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## In This Issue

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Resisting host defense. The innate immune response is the first line of defense against bacterial infections in the nonimmune host. One effective antibacterial strategy is phagocytosis, and virulent bacterial strains have evolved antiphagocytic strategies. Searching for new virulence factors in group B streptococcus, Craig Rubens and colleagues isolated the cspA gene from a highly virulent strain. As they report (pages 61–70), cspA encodes a novel protease that is necessary for the cleavage of human fibrinogen. The protein is localized on the bacterial surface and promotes bacterial survival through evasion of opsonophagocytosis, perhaps through binding of a fibrin-like molecule to the bacterial surface. Genes homologous to cspA exist in other Gram-positive bacteria, suggesting that the mechanism by which it promotes bacterial survival might be common. A new hepatic survival factor. Acute liver failure results from apoptosis and necrosis, and factors that counteract these processes are potentially useful therapeutic agents. Having previously determined that IGF binding protein-1 (IGFBP-1) is required for liver regeneration, Rebecca Taub and colleagues now show (pages 129–139) that IGFBP-1 functions as a survival factor in a mouse model of acute viral hepatitis. A normally sublethal dose of Fas agonist causes massive hepatocyte apoptosis associated with elevated levels of MMP-9 and TGF-β1 in mice lacking IGFBP-1. Pretreatment with IGFBP-1 suppressed MMP-9 and TGF-β1 expression, reduced the level of apoptosis, and [...]



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**Control of whole-body insulin sensitivity.** The AMP-activated protein kinase (AMPK) has been proposed as a fuel sensor that mediates the cellular response to nutritional variation. Of several existing AMPK isoforms, AMPK $\alpha$ 2 is thought to be physiologically active in skeletal muscle. Benoit Viollet and colleagues have generated mice lacking AMPK $\alpha$ 2. As they report (pages 91–98), the mutants are normal with respect to body composition and food intake, but exhibit reduced glucose tolerance. The latter is associated with reduced insulin release and decreased insulin sensitivity of peripheral tissues. However, the metabolic function of mutant isolated skeletal muscle and pancreatic islets is normal, suggesting that the origin of the glucose intolerance is located elsewhere. The authors speculate that AMPK $\alpha$ 2 exerts its function as a fuel sensor by modulating the activity of the sympathetic nervous system.



**SHP-1 and allergic airway inflammation.** The tyrosine phosphatase SHP-1 functions as a negative regulator of several signal transduction pathways, including those downstream of the T cell and IL-4 receptors. As both of these pathways are thought to be critical for successful Th2 cell development, Toshinori Nakayama and colleagues examined the role of SHP-1 in general Th1 and Th2 cell development, and in Th2-dependent allergic responses. As reported on pages 109–119, they found that heterozygous *motheaten* mutants, which lack one copy of SHP-1, exhibited elevated levels of Th2 differentiation and Th2-specific cytokine production upon stimulation when compared with wild-type mice. *Motheaten* heterozygous mice also showed increased allergic responses in an allergic airway inflammation model, suggesting that SHP-1 may function as a negative regulator in the development of allergic responses such as asthma.



**Cannabinoids inhibit skin carcinomas.** Basal and squamous cell carcinomas, collectively referred to as nonmelanoma skin cancers, are two of the most common malignancies diagnosed in humans. Manuel Guzmán and colleagues have previously shown that cannabinoids can induce the regression of murine gliomas in vivo through activation of the widely expressed CB cannabinoid receptors. On pages 43–50, these authors now demonstrate that CB<sub>1</sub>, and a second cannabinoid receptor CB<sub>2</sub>, are expressed in both normal skin and nonmelanoma skin tumors of mice and humans. Administration of CB agonists significantly inhibited skin tumor growth in mice. Two underlying mechanisms seem to be responsible: cannabinoid-treated tumors showed an increase in the number of apoptotic cells, and a decrease in the expression of pro-angiogenic factors such as VEGF and angiopoietin 2. While this suggests that cannabinoids may be utilized in the treatment of skin tumors, further studies will need to investigate their utility as topical therapeutics.