cardiac progenitors in the anterior heart field, and loss of Wnt signaling led to a loss of the right ventricle and defective development of the outflow tract while sparing the left sides of the structures. Isl-1–positive precursors with active Wnt signaling were fated to become outflow tract and right ventricular myocytes. Activation of Wnt signaling led to increased numbers of Isl-1–positive progenitors, increased FGF10 expression, and increased outflow tract development. The direct relationship between Wnt and FGF10 signaling was demonstrated by the finding that FGF10 is a direct target of Wnt/β-catenin signaling in cardiac development. These data identify a pathway by which cardiac progenitor stem cells can be amplified in vivo, thus implicating that these cells could be harnessed for future cardiac reparative therapies.

Insulin in autoimmune diabetes

Understanding the key triggers and autoantigens responsible for autoimmune diseases may lead to more effective therapeutics. In this issue, Nakayama and colleagues study insulin as the antigen in autoimmune diabetes (pages 1835–1843). The authors use their recently established NOD mouse that lacks both native insulin genes and expresses a mutated transgene with alanine at position B16 in preproinsulin (B16:A-dKO mouse). Here the authors explored the conditions that break immune tolerance in the B16:A-dKO model and used different strategies to reintroduce the autoantigenic native insulin sequence. Transplantation of NOD islets expressing the native insulin sequence led to the production of insulin autoantibodies and transient insulitis but did not progress to overt disease. However, spleen cells from the islet-transplanted B16:A-dKO mice transferred disease into both immunodeficient wild-type NOD/SCID and B16:A-dKO NOD/SCID mice. B16:A-dKO mice immunized with native insulin B:9–23 peptide developed insulin autoantibodies. $CD4^+$ T cells from B16:A-dKO mice immunized with native peptide induced the production of insulin autoantibodies when transferred. These data support the role of insulin as a primary triggering autoantigen in autoimmune diabetes.



On the TRAIL to meningitis

The TNF-related apoptosis-inducing ligand (TRAIL) has important regulatory functions in the host immune response. In this issue, Hoffman and colleagues found elevated levels of soluble TRAIL in the CSF of patients with bacterial meningitis; they hypothesized that the TRAIL system is an essential regulator of leukocyte survival in the CSF during meningitis and that recombinant TRAIL could be used to modulate the inflammatory response in invasive infections (pages 2004–2013). Deficiency in TRAIL protracted acute inflammation and increased apoptosis in the hippocampus in experimental meningitis. These deleterious changes were reversed by recombinant TRAIL or by the transplantation of TRAIL-expressing bone marrow cells in a chimeric mouse model, suggesting an autoregulatory role of TRAIL within the infiltrating leukocyte population. Administration of recombinant TRAIL into the subarachnoid space of wild-type mice with meningitis also reduced inflammation and apoptosis. These findings provide the first evidence that TRAIL may act as a negative regulator of acute CNS inflammation. The ability of TRAIL to modify inflammatory responses and to reduce neuronal cell death in meningitis suggests that it could potentially be used as an antiinflammatory agent to treat infections.