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In this issue

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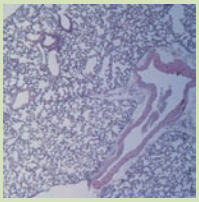
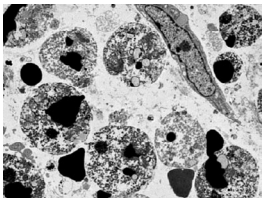
Treg defect contributes to Wiskott-Aldrich syndrome In humans, mutation of the gene encoding Wiskott-Aldrich syndrome protein (WASp) leads to susceptibility to infection with opportunistic pathogens and systemic autoimmunity. Most studies have focused on understanding the defects in T cell activation caused by the WASp deficiency, but Humblet-Baron and colleagues set out to determine whether Tregs (the T cell subset that keeps self-reactive T cells from damaging the body's own tissues) are also impaired in the absence of WASp (pages 407–418). Like WASp-deficient humans, WASp-deficient mice were shown to develop systemic autoimmune disease. This was not caused by a defect in the number of Tregs that developed in the thymus; rather, unlike wild-type Tregs, WASp-deficient Tregs were unable to control autoimmunity when transferred into mice lacking Tregs. Furthermore, WASp-deficient Tregs exhibited defects in peripheral activation and were outcompeted by wild-type Tregs when cotransferred to a wild-type host. Consistent with this finding, the peripheral blood of a WASp-deficient patient in whom a spontaneous revertant mutation occurred in a lymphoid-committed progenitor had substantial numbers of WASp+ Tregs. These cells ameliorated the individual's recurrent episodes of autoimmune hemolytic anemia, indicating that defects in Treg homeostasis, peripheral activation, and function probably contribute to the systemic autoimmunity from which individuals lacking WASp suffer.Tumor cells evade death by autophagy Autophagy is a cellular process that enables cells […]

Treg defect contributes to Wiskott-Aldrich syndrome



In humans, mutation of the gene encoding Wiskott-Aldrich syndrome protein (WASp) leads to susceptibility to infection with opportunistic pathogens and systemic autoimmunity. Most studies have focused on understanding the defects in T cell activation caused by the WASp deficiency, but Humblet-Baron and colleagues set out to determine whether Tregs (the T cell subset that keeps self-reactive T cells from damaging the body's own tissues) are also impaired in the absence of WASp (pages 407–418). Like WASp-deficient humans, WASp-deficient mice were shown to develop systemic autoimmune disease. This was not caused by a defect in the number of Tregs that developed in the thymus; rather, unlike wild-type Tregs, WASp-deficient Tregs were unable to control autoimmunity when transferred into mice lacking Tregs. Furthermore, WASp-deficient Tregs exhibited defects in peripheral activation and were outcompeted by wild-type Tregs when cotransferred to a wild-type host. Consistent with this finding, the peripheral blood of a WASp-deficient patient in whom a spontaneous revertant mutation occurred in a lymphoid-committed progenitor had substantial numbers of $WASp^+$ Tregs. These cells ameliorated the individual's recurrent episodes of autoimmune hemolytic anemia, indicating that defects in Treg homeostasis, peripheral activation, and function probably contribute to the systemic autoimmunity from which individuals lacking WASp suffer.

Tumor cells evade death by autophagy

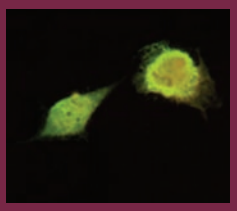


Autophagy is a cellular process that enables cells to turn over the contents of their cytoplasm, targeting them for lysosomal degradation. Autophagy is initiated in tumor cells by chemotherapy and radiation, but it is not known whether this contributes to tumor cell death or helps tumor cells survive the anticancer therapy. In this issue, Amaravadi and colleagues show that in a mouse model of B cell lymphomas, autophagy represents a survival mechanism for tumor cells treated with agents that initiate apoptotic cell death (pages 326–336). In a tumor in which apoptosis was induced by activation of p53 expression, autophagy was observed only in tumor cells not undergoing apoptosis. Treatment of the mice by administering the inhibitor of autophagy chloroquine or by downregulating expression of ATG5 (a protein essential for autophagy) increased the number of tumor cells undergoing apoptosis. Furthermore, treatment of mice by administering chloroquine or by downregulating expression of ATG5 increased the ability of the alkylating chemotherapeutic cyclophosphamide to induce tumor cell apoptosis and tumor regression and to substantially delay tumor recurrence. This indicates that adjunct treatment with inhibitors of autophagy might increase the efficacy of apoptosis-inducing chemotherapeutics in human patients with cancer.

Cbl-b resists *Pseudomonas aeruginosa* infection

The *Pseudomonas aeruginosa* type III secretion system is an important virulence determinant for this major opportunistic pathogen. In this issue, Balachandran and colleagues show that the type III secretion protein exotoxin T (ExoT) is important for bacterial dissemination and that its function is limited by the host ubiquitin ligase Cbl-b (pages 419–427). In vitro analysis demonstrated that when ExoT enters the cytoplasm of a host cell it becomes polyubiquitinated and is thereby targeted for proteasomal degradation. Polyubiquitination was shown to be mediated by the E3 ubiquitin ligase Cbl-b, which is brought into contact with ExoT because it interacts with the ExoT substrate Crk. Consistent with these observations, Cbl-b–deficient mice were more susceptible to both intranasal and systemic infection with *P. aeruginosa* than were wild-type mice, with increased bacterial dissemination detected in the absence of Cbl-b. This study therefore identifies a new role for the E3 ubiquitin ligase Cbl-b as a component of early host defense against infection with *P. aeruginosa*.

The more mutations the better in idiopathic hypogonadotropic hypogonadism



Idiopathic hypogonadotropic hypogonadism (IHH) is an inherited disorder that results in a gonadotropin-releasing hormone (GnRH) deficiency and thereby impaired sexual development. Although IHH is generally considered a monogenic disorder with several single-gene defects associated with the disorder, some mutations show incomplete penetrance, and the presence of a specific genotype does not always cause the same phenotype in different family members. Pitteloud and colleagues set out to investigate the possibility that IHH is not a monogenic disorder (pages 457–463). Indeed, analysis of two separate families with distinct forms of IHH (Kallmann syndrome and normosmic IHH) indicated that different combinations of several gene defects result in different disease phenotypes. In the first family, the individual with the most severe phenotype had both a loss-of-function mutation in one copy of *FGFR1* and a truncation mutation in one copy of *NELF*. His parents and siblings with only one of the mutations exhibited less severe disease. Similarly, in the second family, the most severely affected individual had a different mutation in each of her genes encoding *GNRHR* and a mutation in one copy of *FGFR1*, whereas less severely affected family members did not have all three genetic mutations. This study indicates that IHH is not a monogenic disorder but is an oligogenic disorder, a finding that has implications for the genetic counseling of IHH.