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By John Ashkenas, Science Editor

Insulin in heart development

(See article on pages 629–639.)

Given the profound effects of insulin on energy metabolism and gene expression in virtually all tissues, it is not surprising that systemic deficiency in the insulin receptor (IR) leads to early postnatal death. However, Cre/lox technology has also allowed for the creation of animals lacking the IR specifically in particular cell types, and the more subtle phenotypes in these designer mice offer deeper insights into the effects of insulin resistance in specific energy-storing or -consuming organs in the adult animal. Thus, skeletal muscle-specific IR knockout (MIRKO) mice have been available for several years, and animals lacking the receptor in pancreatic β islet cells, hepatocytes, or brown adipose cells have all been described. Belke et al. now add to this list the CIRKO mouse, which lacks the IR specifically in cardiomyocytes. In young CIRKO animals, the heart is of normal structure but is reduced in size, apparently because the cells themselves remain small. Indeed, CIRKO cardiomyocytes appear immature in several other respects, particularly their preferential use of glucose, rather than fatty acids, as a metabolic fuel and their continued high expression of the β isoform of the myosin heavy chain, which is normally suppressed after fetal development. Interestingly, one well established effect of insulin in the heart, the activation of glucose oxidation, is maintained in CIRKO animals. The authors speculate that endothelial cells or some other insulin-responsive cardiac cell type is responsible for inducing this metabolic change in the cardiac muscle, perhaps as a secondary effect of enhanced eNOS activity. Testing such a model might require the generation of yet another cell type specific IR knockout mouse, this one targeting the endothelium.

Breaking down the walls of immunological ignorance

(See article on pages 651–659.)

T cells that respond to an antigen challenge in vitro but fail to do so in a living animal are said to be in a state of immunological ignorance. Chen and his colleagues have argued for some time that this poorly understood state can help explain the workings—and, crucially, the failings—of immunological surveillance for tumors. Ignorance of tumor antigens has been ascribed to the lack of costimulatory signals, and it appears that one strategy of immune evasion by tumors is the down regulation of otherwise common costimulatory activators. Still, some experimentally induced tumors, expressing known tumor antigens that are targeted by defined CTL clones, can be eliminated when T cells are provided an additional, costimulatory signal. In their current report, Wilcox et al. develop a useful reagent for this purpose, and they show that such a co-stimulatory treatment is not always sufficient to induce tumor regression. The authors injected a monoclonal antibody to the costimulatory mediator CD137, a T cell–borne relative of the TNF receptor. This novel agonistic antibody stimulates the expansion and activation of the necessary CTL clone, allowing animals with one type of carcinoma to undergo a dramatic tumor regression following treatment. Interestingly, another tumor type, a thymoma that displays the same tumor antigen, is refractory to this treatment, indicating that the CTLs remain ignorant of the antigen when it occurs in the latter context. Wilcox et al. find that this ignorant state can be overcome when the animals are provided not just the agonistic antibody, but also an antigenic peptide recognized by the tumor-specific CTL. Hence, they argue that either inadequate levels of the presented antigen or insufficient costimulatory signaling through CD137 can lead to immunological ignorance and allow tumor growth to proceed unchecked. Providing one or both of these signals might therefore heighten the efficiency of tumor surveillance in animals with spontaneous tumors as well.

Proteasome inhibitors for treating psoriasis

(See article on pages 671–679.)

Dexamethasone and other steroids used for treating psoriatic skin inflammation probably act in part by inducing I-κB, thus preventing NF-κB from reaching the nucleus, where it trans-activates target genes involved in T cell-dependent inflammation. Zollner and colleagues now propose a different means to this same end: Since the proteasome is responsible for the regulated turnover of I-κB, proteasome inhibitors might also alleviate psoriasis by blocking NF-κB activation. Indeed, such inhibitors have already been used successfully in animal models of rheumatoid arthritis and multiple sclerosis, conditions that (like psoriasis) are thought to result from T cell exposure to bacterial antigens. Working with human psoriatic skin tissue engrafted onto mice, Zollner et al. confirm that a known bacterial superantigen can provoke psoriatic lesions. They find that proteasome inhibition prevents NF-κB activation in cultured T cells and that it blocks expression of adhesive surface molecules required for T cell homing. In engrafted mice, the inhibitor prevents psoriasis as efficiently as dexamethasone does. These different agents, which can each increase I-κB levels, presumably both silence NF-κB target genes in vivo. In addition, however, proteasome inhibitors might well exert other beneficial effects, since they undoubtedly stabilize a variety of short-lived proteins, some of which could block disease progression by other mechanisms.