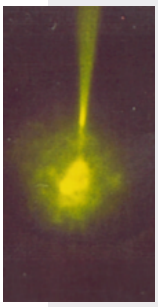
In this issue

By John Ashkenas, Science Editor

Gap junctions regulate insulin secretion

(*See article on pages 235-243.*)

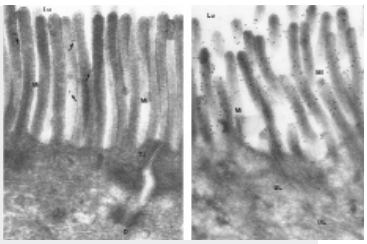


Pancreatic β cells, like other epithelial cell types, are linked to one another through gap junctions that allow ions and other soluble cytoplasmic components to intermingle throughout the tissue. Meda's group has previously implicated this form of junctional communication in the control of insulin secretion. They have reported that when β cells are cultured in isolation so that they cannot make contact with other cells, expression and secretion of insulin is reduced and that, conversely, increased insulin expression in intact tissue causes heightened junctional communication. Now, to probe this correlation further, these authors have developed mice in which a transgene for the exogenous gap junction protein connexin 32 (Cx32) is specifically expressed in these cells. Surprisingly, although islet cells from these transgenic mice show increased intercellular transfer of ions and soluble dyes, these animals are less tolerant, not more tolerant, to glucose, an effect that increases with gene dosage. Moreover, the reduction in glucose-stimulated insulin secretion can also be seen in the whole, perfused pancreas or in isolated islets from transgenic mice. However, isolated cells from parental or transgenic animals show similar glucose sensitivity, suggesting that the effect of the transgene on insulin secretion depends on the formation of gap junctions. Hence, β cells seem to be sensitive to the efficiency of junctional communication, so that quantitative change in either direction from wild-type levels inhibits insulin biosynthesis or secretion. The authors also note that connexins found in different tissues are functionally distinct, raising the possibility that insulin secretion responds to qualitative differences between Cx32 and the connexins that are endogenous to the β cell.

Protein shedding causes a novel form of dietary sugar intolerance

(*See article on pages* 281–287.)

Sucrase-isomaltase (SI) deficiency, an inborn error of metabolism in which the single gene encoding the bipartite SI enzyme is defective, causes severe insensitivity to dietary sucrose and other small saccharides. The two homologous halves of the SI enzyme are transcribed from a single mRNA, and the mature complex consists of a transmembrane isomaltase subunit and a sucrase subunit, which remain tightly associated even after the peptide linkage between them is cleaved during biosynthesis. In the novel disease allele described here by Jacob et al., this complex is synthesized by brush border cells and maintains its enzymatic activities, but a point mutation renders its connection to the surface of the gut unstable, causing it to be clipped and shed from the cell.



A single antibody species recognizes multiple self-antigens in autoimmune disease

(*See article on pages* 217–224.)

Microbial antigens that share structural features of self-epitopes can induce autoimmune diseases that persist long after the bacterial challenge is successfully contained. Galvin et al. have studied the manifestation in different tissues of rheumatic fever (RF), an autoimmune disease that occurs after exposure to streptococci. In this condition, antibodies against streptococcal carbohydrate moieties also react against endogenous proteins, including myosin and other nonglycosylated cytoskeletal proteins, as well as the basement membrane protein laminin. This reaction causes inflammation and cell death in the valve tissue of the heart or in a number of other sites. Hoping to understand the protein interactions that precipitate the tissue-specific effects of RF, Galvin and colleagues have generated human mAb's corresponding to autoantibodies from a patient with RF-associated carditis. One mAb, which they focus on here, recognizes cardiac myosin, and binding studies using peptides that span the myosin molecule show that it binds efficiently to at least two regions of the light meromyosin chain. Interestingly, one of these sites contains a pentapeptide sequence that is almost perfectly shared with laminin. The mAb recognizes the basement membrane of the valve endothelium, a reaction that can be competed away using myosin or the other known antigens. Cultured vein endothelial cells, which express laminin, can be killed by complement-mediated lysis when exposed to this mAb, providing a plausible mechanism for autoimmune carditis in the original patient and, presumably, other individuals with RF.