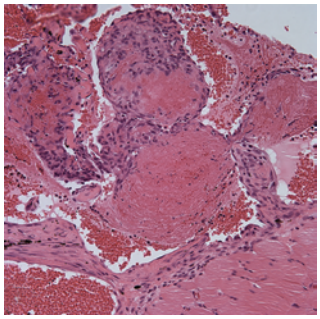
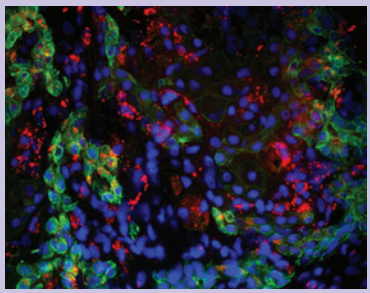
Hemangiomas Nox(4)ious requirement



Hemangiomas, benign endothelial cell–derived tumors, are the most common tumors of infancy. Previous studies indicated that the angiogenic cytokine angiopoietin 2 (Ang2) supports hemangioma growth. To investigate the molecular mechanisms underlying this, Bhandarkar and colleagues compared the ability of polyoma middle T–transformed brain endothelial (bEnd) cells derived from wild-type, *Ang2*$^{+/-}$, and *Ang2*$^{-/-}$ mice to form hemangiomas in nude mice (2359–2365). Surprisingly, *Ang2*$^{+/-}$ bEnd cells were greatly impaired in their ability to form tumors compared with either wild-type or *Ang2*$^{-/-}$ bEnd cells. Although wild-type and *Ang2*$^{+/-}$ bEnd cells formed slow-growing tumors resembling cavernous hemangiomas, *Ang2*$^{-/-}$ bEnd cells generated fast-growing tumors resembling angiosarcomas rather than hemangiomas. Comparative gene array experiments performed in order to understand these differences revealed that NADPH oxidase 4 (*Nox4*) was markedly downregulated in *Ang2*$^{+/-}$ versus *Ang2*$^{-/-}$ bEnd cells. Knocking down Nox4 expression in an Ang2-sufficient bEnd cell line greatly impaired in vivo hemangioma growth, indicating the importance of Nox4 for hemangioma growth. Further analysis identified fulvene-5 as a potent in vitro inhibitor of Nox4, and the drug substantially inhibited in vivo hemangioma growth. The authors therefore conclude that Nox4 is crucial for hemangioma growth and suggest that targeting Nox4, potentially using fulvene derivatives, might provide a way to attenuate hemangioma growth.

NK cells linked to severe infant liver disease

Very little is known about the cause of biliary atresia, a chronic progressive liver disease in newborns that occurs when the extrahepatic bile ducts become obstructed. New research by Shivakumar and colleagues has now linked the innate immune cells known as NK cells to the initiation of biliary atresia in mice (2281–2290). Correlative evidence obtained from analysis of livers of infants with biliary atresia suggests that these cells might also be clinically relevant. Specifically, the NK cells expressing markers of cytotoxicity were found to populate the livers of infants at diagnosis, and this observation triggered the analysis of mice. Consistent with the human data, activated NK cells were the most abundant immune cells in extrahepatic bile ducts at the time of obstruction in a rotavirus-induced mouse model of biliary atresia. Further analysis revealed that these NK cells killed cholangiocytes (i.e., bile duct epithelial cells) ex vivo in a manner dependent upon both contact and natural killer group 2d (Nkg2d). A role for these cells in the initiation of disease was indicated by the demonstration that NK cell depletion and Nkg2d blockade each prevented bile duct injury and subsequent obstruction. The authors therefore suggest that NK cell–mediated damage to the bile duct initiates biliary atresia.



Period 1 clocks sodium balance

Aldosterone increases sodium reabsorption in the kidney. One mechanism underlying this effect is that aldosterone increases expression of the α subunit of the epithelial sodium channel (αENaC). In a previous study to determine the molecular pathway by which aldosterone increases αENaC expression, Gumz and colleagues found that the circadian clock gene Period 1 (*Per1*, which encodes Per1) was the transcript most highly induced by aldosterone in the mouse inner medullary collecting duct cell line mIMCD-3. In a follow-up study, the authors have now determined that Per1 regulates expression of αENaC in the rodent kidney (2423–2434). Initial in vivo analysis in rats confirmed the previous in vitro data: aldosterone administration increased *Per1* transcription in the rat kidney. Further analysis indicated that knocking down Per1 expression in mIMCD-3 cells decreased expression of mRNA encoding αENaC (in the presence and absence of aldosterone), and a similar decrease was observed in mice lacking Per1, which also excreted more sodium in their urine than wild-type controls. As expression of mRNA encoding αENaC seemed to follow a circadian pattern in wild-type mice, the authors suggest that the circadian clock has a role in balancing sodium levels in the body.

Th17 responses protect against lethal parasitic disease

Kala azar (KA) is a lethal visceral disease caused by infection with the protozoan parasite *Leishmania donovani*. In drug-treated individuals recovering from *L. donovani* infection, Th1 responses are associated with protection against repeat infection. However, because expression of two cytokines important for the differentiation and maintenance of Th17 cells is high in *L. donovani*–infected individuals, Pitta and colleagues investigated the role of these cells in protection against KA (2379–2387). Analysis of the cytokines produced by PBMCs from a cohort of *L. donovani*–infected individuals who developed or were protected against KA showed that IL-17 and IL-22, cytokines produced by Th17 cells, were strongly and independently associated with resistance to KA. Furthermore, PBMCs from individuals who developed KA failed to respond effectively to cytokines that induce Th17 responses. As PBMCs from healthy individuals produced high levels of IL-17 and IL-22 when exposed to *L. donovani* in vitro, the authors conclude that IL-17 and IL-22 are induced upon *L. donovani* infection and have important complementary roles in protecting individuals from developing KA. The corollary is that defects in Th17 induction likely increase the risk of developing KA after infection with *L. donovani*.