JCI The Journal of Clinical Investigation

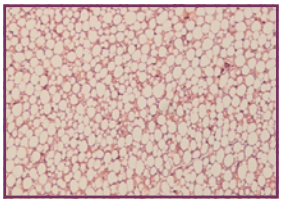
In This Issue

J Clin Invest. 2009;119(1):1-1. https://doi.org/10.1172/JCI38132.

In this issue

Harnessing the power of microRNAs to achieve antitumor immunity Small, noncoding RNA molecules known as microRNAs (miRNAs) are powerful endogenous regulators of gene expression. They repress gene expression by targeting complementary sequences usually found in the 3′ untranslated region of mRNAs. Papapetrou and colleagues have now harnessed an endogenous miRNA that is highly expressed in developing mouse thymocytes and substantially downregulated in postthymic T cells (miR-181a) to segregate expression of lentivirus-encoded proteins in these two cell populations (pages 157–168). Lentiviral vectors were constructed to express an antigen receptor under the control of miR-181a and transduced into mouse bone marrow cells, which were then used to generate hematopoietic chimeric mice. Expression of the antigen receptors was selectively suppressed in developing thymocytes and fully restored in postthymic resting and activated T cells. Using this approach to modulate expression of a chimeric antigen receptor specific for human CD19 (hCD19), the authors showed that although T cells expressing this receptor were undetectable in the thymus, they were present in the periphery, where they provided protection against a subsequent challenge with hCD19+ tumors. When expression of a self-reactive αβ TCR was similarly regulated, developing thymocytes evaded negative selection, and antigen-responsive T cells were detected in the periphery. These data indicate that harnessing miR-181a to regulate expression of transgenic antigen receptors might provide an effective stem […]

Expanding the concept of endothelial dysfunction: abnormal metabolism



Endothelial dysfunction, a common feature of insulin resistance and diabetes, is usually defined as abnormal vasomotor reactivity. However, Kanda and colleagues have now determined that endothelial dysfunction in mice also alters metabolism (pages 110–124). When mice lacking PPARγ, a transcriptional regulator of energy balance, in the endothelium and bone marrow (γEC/BM-KO mice) were fed a high-fat diet (HFD), they exhibited decreased adiposity and improved insulin sensitivity compared with control mice. At the same time, they had marked dyslipidemia, with increased serum FFA and triglyceride (TG) levels at baseline, after fasting, and after olive oil gavage. By using bone marrow transplantation to restore hematopoietic PPARγ in the γEC/BM-KO mice, it was possible to localize these metabolic phenotypes to PPARγ in endothelial cells and to its regulation of certain genes encoding proteins involved in handling fatty acids and TGs. As γEC/BM-KO mice also exhibited impaired vasoreactivity after HFD, the authors suggest that PPARγ in the endothelium integrates metabolic and vascular responses to HFD, thus expanding the concept of endothelial dysfunction to include a metabolic component.

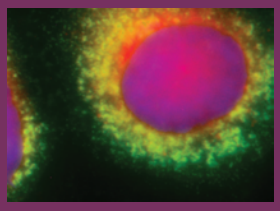
DNA-PKcs: a new candidate gene for SCID

Some individuals with the inherited primary immunodeficiency disease SCID lack both B cells and T cells (i.e., they have T^-B^- SCID). It is caused by defects in V(D)J recombination, and in most cases this is a result of mutations in either *RAG1* or *RAG2*. Most of the remaining patients are hypersensitive to ionizing radiation, i.e., they have radiosensitive T^-B^- SCID (RS-SCID). Many of these individuals have mutations in either *Artemis* or *LIG4*, resulting in defects in the nonhomologous end-joining (NHEJ) DNA repair pathway and thus failure of functional V(D)J recombination. However, van der Burg and colleagues have now identified a patient with RS-SCID who has a missense mutation (L3062R) in the gene encoding DNA-dependent protein kinase catalytic subunit (DNA-PKcs) (pages 91–98). The mutation resulted in Ig genes with long P-nucleotide stretches in the coding joints. Surprisingly, mutant DNA-PKcs protein exhibited normal kinase activity. Further, it accumulated at the appropriate sites and retained the ability to recruit the NHEJ protein Artemis to these sites. However, it was unable to induce sufficient Artemis activation, leading to a defect in NHEJ and thereby V(D)J recombination. The authors therefore conclude that *DNA-PKcs* is a candidate gene for RS-SCID, even in individuals who have normal DNA-PKcs kinase activity.

Harnessing the power of microRNAs to achieve antitumor immunity

Small, noncoding RNA molecules known as microRNAs (miRNAs) are powerful endogenous regulators of gene expression. They repress gene expression by targeting complementary sequences usually found in the 3′ untranslated region of mRNAs. Papapetrou and colleagues have now harnessed an endogenous miRNA that is highly expressed in developing mouse thymocytes and substantially downregulated in postthymic T cells (miR-181a) to segregate expression of lentivirus-encoded proteins in these two cell populations (pages 157–168). Lentiviral vectors were constructed to express an antigen receptor under the control of miR-181a and transduced into mouse bone marrow cells, which were then used to generate hematopoietic chimeric mice. Expression of the antigen receptors was selectively suppressed in developing thymocytes and fully restored in postthymic resting and activated T cells. Using this approach to modulate expression of a chimeric antigen receptor specific for human CD19 (hCD19), the authors showed that although T cells expressing this receptor were undetectable in the thymus, they were present in the periphery, where they provided protection against a subsequent challenge with $hCD19^+$ tumors. When expression of a self-reactive αβ TCR was similarly regulated, developing thymocytes evaded negative selection, and antigen-responsive T cells were detected in the periphery. These data indicate that harnessing miR-181a to regulate expression of transgenic antigen receptors might provide an effective stem cell–based cancer immunotherapy.

Cardiomyocytes NIXed by cell death



If apoptosis occurs inappropriately, it can cause or contribute to disease; for example, apoptosis mediated by the proapoptotic BCL2 family member NIX contributes to heart failure due to cardiac hypertrophy by facilitating loss of cardiomyocytes. Previous in vitro data suggest that proapoptotic BCL2 family members can directly cause apoptosis by increasing mitochondrial permeability and indirectly cause cell death by enhancing ER-mitochondrial calcium transfer. Now, Diwan and colleagues have shown that NIX localizes to both the ER/sarcoplasmic reticulum (ER/SR) and mitochondria in vivo, specifically in cardiomyocytes isolated from mice subjected to pressure overload (pages 203–212). The in vivo consequence of this was modulation of the calcium content of the ER/SR: compared with the ER/SR calcium content in wild-type mice, the ER/SR calcium content was increased in mice overexpressing NIX in the heart and decreased in NIX-deficient mice. In the NIX-deficient mice, this was associated with protection in a model of apoptotic cardiomyopathy, as genetic engineering to restore NIX expression elevated the ER/SR calcium content to normal and resulted in cardiomyopathy. The authors therefore suggest that NIX mediates cardiomyocyte cell death in mice by activating the intrinsic mitochondrial apoptotic pathway and by modulating ER/SR calcium stores to stimulate mitochondrial disruption and thereby cell death.