

In This Issue

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Humans MIFed by West Nile virus Infection with West Nile virus (WNV) can cause lethal encephalitis, and there are currently no vaccines or specific therapeutics for use in humans. In this issue (pages 3059–3066), Arjona and colleagues provide evidence suggesting that the proinflammatory cytokine macrophage migration inhibitory factor (MIF) might provide a target for developing therapeutics to treat WNV encephalitis. Infection with WNV increased the amount of MIF found in the plasma and cerebrospinal fluid of humans and the amount of MIF found in the spleens and brains of mice. In mice, the absence of MIF activity (through treatment with a small molecule inhibitor, treatment with a MIF-specific neutralizing antibody, or deletion of the gene encoding MIF) increased survival after infection with WNV. Decreased lethality in MIF-deficient mice was associated with decreased viral load and decreased leukocyte infiltration in the brain, as well as decreased permeability of the blood-brain barrier, in the early stages of encephalitic disease. However, viral load and leukocyte infiltration in the brain increased at later time points after infection with WNV. The authors therefore suggest that the delay in viral neuroinvasion in the absence of MIF is sufficient to enhance clearance of the virus in the periphery and thereby improve survival. It takes two to tango: IL-10 and IL-13R α 2 control Th2 immunity The role of IL-10 [...]

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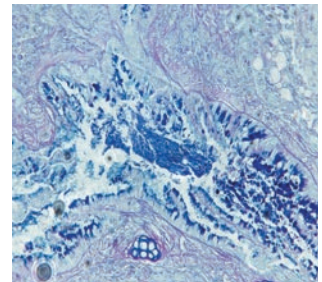


Humans MIFfed by West Nile virus

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It takes two to tango: IL-10 and IL-13R α 2 control Th2 immunity

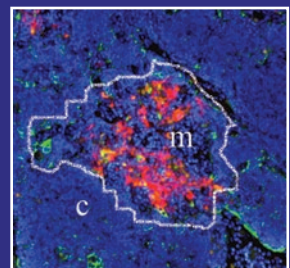
The role of IL-10 in controlling Th2-mediated immunity is unclear because although it limits Th2-driven inflammation, it does not curb Th2-associated pathologies. Wilson and colleagues now provide some insight into this issue by showing that in mice, IL-10 and the decoy receptor IL-13R α 2 regulate Th2-driven inflammation and Th2-associated pathologies, respectively (pages 2941–2951). In a model of acute Th2-mediated allergic airway inflammation, although leukocyte infiltration was increased in IL-10-deficient mice, airway hyperreactivity (AHR) was decreased. Similarly, in a model of chronic Th2 responses (chronic infection with the helminth *Schistosoma mansoni*), although granulomatous inflammation was increased in IL-10-deficient mice, liver fibrosis was decreased. By contrast, for both the acute and chronic disease, if mice lacked IL-10 and IL-13R α 2 the inflammatory and pathological responses (AHR and liver fibrosis, respectively) were increased. This study indicates that the presence of Th2-driven inflammation does not always correlate with the presence of associated pathologies, leading the authors to suggest that modulating the activity of both IL-10 and IL-13 might be a good approach to treat various Th2-driven diseases, including asthma and chronic infection with helminths.



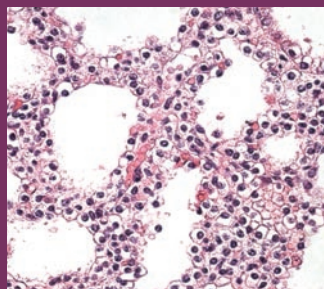
Ghrelin stops the thymus getting old

The deterioration in immune function that occurs as an individual ages is thought to happen because the thymus involutes with age, causing a dramatic decrease in T cell output. In this issue (pages 2778–2790), Dixit and colleagues show that expression in the mouse thymus of both the hormone ghrelin, which is better known as a stimulator of food intake, and its receptor decrease with age. The physiological relevance of this was highlighted by the observation that infusion of ghrelin into old, but not young, mice markedly increased thymic mass, improved thymic architecture, and increased thymocyte and thymic epithelial cell numbers. These changes were associated with increased T cell output and increased diversity of the TCR repertoire of the peripheral T cell population. Increased T cell output was the downstream effect of the presence in the thymus of increased numbers

of early T lineage progenitors. Consistent with these observations, age-associated thymic involution was accelerated in mice lacking either ghrelin or its receptor. The authors therefore caution that care should be taken when considering blocking ghrelin as a potential approach for treating individuals who are obese.



Pten BASCs in the glory of a new role in the lung



Loss of the protein Pten is observed in a high proportion of lung adenocarcinomas. To more clearly analyze the role of Pten in the prevention of lung adenocarcinomas and assess its function in normal lung development, Yanagi and colleagues generated mice in which a bronchoalveolar epithelium-specific null mutation in *Pten* could be induced by exposure to doxycycline (pages 2929–2940). Most mice in which Pten was eliminated in the bronchoalveolar epithelium in utero died of hypoxia soon after birth, in part because distal alveolar epithelial cell differentiation was impaired.

Any surviving mice, as well as most mice in which Pten was eliminated in the bronchoalveolar epithelium 3–4 weeks after birth, developed lung tumors, most of which were adenocarcinomas. Consistent with the notion that lung adenocarcinomas arise from bronchioalveolar stem cells (BASCs), mice in which Pten was eliminated in the bronchoalveolar epithelium had increased numbers of BASCs compared with WT mice. This study therefore identifies an essential role in mice for the Pten signaling pathway in normal lung development, BASC homeostasis, and prevention of lung adenocarcinomas, leading the authors to suggest that the Pten signaling pathway might provide a good target for the development of therapeutics to treat individuals with lung adenocarcinomas.