JCI The Journal of Clinical Investigation

In This Issue

John Ashkenas

J Clin Invest. 2001;108(1):1-1. https://doi.org/10.1172/JCI119929.

In this issue

Glucose stabilization and the progression of diabetes (See article on pages 63– 72, 153– 160.) Insulin resistance, the failure of glucose homeostasis in the face of high levels of insulin, often foreshadows the onset of type 2 diabetes. To tease apart the contribution of insulin resistance in different organs to this progression, several groups have produced mice with genetic defects that affect glucose metabolism only in specific organs, such as the pancreas or liver. Here, Kim et al. explore the phenotype of a recently described mouse strain lacking the glucose transporter GLUT4 specifically in skeletal muscle, the tissue type that is responsible for the bulk of blood glucose uptake following insulin stimulation. Because these mice show increasing hyperglycemia as they age, eventually becoming diabetic, the authors tested the idea that glucose toxicity drives the progression of this disease. They show here that a drug treatment favoring excretion of excess glucose blocks the development of insulin resistance in brown and white adipose tissue, as well as in the liver and muscle, suggesting that mild hyperglycemia per se promotes insulin resistance and sets the stage for type 2 diabetes. Also in this issue, Ryu et al. show that in a mouse model of type 1 diabetes, treatments blocking autoimmune responses can allow for successful ß cell engraftment to reverse the diabetic phenotype. […]

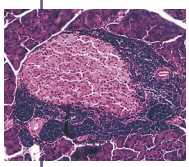
In this issue

By John Ashkenas, Science Editor

Glucose stabilization and the progression of diabetes

(See articles on pages 63–72, 153–160.)

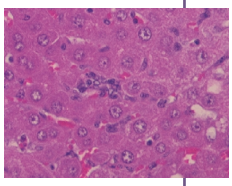
Insulin resistance, the failure of glucose homeostasis in the face of high levels of insulin, often foreshadows the onset of type 2 diabetes. To tease apart the contribution of insulin resistance in different organs to this progression, several groups have produced mice with genetic defects that affect glucose metabolism only in specific organs, such as the pancreas or liver. Here, Kim et al. explore the phenotype of a recently described mouse strain lacking the glucose transporter GLUT4 specifically in skeletal muscle, the tissue type that is responsible for the bulk of blood glucose uptake following insulin stimulation. Because these mice show increasing hyperglycemia as they age, eventually becoming diabetic, the authors tested the idea that glucose toxicity drives the progression of this disease. They show here that a drug treatment favoring excretion of excess glucose blocks the development of insulin resistance in brown and white adipose tissue, as well as in the liver and muscle, suggesting that mild hyperglycemia per se promotes insulin resistance and sets the stage for type 2 diabetes. Also in this issue, Ryu et al. show that in a mouse model of type 1 diabetes, treatments blocking autoimmune responses can allow for successful β cell engraftment to reverse the diabetic phenotype. Remarkably, in this case as well, successful control of hyperglycemia favors the long-term suppression of the disease and allows for restored function by the endogenous β cells of the pancreas. Palmer (pp. 31–33) discusses these latter findings in light of recent data from a large clinical trial testing the effects of aggressive maintenance of normal blood glucose levels on progression of type 1 diabetes.



Targeting metastatic disease with gene therapy

(See article on pages 83–95.)

Because hepatocytes are constantly exposed to portal blood, the liver can be readily transduced with injected transgenes. Noting that this organ is also particularly prone to taking up metastatic colorectal tumor cells, Tada and colleagues have proposed to use gene therapy to render the liver a less hospitable environment for exogenous tumors. The authors show here that, following intravenous injection of recombinant adenovirus, the antitumor cytokine IFN-β is efficiently expressed in mouse hepatocytes, where it persists over a period of weeks. The expression of the cytokine not only blocks the progression of human micrometastases but can also eliminate existing human tumors in the treated mice, a condition that better mimics the likely clinical presentation of the disease. Taking advantage of the fact that human and murine IFN-β fail to recognize each other's receptors, Tada et al. also show that IFN-β can play two beneficial roles, causing cytotoxicity directly in the implanted tumor cells and stimulating host natural killer cells to attack the tumor cells and promote tumor regression.



T cell killing in ADA-SCID

(See article on pages 131–141.)

Although many different molecular defects can lead to immunodeficiency, mutations in the adenosine deaminase (*ADA*) gene were the first identified lesions that cause severe combined immunodeficiency (SCID), affecting both B and T cell development. Despite this long history, the cellular events that lead to the death of lymphocytes in children with diseases of purine metabolism, such as ADA-SCID, have never been clear. ADA carries out a crucial step in the catabolism of adenosine and dATP. Because both of these molecules (the former a well known extracellular signaling molecule, and the latter a cytotoxic compound— at least when it is found at levels in excess of the usual cellular reserves for deoxynucleotides) accumulate in the ADA-deficient thymus, Apasov and coworkers have examined T cell development in young $Ada^{-/-}$ mice. Here they describe events at the stage when CD4/CD8 double negative T cells would normally undergo positive selection. Apasov et al. show that T cell receptor activation in $Ada^{-/-}$ lymphocytes is inhibited by exogenous adenosine, and they suggest a model in which excess extracellular adenosine and toxic levels of dATP cooperate to promote apoptosis of developing T cells. The B cell and natural killer cell defects seen in these animals were not addressed in this work, but it may be interesting to examine the fate of these cells in ADA-deficient animals, considering that a related metabolic disorder, nucleoside phosphorylase deficiency, leads not to SCID but to a specific loss of T cells.