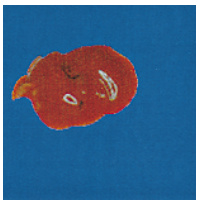
In this issue

By John Ashkenas, Science Editor

Fat as a target of TZD action

See article on pages 1221–1228

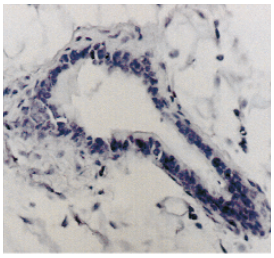
Obesity is well known as a risk factor for diabetes mellitus, but curiously, the complete absence of adipose tissue is not protective but actually causes diabetes. In humans with lipoatrophy, as well as in mouse models of this condition, blood glucose is abnormally high and physiological responses to insulin are blunted. Chao et al. have pursued this paradox by studying the responses of lipoatrophic and obese mice to thiazolidinediones (TZDs), antidiabetic drugs that heighten insulin responsiveness. They report here that mice lacking adipose tissue differ from obese diabetic animals in that they do not benefit from the glucose-lowering effects of TZDs. Nevertheless, some of the other effects of these drugs — increased lipid oxidation and lowered circulating lipid levels — still occur in these animals. The authors note that both obese and lipoatrophic animals accumulate abnormal quantities of lipid in their livers, and they show that expression of the transcription factor PPARγ, the known target for TZD action, is greatly increased in such steatotic livers. Moreover, some TZDs greatly exacerbate this steatosis, which may in part account for their beneficial effects on circulating lipid levels. These findings suggest a possible link between steatosis and diabetes, but it is unclear how lipid accumulation in the liver could affect glucose metabolism in other tissues. The present evidence that adipose tissue is essential for TZDs' antidiabetic effect conflicts with earlier findings that relied on a different, and less severely affected, mouse model of lipoatrophy. Which of these models best matches human lipoatrophic diabetes remains an open question.



Fas in mammary involution

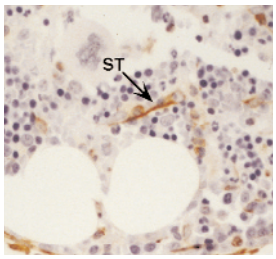
See article on pages 1209–1220

Pregnancy and lactation induce dramatic changes to the function and morphology of the mammary gland, including proliferation of breast epithelial cells, elaboration of secretory ducts and alveoli, and onset of milk production. Once nursing ceases, all of these changes are reversed, returning the tissue to a condition much like its prepregnant state. In the involuting mammary of the mouse, the death of differentiated epithelial cells occurs in at least two defined stages: an initial wave of apoptotic cell death that peaks 2 days after weaning, and a later stage, beginning a few days later, when the extracellular matrix surrounding the mammary alveoli begins to break down. Song and colleagues report here that the first wave of apoptosis requires the binding of the cell death regulatory protein Fas to its ligand, FasL. By following the expression of Fas and FasL, the authors show that, although the two proteins are each present at different times before, during, and after pregnancy, they are not coexpressed at substantial levels until the early phase of involution. Furthermore, in mutant animals lacking one or the other of these gene products, epithelial cell death is delayed by several days. Song et al. conclude that the initial phase of apoptosis is lacking in these animals, consistent with reports that other players in the Fas-dependent cell death pathway are active during the early phase of involution. More work in this system will be required to learn how the Fas-independent cell death seen in the mutant animals relates to the normal second phase of involution.



Explaining the persistence of hepatitis C

See article on pages 1239–1249



Hahn and colleagues previously showed that of the major hepatitis C virus (HCV) proteins, only one, the nucleocapsid core protein, can confer on a carrier virus the ability to evade the host animal's immune system. Because this finding might help to explain the long-term viral persistence that makes hepatitis C intractable, this group has now screened for lymphocyte proteins that can interact specifically with the viral core protein. Here they show that gC1qR, a receptor for complement protein C1q, is one such binding partner for core protein, and they identify the domains required on each protein that allow for this interaction. C1q, the endogenous ligand for this receptor, is also known to suppress T cell function, although C1q and the HCV core protein bind distinct sites on the gC1qR. Kittlesen et al. confirm that purified core protein blocks T-cell proliferation in a cell culture assay. They also show that blocking antibodies to the core protein or to gC1qR can abolish this effect, raising the question of why endogenous anti-core antibodies do not have a similar protective effect in infected individuals. Nonetheless, in light of the earlier finding that an active T-cell response to core protein correlates with suppression of HCV, the present work may open the door to developing immune or other therapies for chronic hepatitis C.