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In This Issue

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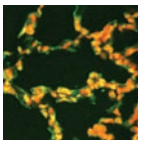
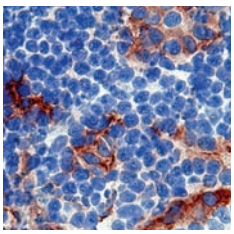
NF-κB protects young lung Acute hyperoxia causes more damage to the adult than to the neonatal lung. The molecular mechanisms that underlie this differential response to hyperoxia remain primarily unknown. Phyllis Dennery and colleagues examined NF-κB activity under conditions of hyperoxia (pages 669–678). Upon exposure to a hyperoxic environment, NF-κB binding increased in neonatal but not in adult primary lung-cell cultures. Similar results were obtained in vivo using transgenic mice that carried the luciferase gene under the control of two NF-κB consensus sequences linked to a minimal promoter. Under these conditions, luciferase expression was higher in the neonatal lung than in that of the adult. Examination of different molecular factors in the NF-κB pathway indicated that NF-κB activity was increased in neonatal lungs as shown by the presence of elevated levels or increased phosphorylation or degradation of several molecular components in this pathway. Bcl-2 levels were likewise higher, suggesting that antiapoptosis activity is important in the protection of neonatal lungs from hyperoxic damage. The use of antibodies against different proteins in the NF-κB complex indicated that the p50 protein is necessary for protective activity, and p50–/– neo mice showed increased lung damage and increased mortality under hyperoxic conditions compared to wild-type mice. These data provide evidence that NF-κB mechanisms of activation change with maturity and may play an important role […]

NF-κB protects young lung



Acute hyperoxia causes more damage to the adult than to the neonatal lung. The molecular mechanisms that underlie this differential response to hyperoxia remain primarily unknown. Phyllis Dennery and colleagues examined NF-κB activity under conditions of hyperoxia (pages 669–678). Upon exposure to a hyperoxic environment, NF-κB binding increased in neonatal but not in adult primary lung-cell cultures. Similar results were obtained in vivo using transgenic mice that carried the luciferase gene under the control of two NF-κB consensus sequences linked to a minimal promoter. Under these conditions, luciferase expression was higher in the neonatal lung than in that of the adult. Examination of different molecular factors in the NF-κB pathway indicated that NF-κB activity was increased in neonatal lungs as shown by the presence of elevated levels or increased phosphorylation or degradation of several molecular components in this pathway. Bcl-2 levels were likewise higher, suggesting that antiapoptosis activity is important in the protection of neonatal lungs from hyperoxic damage. The use of antibodies against different proteins in the NF-κB complex indicated that the p50 protein is necessary for protective activity, and *p50*$^{-/-}$ neo mice showed increased lung damage and increased mortality under hyperoxic conditions compared to wild-type mice. These data provide evidence that NF-κB mechanisms of activation change with maturity and may play an important role in protecting the neonatal lung from hyperoxic damage.

A JAM-A in DC traffic



The transmembrane adhesive protein junctional adhesion molecule (JAM-A) is expressed in endothelial and epithelial cells, platelets, and leukocytes. JAM-A is present in intracellular junctions and is distributed in the cell in the same manner as other components of tight junctions. Elisabetta Dejana and colleagues have now found that JAM-A is also present in DCs and have developed a *JAM-A*$^{-/-}$ mouse to examine the biological role JAM-A plays in DC (pages 729–738). Motility studies, both in vivo and in vitro, showed that in the absence of JAM-A, DC migration increased. In vitro, DC showed greater random motility and ability to transmigrate across lymphatic endothelial cells, while in vitro there was increased DC migration to lymph nodes. *JAM-A*$^{-/-}$ mice also had increased contact hypersensitivity, as shown by a significant increase in the number of FITC/CD11c double-positive cells from draining lymph nodes of *JAM-A*$^{-/-}$ mice compared to wild-type mice. Further, wild-type mice that had adoptive transfer of *JAM-A*$^{-/-}$ DC also showed enhanced contact hypersensitivity. These studies provide evidence that JAM-A is involved in a process that inhibits DC trafficking to the lymph nodes and the activation of specific immune responses.

Liver or lymph: immunity in the balance

The liver is a place of immunological contradiction; it has high immunotolerance, but it is also a region that effects an immune response to a variety of pathogens and is itself subject to immunopathological disease. Patrick Bertolino and colleagues used transgenic mice models that specifically express antigen in the liver or lymph nodes to examine the mechanisms that mediate these paradoxical activities (pages 701–712). The authors found that when $CD8^+$ T cell activation and proliferation occurred in the lymph nodes, there was a strong cytotoxic T lymphocyte response ultimately followed by the development of hepatitis. If there was intrahepatic $CD8^+$ T cell activation, however, the cytotoxic T cell response was defective and did not result in the development of hepatitis. These data indicate that T cell priming within the lymph nodes is required for automimmunity. This study further demonstrates that competition between the liver and lymph nodes as the site of primary T cell activation plays a major role in determining the balance between tolerance and immunity. This may have important implications for transplantation studies and for the development and treatment of immune-mediated liver disease.

ZA zings cervical cancer

High-risk human papilloma viruses (HPVs) are associated with 80–90% of invasive cervical cancers and with particular premalignant stages of cervical intraepithelial neoplasia (CIN). Progression of CIN to invasive cervical cancer is associated with angiogenesis. To explore the molecular control of angiogenesis in cervical cancer progression, Douglas Hanahan and colleagues used a mouse model that expresses HPV-16 under the keratin-14 promoter and that, when exposed to low doses of 17β-estradiol, develops cervical cancer (pages 623–633). The researchers showed that cervical carcinomas in this mouse model had several characteristics similar to human cervical cancer including increased angiogenesis in high-grade CIN and carcinomas; increased expression of MMP-9, which preceded angiogenesis; and mobilization of VEGF via MMP-9. Further investigation revealed that infiltrating macrophages were the source of MMP-9 expression. The researchers treated these mice with a bisphosphonate, zoledronic acid (ZA), an MMP inhibitor that is FDA-approved for treatment of patients with bone metastases. ZA treatment in the mouse model impaired angiogenesis and slowed cervical tumor progression and growth. ZA acted by decreasing MMP-9 expression as well as by inhibiting MMP-9 proteolytic activity. This study provides evidence that ZA may be useful for therapy in cervical cancer and other diseases resultant from MMP-9 expression through macrophage infiltration.