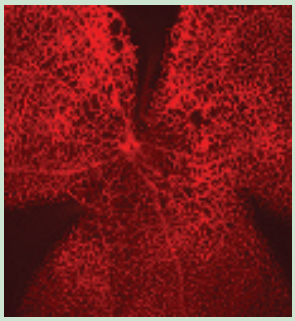
Eyeing up a role for $S1P_2R$ in neovascularization

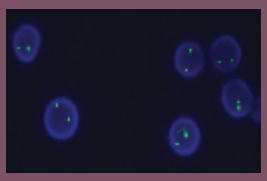


The presence of abnormal vasculature in the eye causes diseases such as diabetic retinopathy and retinopathy of prematurity and results in vision loss in millions of individuals worldwide. Understanding the molecular mechanisms controlling vascular development in the retina under normal and pathological conditions is therefore an area of intensive research. In this issue (pages 2506–2516), Skoura and colleagues show that under normal conditions vascular development is indistinguishable in wild-type mice and sphingosine 1–phosphate 2 receptor–deficient ($S1P_2R$-deficient) mice. By contrast, hypoxia induces pathological neovascularization only in wild-type mice; in $S1P_2R$-deficient mice vascularization occurs normally. The absence of pathological neovascularization in $S1P_2R$-deficient mice was associated with decreased inflammatory cell infiltration of the retina, decreased expression of the proinflammatory enzyme cyclooxygenase-2 by vascular ECs, and increased expression of eNOS in the retina. This demonstration that $S1P_2R$-driven inflammation is an important event in pathological neovascularization led the authors to suggest that inhibiting $S1P_2R$ activation in the retina might provide a new therapeutic approach to treating ocular diseases caused by abnormal vasculature formation in the eye.

Two paths to cardiomyocyte apoptosis

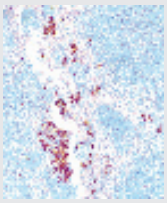
Changes in the size, shape, and function of the heart (cardiac remodeling) contribute to the onset and progression of heart failure. In mice, adverse cardiac remodeling caused by sustained cardiac inflammation — achieved by overexpressing secretable TNF in cardiomyocytes (MHCsTNF mice) — has been shown to be accompanied by increased cardiomyocyte apoptosis and decreased cardiomyocyte expression of the antiapoptotic molecule Bcl-2. In this issue (pages 2692–2701), Haudek and colleagues now show that sustained cardiomyocyte overexpression of Bcl-2 in MHCsTNF mice abrogates adverse cardiac remodeling. However, although cardiomyocyte apoptosis was decreased, it was not completely eliminated. Further analysis revealed that Bcl-2 inhibited the intrinsic apoptotic pathway of cell death activated by sustained TNF signaling but did not block the extrinsic apoptotic pathway of cell death activated by sustained inflammation. These data led the authors to suggest that the extent of cardiomyocyte apoptosis is a key factor in determining whether adverse cardiac remodeling occurs.

New SNP for AML



Mice lacking a specific distal upstream regulatory element (URE) that controls the level of expression of the gene encoding the transcription factor PU.1 have decreased expression of PU.1 in the bone marrow and develop acute myeloid leukemia (AML). When Steidl and colleagues analyzed the equivalent URE in humans, they found that, compared with individuals with AML characterized by a normal karyotype, individuals with AML characterized by a complex karyotype more frequently had a SNP that decreased the URE enhancer activity (pages 2611–2620). The SNP disrupted the binding of the transcriptional regulator special AT-rich sequence binding protein 1 (SATB1) to the URE. Further analysis showed that SATB1 positively regulates *PU.1* expression during myeloid cell development, specifically in granulocyte-macrophage progenitors (GMPs) and megakaryocyte-erythrocyte progenitors (MEPs). Of clinical relevance, GMPs and MEPs from individuals with AML who were homozygous for the SNP had decreased levels of *PU.1* compared with the same progenitor cells from individuals with AML who were not homozygous for the SNP. This study highlights the fact that SNPs in distal regulatory regions, as well as SNPs in coding regions and proximal regulatory elements, can dramatically affect gene expression levels and indicates that they might have a role in the development of cancer.

Tumors induce distinct Treg-mediated suppression



Although tumors express antigens that the immune system should respond to, they are not rejected by the immune system, which tolerates the tumor. Several molecules and cell types have been implicated in the induction of tumor-specific immune tolerance, including, in mice, a small population of plasmacytoid DCs (pDCs) that are found in tumor-draining lymph nodes (TDLNs) and that express indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan. In this issue (pages 2570–2582), Sharma and colleagues now show how these IDO-expressing pDCs induce tumor-specific immune tolerance. These cells were found to directly activate the suppressive function of resting $CD4^+CD25^+Foxp3^+$ Tregs in an IDO-dependent manner both in vivo and in vitro. Suppression by Tregs activated by IDO-expressing pDCs from TDLNs was mediated by interactions between programmed cell death 1 (PD-1) and its ligands, a mechanism of suppression that is distinct from that employed by Tregs activated by CD3-specific antibodies. Importantly, immune suppression in TDLNs was abrogated by treating mice with both a chemotherapeutic drug and a chemical inhibitor of IDO but not either agent alone, leading the authors to suggest that combining IDO inhibitors with chemotherapeutic agents might improve the efficacy of chemotherapeutics in individuals with cancer.