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In This Issue

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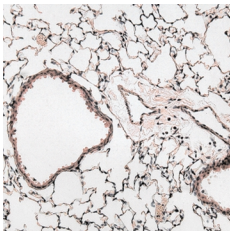
β-Arresting asthma. Asthma is an inflammatory disorder of the airways mediated by Th2. Migration of Th2 cells to the lung is key to their inflammatory function and is regulated in large part by chemokine receptors. Robert Lefkowitz and colleagues show (pages 566–574) that allergen-sensitized mice with a targeted deletion of the gene encoding β-arrestin-2 (a G protein–coupled receptor regulator) do not accumulate lymphocytes in their airways, nor do they demonstrate other physiological and inflammatory features characteristic of asthma. Their airway response to lipopolysaccharide, however, was found to remain fully functional. Because β-arrestin-2 regulates the development of allergic inflammation at a proximal step in the inflammatory cascade, targeting this protein may become a treatment for asthma.A new cathepsin in the thymus. Preceding the loading of immunogenic peptides onto MHC class II molecules on the cell surface, lysosomal proteases such as the cathepsins must drive the maturation of MHC class II molecules by degradation of the MHC class II chaperone invariant chain to generate class II–associated invariant chain peptides. Eva Tolosa and colleagues have now characterized the function of a new human cathepsin (Cathepsin V) exclusively expressed in the thymic cortex and testis (pages 517–526). The authors show that Cathepsin V is the protease that mediates invariant chain release in the class II processing pathway in the human thymus. Comparison of Cathepsin […]



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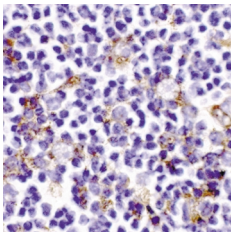
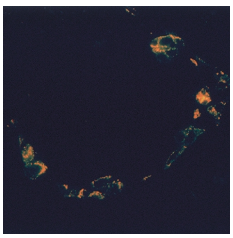
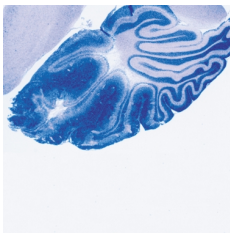


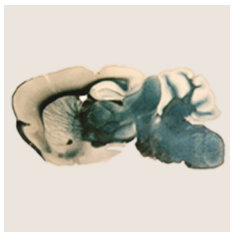
A new cathepsin in the thymus. Preceding the loading of immunogenic peptides onto MHC class II molecules on the cell surface, lysosomal proteases such as the cathepsins must drive the maturation of MHC class II molecules by degradation of the MHC class II chaperone invariant chain to generate class II–associated invariant chain peptides. Eva Tolosa and colleagues have now characterized the function of a new human cathepsin (Cathepsin V) exclusively expressed in the thymic cortex and testis (pages 517–526). The authors show that Cathepsin V is the protease that mediates invariant chain release in the class II processing pathway in the human thymus. Comparison of Cathepsin V expression in thymi from myasthenia gravis patients and healthy controls revealed a significantly higher expression level in the pathological samples, suggesting a potential involvement of this protease in the immunopathogenesis of this disease.



Neurodegeneration and diabetes come together. In order to elucidate the underlying mechanisms leading to the development of diabetes in humans, Michael Ristow and colleagues created a β cell–specific knockout of *frataxin* in mice (pages 527–534). Reduced expression of *frataxin* due to triplet repeats is known to cause an autosomal recessively inherited disease, Friedreich ataxia, in humans. Mice were born healthy, but subsequently developed impaired glucose tolerance progressing to overt diabetes mellitus. The secretory defect was caused by reduced β cell mass due both to a decreased cell growth and an increase in the frequency of apoptosis, which was caused by the overproduction of reactive oxygen species in the absence of *frataxin*. These observations might provide insight into the deterioration of β cell function observed in human type 2 diabetes.



Interfering interferons in medulloblastoma. Type I interferons (IFN-α and IFN-β) are crucial in antiviral defense and immune regulation, and signal via activation of STAT1 and STAT2. Iain Campbell and colleagues show that in $STAT2^{-/-}$ transgenic mice, IFN-α retains potent biological activity in the CNS, mediating a type I–like immune response with IFN-γ gene expression and signaling in the brain associated with the development of medulloblastoma (page 535–543). Further, the authors show the Sonic hedgehog (Shh) signaling pathway, which is implicated in the development of medulloblastoma, is activated in granule neurons, and this process can be mediated by IFN-γ. These findings show the dire consequences of STAT2-independent type I IFN signaling and reveal a previously unknown link between the immune system and the pathogenesis of developmental disorders and tumorigenesis of the CNS due to dysregulated Shh signaling mediated by IFN-γ.



MOG: a minor CNS myelin protein, a major self-antigen. Myelin/oligodendrocyte glycoprotein (MOG), a minor myelin protein, is involved in inflammatory demyelinating diseases of the CNS such as multiple sclerosis (MS) and in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Danielle Pham-Dinh and colleagues have now generated a mouse lacking a functional *mog* gene in order to assess the role of MOG as a target autoantigen in EAE (pages 544–553). In contrast to wild-type mice, which developed severe EAE following immunization with whole myelin, $MOG^{-/-}$ mice had a mild phenotype, demonstrating that the anti-MOG autoimmune response is a major pathogenic component of the anti-myelin immune response. The lack of tolerance to MOG may be responsible for the high level of pathogenicity of the anti-MOG immune response as well as the high susceptibility of most animal strains to EAE induced by MOG. Therefore, immunotherapy aimed at inducing tolerance to MOG might be beneficial in the treatment of MS.