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# In This Issue

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**In this issue**

Efficient T-cell trafficking without ß7 integrins (See article on pages 1541–1552.) Among their many crucial roles, integrins allow lymphocytes to adhere to the endothelium and to migrate across it into infected tissues. The ß7 integrins α4ß7 and Eß7 have been implicated in trafficking of lymphocytes to the epithelial lining of the intestine and in the retention of lymphocytes at this site. Earlier work suggested that these integrins were essential for controlling infections by diarrhea-inducing rotaviruses, which proliferate in the intestinal mucosa, but the current report by Kuklin and colleagues tells a different tale. These authors show that in mice lacking ß7 integrins, immune responses to rotavirus infection are indeed abnormal. In particular, B cell-mediated secretion of antiviral IgA is lacking in these mutant animals, consistent with other work showing that that B-cell trafficking to gut-associated lymphoid tissue depends on ß7 integrins. In addition, CD8+ T cells from ß7-deficient mice reach the intestinal epithelium in smaller numbers following rotavirus infection, relative to similarly infected wild-type animals. Nevertheless, some CD8+ T cells do reach the site of infection, by means of still-uncharacterized adhesive interactions, and these cells are sufficient to clear the virus efficiently from the gut. Indeed, the infection is resolved equally quickly in wild-type and mutant animals.Tissue proteolysis and male infertility (See article on pages 1531–1539.) Here, Uhrin et al. […]



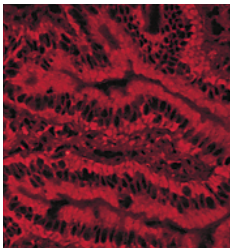
# *In this issue*

*By John Ashkenas, Science Editor*

### Efficient T-cell trafficking without $\beta_7$ integrins

(*See article on pages 1541–1552*)

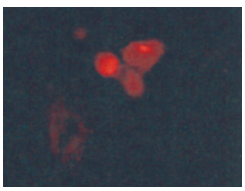
Among their many crucial roles, integrins allow lymphocytes to adhere to the endothelium and to migrate across it into infected tissues. The $\beta_7$ integrins $\alpha_4\beta_7$ and $\alpha_E\beta_7$ have been implicated in trafficking of lymphocytes to the epithelial lining of the intestine and in the retention of lymphocytes at this site. Earlier work suggested that these integrins were essential for controlling infections by diarrhea-inducing rotaviruses, which proliferate in the intestinal mucosa, but the current report by Kuklin and colleagues tells a different tale. These authors show that in mice lacking $\beta_7$ integrins, immune responses to rotavirus infection are indeed abnormal. In particular, B cell–mediated secretion of antiviral IgA is lacking in these mutant animals, consistent with other work showing that that B-cell trafficking to gut-associated lymphoid tissue depends on $\beta_7$ integrins. In addition, $CD8^+$ T cells from $\beta_7$-deficient mice reach the intestinal epithelium in smaller numbers following rotavirus infection, relative to similarly infected wild-type animals. Nevertheless, some $CD8^+$ T cells do reach the site of infection, by means of still-uncharacterized adhesive interactions, and these cells are sufficient to clear the virus efficiently from the gut. Indeed, the infection is resolved equally quickly in wild-type and mutant animals.



### Tissue proteolysis and male infertility

(*See article on pages 1531–1539*)

Here, Uhrin et al. describe the targeted disruption of the *PCI* gene, which encodes the protein C inhibitor. This member of the serpin family of proteinase inhibitors was originally known for its role in regulating thrombosis, but its biochemical specificity is broad, as is its distribution in human extravascular tissues. $PCI^{-/-}$ mice are indistinguishable from their wild-type littermates in most respects, but males are infertile, due to profound defects in sperm development. Remarkably, human male infertility is also associated with a lack of PCI in the seminal fluid — normally a rich source of this proteinase inhibitor in both humans and mice. Uhrin and coworkers propose that the absence of PCI perturbs the balance of endogenous proteinases and proteinase inhibitors in the male reproductive tract. As measured in vitro using artificial substrates, the activity of multiple serine proteinases in the testis is greatly increased in the mutant males. Presumably as a consequence of this unbalanced proteolytic activity, the histological structure of the seminiferous tubules is disrupted, with considerable cell death among Sertoli cells and spematogenic precursor cells. Sperm cells themselves are abnormal and are incapable of binding oocytes, even from wild-type females. Because of the multiple defects in the testis that could account for the abnormalities in the sperm, the present findings do not address whether the loss of PCI directly affects sperm-associated proteinases, such as the serine proteinase acrosin.



### Clearing the brain of amyloid peptides

(*See article on pages 1489–1499*)

Although the synthesis and pathological role of amyloid peptides are matters of great interest and controversy, the opposing process of amyloid clearance from the brain has received far less attention. Derived from the amyloid precursor protein, the amyloid $\beta_{1\text{-}40}$ peptide is found in soluble form in the interstitial fluid of the brain, as well as in plaques that form in the brains of individuals with Alzheimer's disease (AD). This peptide also interacts with numerous cell surface proteins, such as the LDL receptor-related proteins LRP-1 and -2, and with secreted proteins such as apolipoprotein E. Here, Shibata et al. analyze the kinetics of efflux of this peptide by injecting it in radiolabeled form into the brains of mice. They show that the peptide is cleared from the central nervous system primarily by vascular transport and that the peptide is not degraded by local proteinases but remains stable until it crosses the blood-brain barrier. This vascular transport is significantly less efficient in older mice, suggesting a possible explanation of the age-dependence of AD. The authors also show that interfering with LRP-1 partially blocks the efflux of the peptide, and they suggest that the downregulation of this receptor could account for both the timing and the tissue localization of amyloid in AD patients. Shibata and coworkers have also tested the efflux of amyloid $\beta_{1\text{-}40}$ peptide in ApoE-deficient mice. Their finding that amyloid clearance is diminished in these mice suggests a previously unsuspected role for ApoE in this disease pathway, distinct from its putative role in amyloidogenesis. If confirmed, this finding could complicate the interpretation of genetic variation in *ApoE* and its relevance to the risk of AD.