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In This Issue

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γδ T cells in innate anti-bacterial defenses (See article on pages 1349–1357.) Innate immune responses, by definition, exist prior to infection and do not involve immunological memory. For this reason, innate responses are useful for host defense soon after initial exposure to an infectious agent, which must be kept at bay at least until a specific response can be mounted. Such innate responses, including phagocytosis of infectious agents and their destruction by endogenous antibiotic substances, are generally contrasted with the clonal immune system of B and T cells. However, certain branches of the clonal system show intrinsic specificity for bacteria, as in the case of some of the so-called "natural" antibodies, which carry non-mutated germline immunoglobulin variable-region gene segments. Wang et al. have now identified a counterpart of such B cells in the cellular immune system. T cells bearing the γδ receptor type Vγ2Vδ2 are sufficient to control infections with certain gram-negative or gram-positive bacteria in mice that otherwise lack B or T cells. Vγ2Vδ2 T cells represent a small but significant fraction of T cells in the peripheral blood of healthy animals. Although exposure to bacterial metabolites can dramatically increase their representation, even at their initial low level they afford the host substantial protection from septic infections. Such cells become activated by exposure to any of several bacterial metabolites […]

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By John Ashkenas, Science Editor

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Foxo1 and insulin resistance in kidney cells

(See article on pages 1359–1367.)

As a normal aspect of energy metabolism, cells in the kidney, much like those in the liver, respond to insulin by suppressing the metabolic pathways by which glucose is generated and released. In the healthy kidney, expression of the enzyme glucose-6-phosphatase (G6p), which controls a key step in glycogen breakdown, is suppressed by insulin. Curiously, this and other aspects of the transcriptional control by insulin are lacking in cultured kidney cells. In hopes of uncovering a general mechanism by which insulin sensitivity could be gained or lost, Nakae et al. have now studied insulin responses in kidney epithelial cell lines. They show here that the transcription factor Foxo1, which is present in the normal tissue and is weakly expressed in the cell line, is sufficient to restore insulin regulation of transcripts that are sensitive to glucose levels. Previous work had suggested that Foxo1 binding to the *G6p* promoter accounts for activation of gene expression by glucose and the corresponding silencing of expression following insulin treatment. The present work shows that he transcription factor becomes phosphorylated and is excluded from the nucleus following insulin treatment, which may explain at least some of the suppressive effect of this hormone on *G6p* and related genes. Whether reduced expression or increased phosphorylation of Foxo1 contributes to the loss of insulin sensitivity seen in vivo in the kidney or other organs remains to be tested.

DDR2 and hepatic fibrosis

(See article on pages 1369–1378.)

Deposition of interstitial collagen in abnormal locations, the hallmark of fibrosis, can occur in many organs following physical trauma or other kinds of insults. Olaso and coworkers report here that type I collagen accumulation in the liver is not just a marker for this fibrotic response, but actually helps to perpetuate damage to hepatic tissue following injury. They show further that the collagen receptor DDR2, rather than any of the better studied ECM receptors of the integrin family, is at the heart of this harmful response. Transcription of DDR2, a receptor tyrosine kinase that signals in response to triple helical collagen in the surroundings, is induced early during the activation of hepatic stellate cells. These mesenchymal cells are responsible for collagen I biosynthesis following injury, and Olaso et al. show that stellate cell DDR2 is phosphorylated in response to collagen stimulation, leading the cells to divide and to express the degradative enzyme MMP2. The cells that express this enzyme adopt an invasive phenotype in culture, which probably explains their ability to invade the subendothelial space and remodel the ECM, replacing the normal basement membrane constituents with fibrotic material. The newly deposited collagen would then further activate stellate cell proliferation and invasion in an autocrine manner. However, this destructive cycle can apparently be broken by blocking DDR2 function, collagen deposition, or MMP2 activity. Interestingly, providing large amounts of normal basement membrane as a substratum also reverts the activated phenotype of stellate cells and can suppress their expression of DDR2.