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In This Issue

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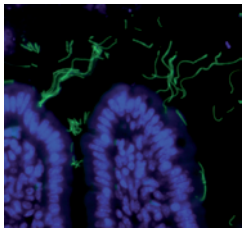
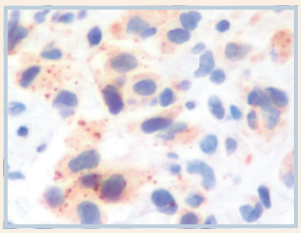
Girls deficient in ITK at risk for EBV infection Boys with mutations in either SLAM-associated protein (SAP) or X-linked inhibitor of apoptosis (XIAP), both of which are X-chromosome genes, develop X-linked lymphoproliferative disease (XLP). Following infection with EBV, boys with XLP frequently develop fatal immune dysregulation. Now, Kirsten Huck and colleagues have identified two girls from a consanguineous Turkish family who died after developing severe immune dysregulation following infection with EBV (pages 1350–1358). Detailed analysis revealed that both girls were homozygous for a missense mutation in IL-2–inducible T cell kinase (ITK) that resulted in an amino acid substitution (R335W) in the SH2 domain of ITK. Consistent with the hypothesis that the R335W mutation impaired the stability of ITK, in silico modeling predicted that the mutation would destabilize the SH2 domain and no R335W mutant protein was detected following overexpression in 293 T cells. As the EBV-associated immune dysregulation in the two ITK-deficient girls resembled that observed in boys with XLP, the authors suggest ITK deficiency should be considered as a molecular cause by those caring for patients with EBV-associated lymphoproliferative disorders.Cd1d controls intestinal colonization with bacteria The mammalian intestines are home to a large number of species of bacteria, the identity of which affects both tissue homeostasis and the occurrence of immune-mediated pathology. Despite the importance of these commensal bacteria, […]

Cd1d controls intestinal colonization with bacteria



The mammalian intestines are home to a large number of species of bacteria, the identity of which affects both tissue homeostasis and the occurrence of immune-mediated pathology. Despite the importance of these commensal bacteria, little is known about the host factors that control their colonization of the intestines. However, Edward Nieuwenhuis and colleagues have now identified a role for the MHC class I–like molecule Cd1d in regulating intestinal colonization in mice (1241–1250). When analyzed under specific pathogen–free or germ-free conditions and compared with control wild-type mice, Cd1d-deficient mice exhibited increased colonization of the small intestine following intragastric administration of *Pseudomonas aeruginosa*, *E. coli*, *Staphylococcus aureus*, or *Lactobacillus gasseri*. By contrast, activation of Cd1d-restricted NKT cells prevented intestinal colonization of specific pathogen–free wild-type mice with *P. aeruginosa* and *E. coli*. Mechanistically, Paneth cells, which are found only in the small intestine, in germ-free Cd1d-deficient mice exhibited a defect in degranulation following bacterial colonization, whereas activation of NKT cells seemed to enhance degranulation. The authors therefore conclude that Cd1d controls colonization of the intestines with commensal and pathogenic bacteria via a pathway that involves Paneth cells.

Cannabinoids induce tumor cell death



Promising preclinical data led to a recent pilot phase I clinical trial to test the antitumoral effects of cannabinoids, specifically the cannabinoid Δ^9-tetrahydrocannabinol (THC), the main active component of marijuana. María Salazar and colleagues have now provided insight into the mechanism by which THC exerts antitumor effects, showing that it induces human glioma cell death through stimulation of autophagy (1359–1372). Analysis of human astrocytoma cell lines and a primary culture of human glioma cells indicated that THC treatment induced autophagy and subsequent apoptotic cell death via activation of an ER stress response. Importantly, administration of THC to mice bearing tumors derived from human astrocytoma cell lines also induced autophagy-mediated tumor cell death and decreased tumor growth, and analysis of tumors from two patients with recurrent glioblastoma multiforme receiving THC intracranially showed signs of autophagy. The authors hope that the identification of the pathway by which THC mediates human tumor cell death will provide more support for the development of cannabinoids as a potential treatment for human cancers and will assist in the design of new anticancer therapeutics.

Girls deficient in ITK at risk for EBV infection

Boys with mutations in either SLAM-associated protein (*SAP*) or X-linked inhibitor of apoptosis (*XIAP*), both of which are X-chromosome genes, develop X-linked lymphoproliferative disease (XLP). Following infection with EBV, boys with XLP frequently develop fatal immune dysregulation. Now, Kirsten Huck and colleagues have identified two girls from a consanguineous Turkish family who died after developing severe immune dysregulation following infection with EBV (1350–1358). Detailed analysis revealed that both girls were homozygous for a missense mutation in IL-2–inducible T cell kinase (*ITK*) that resulted in an amino acid substitution (R335W) in the SH2 domain of ITK. Consistent with the hypothesis that the R335W mutation impaired the stability of ITK, in silico modeling predicted that the mutation would destabilize the SH2 domain and no R335W mutant protein was detected following overexpression in 293 T cells. As the EBV-associated immune dysregulation in the two ITK-deficient girls resembled that observed in boys with XLP, the authors suggest ITK deficiency should be considered as a molecular cause by those caring for patients with EBV-associated lymphoproliferative disorders.

How lithium protects neurons during cranial radiation

Cranial radiation therapy to treat brain cancer can damage hippocampal neurons, causing long-term neurological deficiencies, particularly in children. Previous studies have indicated that lithium, which is used to treat bipolar disorder, protects hippocampal neurons from radiation-induced apoptosis and improves the cognitive performance of irradiated mice. Now, Eddy Yang and colleagues have determined the mechanism by which lithium protects mouse hippocampal neurons from irradiation (1124–1135). In vitro analysis indicated that repair of chromosomal double-strand breaks (DSBs) was accelerated in lithium-treated hippocampal neurons and that it was mediated by the nonhomologous end-joining (NHEJ) repair pathway. A similar increase in NHEJ-mediated DSB repair was observed in lithium-treated irradiated mice. As the ability of lithium to protect hippocampal neurons from radiation-induced apoptosis was abrogated both in mice lacking the DNA-dependent protein kinase (DNA-PK) catalytic subunit, which is essential for NHEJ, and in mouse hippocampal cells treated with a DNA-PK inhibitor, the authors conclude that lithium protects hippocampal neurons by promoting the NHEJ repair pathway. Further, as lithium did not protect human and mouse glioma cell lines from radiation-induced apoptosis, the authors suggest that lithium should be considered as a possible treatment during cranial irradiation to reduce the long-term neurological side effects of this therapy, particularly in children.