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In This Issue

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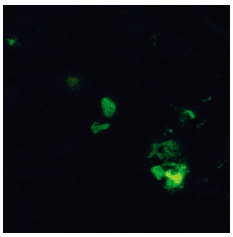
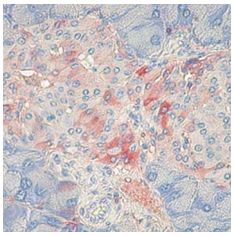
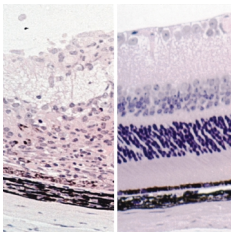
The risks and benefits of accelerating suicide. Failure to undergo activation-induced cell death is a major cause of autoimmune diseases, suggesting that enhancing a T cell's sensitivity to apoptosis might have therapeutic potential for the treatment of autoimmunity. Based on the fact that the PKC inhibitor Bis VIII can sensitize CD4+ T cells for death receptor-induced apoptosis, Thomas Brunner and colleagues analyzed the ability of Bis VIII to sensitize CD8+ T cells for accelerated suicide and the consequences of a CD8+ T cell-mediated response. Their findings (pages 1191–1199) - that Bis VIII is able to sensitize CD8+ cells but decreases the normal protective immune response - suggest that resistance to death receptor-mediated apoptosis is necessary for mounting an efficient immune response against life-threatening infections. Bis VIII-based therapies for autoimmune diseases, therefore, must be applied under well-controlled conditions to avoid immune deficiency against opportunistic viral or bacterial infections.Alterations in PDX1 levels affect islet survival. PDX1 belongs to a family of homeobox genes that regulate initial pancreatic development and the lifelong maintenance of insulin-producing β cells. Human heterozygote carriers develop MODY4, a form of maturity-onset diabetes of the young, a monogenic form of type 2 diabetes characterized by early disease onset, autosomal-dominant inheritance, and defective insulin secretion. In studying Pdx1+/- mice, Kenneth Polonsky and colleagues found that Pdx1+/- islets and β cells […]



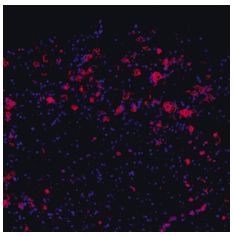
The risks and benefits of accelerating suicide. Failure to undergo activation-induced cell death is a major cause of autoimmune diseases, suggesting that enhancing a T cell's sensitivity to apoptosis might have therapeutic potential for the treatment of autoimmunity. Based on the fact that the PKC inhibitor Bis VIII can sensitize $CD4^+$ T cells for death receptor–induced apoptosis, Thomas Brunner and colleagues analyzed the ability of Bis VIII to sensitize $CD8^+$ T cells for accelerated suicide and the consequences of a $CD8^+$ T cell–mediated response. Their findings (pages 1191–1199) – that Bis VIII is able to sensitize $CD8^+$ cells but decreases the normal protective immune response – suggest that resistance to death receptor–mediated apoptosis is necessary for mounting an efficient immune response against life-threatening infections. Bis VIII–based therapies for autoimmune diseases, therefore, must be applied under well-controlled conditions to avoid immune deficiency against opportunistic viral or bacterial infections.



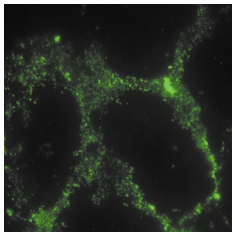
Alterations in PDX1 levels affect islet survival. *PDX1* belongs to a family of homeobox genes that regulate initial pancreatic development and the lifelong maintenance of insulin-producing β cells. Human heterozygote carriers develop MODY4, a form of maturity-onset diabetes of the young, a monogenic form of type 2 diabetes characterized by early disease onset, autosomal-dominant inheritance, and defective insulin secretion. In studying $Pdx1^{+/-}$ mice, Kenneth Polonsky and colleagues found that $Pdx1^{+/-}$ islets and β cells were more susceptible to apoptosis at basal glucose concentrations when compared to controls (pages 1147–1160). They also observed early abnormalities in islet architecture in the $Pdx1^{+/-}$ mutants. The data suggest that increased apoptosis and abnormal regulation of islet number and β cell mass are key mechanisms by which partial PDX1 deficiency leads to defective insulin secretion and diabetes.



Modeling uveitis. Intraocular inflammatory disease, or uveitis, appears to be due in large part to noninfectious, cell-mediated mechanisms. Experimental autoimmune uveitis (EAU) in animals has been a valuable tool for better understanding underlying mechanisms of this disorder and also has provided the possibility of evaluating new approaches to therapy. Both human uveitis and EAU are genetically controlled. Human autoimmune uveitis, in which patients exhibit immunological responses to retinal antigens, has been associated with HLA genes. As they report (pages 1171–1180), Rachel Caspi and colleagues have now succeeded in generating a "humanized" transgenic mouse model of EAU in which disease-relevant epitopes appear to be largely restricted by the human class II molecules. These mice offer a more relevant approximation of human uveitis and should facilitate the characterization of uveitogenic epitopes presented by different HLA class II types.



Cannabinoids and multiple sclerosis. Previous in vitro studies have demonstrated the immunomodulatory effects of cannabinoids; however, little is known about their immunosuppressive properties in autoimmune diseases such as multiple sclerosis (MS). Using a mouse model of virus-induced chronic–progressive MS, Stephen Miller and J. Ludovic Croxford investigated the immunosuppressive potential of the cannabinoid receptor agonist R(+)WIN55,212 (pages 1231–1240). The authors demonstrated that R(+)WIN55,212, when given at the time of initial infection, can suppress the development of MS-like disease. When administered at the onset of symptoms or during established disease, R(+)WIN55,212 significantly inhibited levels of IL-1β, IL-6, TNF-α, and IFN-γ, important inflammatory mediators in the induction and progression of autoimmune disease in a number of MS-like mouse models of disease and presumably in MS. The data suggest that the potent immunosuppressive properties of R(+)WIN55,212 or other cannabinoids may have therapeutic potential in halting disease progression in individuals with MS in addition to providing symptomatic relief of limb spasticity, tremor, and pain.



Factor H: protector of tissue integrity. Factor H is a potent suppressor of the alternative complement pathway. As a complement regulator, Factor H maintains tissue integrity and possesses anti-inflammatory properties. Mutations in the gene encoding factor H have been found in individuals with hemolytic uremic syndrome. These patients have widespread microthrombi and reactive endothelial proliferation. As a consequence, they suffer from hemolytic anemia, thrombocytopenia, and acute renal failure. On pages 1181–1190, Peter Zipfel and colleagues describe the functional consequences of three-point mutations in the factor H gene associated with hemolytic uremic syndrome. The features of the defective protein help to explain progression of vascular damage in patients and underline a role for factor H in tissue integrity during thrombus formation.