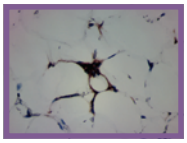
Th17 cells convert to IFN-γ secretion to cause diabetes

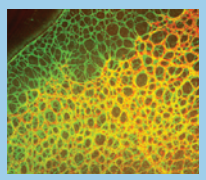
IL-17–secreting Th17 cells are pathogenic in mouse models of some autoimmune diseases, including MS and RA. However, it is not clear whether they contribute to the development of type 1 diabetes, which is commonly thought to be driven by IFN-γ–secreting Th1 cells. To address this issue, Bending, De La Peña, and colleagues isolated naive $CD4^+$ T cells from transgenic mice expressing a TCR specific for a pancreatic islet antigen and cultured them under either Th1- or Th17-polarizing conditions before infusing the cells into NOD/SCID mice and assessing their ability to induce autoimmune diabetes (565–572). NOD/SCID mice that received Th17-polarized cells developed diabetes with kinetics that were similar to those of Th1-polarized cell recipients. Surprisingly, Th17-polarized cells were prevented from inducing diabetes when the NOD/SCID recipients were treated with an antibody that neutralizes IFN-γ; antibodies that neutralize IL-17 provided no protection. Further analysis confirmed that the ability of Th17-polarized cells to induce diabetes in NOD/SCID recipients was not due to the presence of contaminating IFN-γ–secreting cells; rather, after transfer into NOD/SCID recipients, the highly purified Th17-polarized cells converted to IFN-γ secretion and expression of the Th1-associated gene *Tbet*. The authors therefore suggest that Th17 cells exhibit plasticity that is influenced by the local cytokine microenvironment.

Human resistin contributes to insulin resistance



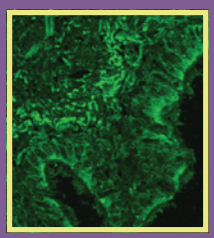
The development of insulin resistance in individuals who are obese is linked to many factors, including dysregulated production of adipocyte-derived factors (adipokines). Although the adipokine resistin clearly contributes to the development of insulin resistance in mice, previous studies failed to determine such a clear association in humans. One confounding factor is that resistin is produced mainly by macrophages in humans, whereas it is produced by adipocytes in mice. To overcome this issue, Qatanani and colleagues generated humanized resistin mice, which lack mouse resistin and express human resistin in macrophages (531–539). When fed a high-fat diet, these mice developed white adipose tissue inflammation more rapidly than did control mice, and this was associated with accelerated lipid dysregulation and insulin resistance. The exacerbated insulin resistance in humanized resistin mice was caused by lipid accumulation in skeletal muscle, which induced activation of the Pkcθ signaling pathway and subsequent serine phosphorylation of Irs-1. The authors therefore conclude that mouse and human resistin, although produced by different cells, both contribute to the development of insulin resistance. They further suggest that resistin probably constitutes an important link between obesity, inflammation, and insulin resistance in humans.

Antioxidants can prevent photoreceptor degeneration



Retinal neovascularization can result in impaired vision. In a number of disease states, including macular telangiectasia (MacTel) and retinal angiomatous proliferation (RAP), it is associated with local photoreceptor degeneration. Dorrell and colleagues have now determined that mice lacking VLDL receptor (VLDLR) have a retinal phenotype similar to that observed in individuals with either MacTel or RAP (611–623). In particular, focal loss of photoreceptors was observed in areas of neovascularization. Consistent with the demonstration that neovascularization and photoreceptor loss in the retinas of *Vldlr*$^{-/-}$ mice was associated with increased levels of markers of oxidative stress, daily oral administration of a cocktail of antioxidants prevented photoreceptor degeneration and preserved visual function, although it did not correct the underlying vascular defect. An alternative, cell-based therapy, whereby the neurotrophic factor neurotrophin-4 was delivered to local endogenous activated Müller cells at sites of retinal neovascularization by intravitreal injection of neurotrophin-4–encoding adeno-associated virus, also provided protection against photoreceptor loss. The authors suggest that both these approaches might help preserve neuron function, and therefore visual function, in individuals with MacTel and RAP.

Role of CTLs in COPD becomes clearer



Chronic obstructive pulmonary disease (COPD) is a progressive, lethal pulmonary disease often precipitated by emphysema, which is characterized by chronic inflammation. Although recent findings suggest lymphocytes contribute to this chronic inflammation, there is no evidence that they are pathogenic. However, Borchers and coworkers have now shown that in vivo and in vitro exposure of mouse airway epithelium to cigarette smoke induces expression of retinoic acid early transcript 1 (RAET1), an activating ligand for the NK cell group 2D (NKG2D) receptor expressed by CTLs, enabling the epithelial cells to activate CTLs (636–649). Consistent with CTLs having a pathogenic role in COPD, in mice engineered to allow for the conditional expression of *Raet1a* only in pulmonary epithelial cells, induction of RAET1 expression induced emphysema-like disease that was reversible by NKG2D blockade. As the authors found increased expression of a human NKG2D ligand in lung tissue from smokers with normal lung function and current and former smokers with COPD, but not in lung tissue from individuals who had never smoked, they suggest that persistent NKG2D ligand expression in pulmonary epithelium contributes to the development of COPD via activation of CTLs.