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In This Issue

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Initiation of Crohn disease Increasing evidence points to the central importance of enteric bacteria in the initiation of Crohn disease (CD). The ileal mucosa of CD patients is abnormally colonized by adherent-invasive E. coli (AIEC) that are able to adhere to and invade intestinal epithelial cells. Barnich et al. now show that CD-associated AIEC adhere to the brush border of primary ileal enterocytes isolated from CD patients but not controls without inflammatory bowel disease (pages 1566–1574). AIEC adhesion is dependent on type 1 pili expression on the bacterial surface and on carcinoembryonic antigen–related cell adhesion molecule 6 (CEACAM6) expression on the apical surface of ileal epithelial cells. CEACAM6 acts as a receptor for AIEC adhesion and is abnormally expressed by ileal epithelial cells in CD patients. In vitro studies show increased CEACAM6 expression in cultured intestinal epithelial cells after IFN-γ or TNF-α stimulation as well as after infection with AIEC bacteria, indicating that AIEC can promote its own colonization in CD patients. The authors hypothesize that patients expressing a basal level of CEACAM6 would be genetically predisposed to develop ileal CD and that the presence of AIEC bacteria and the secretion of IFN-γ and TNF-α would lead to an amplification loop of colonization and inflammation. Major role for NF-κB in pancreatitis The NF-κB transcription factors play a prominent role in […]

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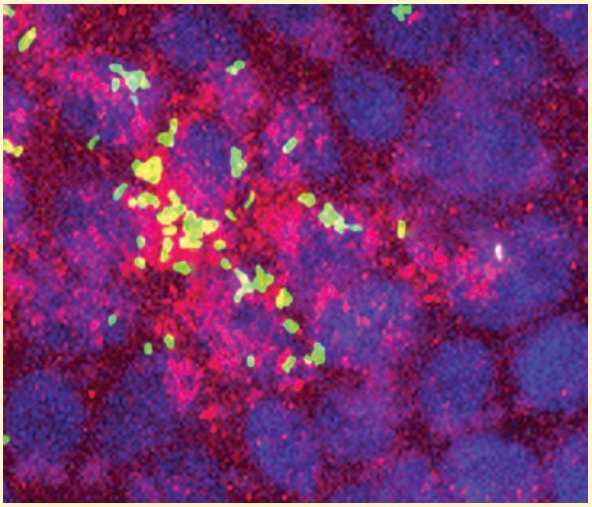
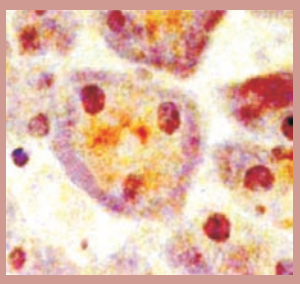
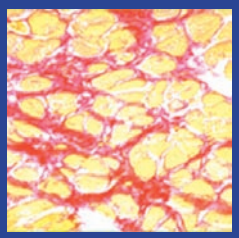


Major role for NF-κB in pancreatitis

The NF-κB transcription factors play a prominent role in controlling the integration of innate immunity into the inflammatory response and adaptive immunity, and activation of NF-κB is detectable very early in the course of experimental pancreatitis. NF-κB represents a family of transcription factors composed of 5 members: p50, p52, RelA/p65, RelB, and c-Rel. The pivotal regulation of NF-κB occurs through phosphorylation of inhibitor of NF-κB (IκB) proteins, mediated by the IκB kinase (IKK) complex. Two studies in the current issue focus on the roles for NF-κB and its cofactors, RelA/p65 and IKK2, in acute pancreatitis. Baumann and colleagues describe the generation of a mouse model that allows both the conditional activation and the suppression of IKK activity selectively in acinar cells of the adult pancreas. This model provides evidence that ectopic IKK2 activation is able to induce acute pancreatitis, whereas repression of IKK activity attenuates cerulein-induced pancreatitis (pages 1502–1513). Blocking NF-κB activation ameliorated cerulein-induced pancreatitis, while activation of IKK2 resulted in full-blown acute pancreatitis within hours. All features of acute pancreatitis seen in humans were observed, including fibrosis. These effects were a result of transcriptional activation of the cytokine TNF-α, and pharmacological blockade of TNF-α significantly attenuated early pancreatitis. Using a second model of pancreatitis, Algül and colleagues analyze the role of endogenous RelA/p65 during acute pancreatitis using a Cre-*loxP* strategy (pages 1490–1501). Selective inactivation of RelA/p65 in the pancreas did not improve, but rather worsened, the course of acute pancreatitis, a phenotype that was not expected. Expression and induction of the protective pancreas-specific acute phase protein pancreatitis-associated protein 1 (PAP1) depended on RelA/p65. Lentiviral gene transfer of PAP1 cDNA reduced the extent of necrosis and infiltration in the pancreata of mice with selective inactivation of RelA/p65. Together, the studies show how important NF-κB and its regulators are in the development of acute pancreatitis.



Cardioprotection during mechanical overload



Although ST2, an IL-1 receptor family member, is a potentially useful biomarker in heart diseases such as heart failure and myocardial infarction, the pathophysiological role of ST2 in the myocardium has been unclear, largely due to the lack of a known ligand for ST2. Here, Sanada and colleagues show that the recently described ligand IL-33 is synthesized by cardiac fibroblasts and abrogates angiotensin II– and phenylephrine-induced hypertrophy in cardiomyocytes (pages 1538–1549). The authors found that targeted deletion of ST2 in mice enhanced cardiac hypertrophy and fibrosis following mechanical overload and impaired contractility and survival, while administration of purified recombinant IL-33 improved pathological changes and survival in wild-type mice, but not in $ST2^{-/-}$ mice. These data suggest that IL-33/ST2 signaling is a crucial cardioprotective mechanism and provide new insight into the paracrine signaling between cardiomyocytes and cardiac fibroblasts during mechanical overload.