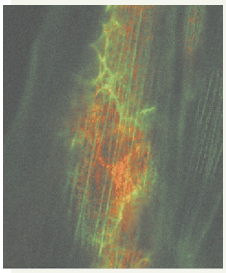
In this issue

By John Ashkenas, Science Editor

GLUT4 in membrane ruffles

(See the article on pages 371–381.)

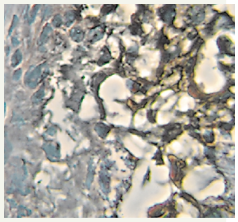
In normal myocytes, insulin treatment activates glucose uptake to the muscle by promoting the cell surface delivery of cytoplasmic storage vesicles that contain the glucose transporter GLUT4. Like other examples of regulated membrane dynamics, this process involves the local rearrangement of the cortical actin cytoskeleton. Tong et al. have applied sophisticated microscopic imaging to follow the intracellular events that mediate this physiologically important response. They show here that GLUT4 is inserted into the myotube plasma membrane at regions of membrane ruffling, where cytoskeletal remodeling takes place. Perturbing the cytoskeleton with specific drugs not only blocks the formation of the membrane ruffles, but also prevents the delivery of GLUT4 to the cell surface. The authors also provide tantalizing clues that these membrane-cytoskeletal interactions go awry in diabetes. In cultured myotubes, the high insulin and glucose levels that prevail with advancing insulin resistance are sufficient to block the formation of membrane ruffles and the fusion of GLUT4-containing vesicles with the cell surface. The reason for this diminished response is not understood, but if it reflects events in vivo, it could provide a novel explanation for the loss of glucose homeostasis by muscle and thus help explain the progression of insulin resistance to diabetes.



Harnessing the autoimmune response

(See the article on pages 415–423.)

Molecular mimicry, structural similarity between viral proteins and host molecules, is thought to explain the genesis of self-specific antibodies in autoimmune disease. Here, Chackerian and coworkers propose a means to turn this pathological response to clinical advantage. The same group previously showed that one of the major capsid proteins of bovine papillomavirus can assemble spontaneously, even without other viral components, to form a population of virus-like particles (VLPs). They have now developed a versatile technique by which peptides can be conjugated to VLPs, a form in which even normally non-immunogenic self epitopes can elicit high titers of specific antibodies. Vaccination of mice with VLP-conjugated TNF-α peptides yields IgGs that inhibit this cytokine and can block or delay the onset of experimentally induced arthritis — a disease process that is driven by high levels of TNF-α. This robust immune response, as compared with that seen in control vaccinations with unconjugated TNF-α peptides, seems to reflect relatively late events in the activation of self-specific B cells. IgM titers are not dramatically different when animals are exposed to the epitope in either conjugated or unconjugated form, but at some point during or after their commitment to IgG production, mature B cells become strongly influenced by the structural context of the epitope. Presumably, VLP conjugation could be used to generate neutralizing antibodies to, and provide long-term suppression of, a variety of self or foreign molecules.



The protective role of secreted CD14

(See the article on pages 485–493.)

The acute-phase response to the presence of LPS or other bacterial metabolites, a key aspect of host defense against infection, can unfortunately be fatal in its own right. The signaling pathway by which LPS elicits cytokine secretion by monocytes is now fairly well understood, but less is known about the protective mechanisms that limit the hazardous effects of LPS. The liver filters out the bulk of injected LPS within minutes, and much of the remainder is neutralized by binding to HDL and other circulating lipoproteins. Kitchens et al. now propose an additional level of control, related to interactions between LPS and its receptor, CD14. A soluble, circulating form of the molecule, sCD14, competes with the monocyte surface-bound form for LPS binding and apparently mediates the transfer of LPS to HDL. Increasing sCD14 should therefore drive LPS from the cell surface to a biologically inactive form. Interestingly, sera from individuals suffering trauma and sepsis accumulate high levels of sCD14. To test the possibility that this protein moderates the systemic effects of LPS, Kitchens and colleagues immunodepleted sCD14 from sera from people with varying severity of sepsis and studied its effects on LPS binding in cultured monocytes. Both the exposure of cells to LPS and the consequent secretion of inflammatory cytokines increased when they were cultured with immunodepleted serum. Adding recombinant sCD14 back to control or immunodepleted serum samples had the opposite effect. The fate of LPS after it binds sCD14 is still uncertain. Because HDL levels decline precipitously during sepsis, the authors suggest that other lipoproteins may serve as a sink for LPS under these conditions.