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In This Issue

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Insulin's effects on circulating angioblasts (See article on pages 571–578.) Here, Schatteman and coworkers report that neovascularization is delayed in animals with type I diabetes, pointing to the potential value of cell-based therapies for ischemic injury in diabetic individuals. After ischemia in the limbs, CD34+ circulating endothelial precursors (angioblasts) are recruited, allowing new vessels to form and increasing the perfusion of the injured site. Schatteman et al. show that the recovery of blood flow is accelerated by providing exogenous CD34+ cells to diabetic mice but not to similarly injured mice whose pancreatic function is normal, presumably because the latter have adequate numbers of active angioblasts for efficient recovery. In vitro angioblast differentiation is sensitive to levels of insulin but apparently insensitive to glucose levels, suggesting that hyperglycemia per se does not affect this process but that hypoinsulinemia might. This appears to be the case in humans as well: Differentiated angioblasts from type I diabetic subjects cannot be maintained efficiently in culture, but similar cells from healthy donors survive and proliferate. Because cells from type II diabetics – who, unlike type I diabetics, are normally hyperinsulinemic – are similar to healthy subjects' cells, it appears that exposure to insulin prior to harvesting has lasting effects on the viability or function of these cells. For more on the effects of diabetes on […]

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By John Ashkenas, Science Editor

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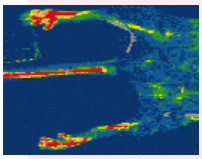
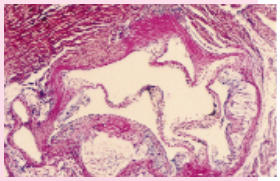
Here, Schatteman and coworkers report that neovascularization is delayed in animals with type I diabetes, pointing to the potential value of cell-based therapies for ischemic injury in diabetic individuals. After ischemia in the limbs, $CD34^+$ circulating endothelial precursors (angioblasts) are recruited, allowing new vessels to form and increasing the perfusion of the injured site. Schatteman et al. show that the recovery of blood flow is accelerated by providing exogenous $CD34^+$ cells to diabetic mice but not to similarly injured mice whose pancreatic function is normal, presumably because the latter have adequate numbers of active angioblasts for efficient recovery. In vitro angioblast differentiation is sensitive to levels of insulin but apparently insensitive to glucose levels, suggesting that hyperglycemia per se does not affect this process but that hypoinsulinemia might. This appears to be the case in humans as well: Differentiated angioblasts from type I diabetic subjects cannot be maintained efficiently in culture, but similar cells from healthy donors survive and proliferate. Because cells from type II diabetics — who, unlike type I diabetics, are normally hyperinsulinemic — are similar to healthy subjects' cells, it appears that exposure to insulin prior to harvesting has lasting effects on the viability or function of these cells. For more on the effects of diabetes on tissue repair, this time involving keratinocytes in a model of cutaneous wound healing, see Frank et al. (pages 501–509).



PPARγ agonists block coronary artery disease

(*See article on pages 523–531*)

Drugs that activate the transcription factor peroxisome proliferator–activated receptor γ (PPARγ) provide the first means available to treat insulin resistance and to prevent diabetes and its cardiovascular complications. As several of the authors in the current Perspective series note, such drugs exert diverse effects in numerous cell types, so their use in treating atherosclerosis presents complex questions. Here, however, Li et al. confirm that such drugs are likely to be beneficial. In male LDL receptor–deficient mice (but, curiously, not in female mice of the same disease-prone strain), structurally distinct PPARγ agonists cause a dramatic reduction in the expression of inflammatory markers in the artery wall and the size of atherosclerotic lesions. These effects also correlate with improved insulin sensitivity, indicating that some of the benefits of the treatment may relate to systemic effects on energy metabolism. The absence of a protective effect in females is unexpected, given previous experience with these drugs, but the current data may be partly explained by an increase in atherogenic lipoprotein levels in treated female mice, perhaps related to drug interactions with endogenous estrogen. The authors also note that many of the relevant human studies involved postmenopausal women, who would not be subject to such an effect.



Sexually dimorphic gene expression in the heart

(*See article on pages 589–597*)

Whereas the sex-specific effects on heart disease of PPARγ agonists, noted by Li et al., are largely unexplained, Kadokami and colleagues now report a mechanism underlying another aspect of the cardiac pathophysiology that differs between male and female mice. These authors have developed a transgenic mouse strain in which the cytokine TNF-α is constitutively expressed in cardiac muscle. Although the transgene is expressed equally in male and female hearts, males of this strain are far more prone to die of congestive heart failure within their first 6 months. Kadokami et al. report that two receptors for this cytokine, TNFR1 and TNFR2, are more highly expressed in male cardiac tissue, both in transgenic and in wild-type strains; other cytokines and cytokine receptors are normally expressed at similar levels in males and females. This previously unsuspected sexual dimorphism can have functional consequences, since cardiac explants from wild-type males generate the second messenger ceramide in response to TNF-α at twice the rate seen in female explants. Hence, the level of receptor expression appears to be limiting for responses to this cytokine and could account for the male-specific mortality in the transgenic mice. Since cardiac muscle generally becomes exposed to high levels of TNF-α only during heart failure, the dimorphic expression of the receptors cannot explain differences in incidence of such episodes. However, if it proves to apply to humans as well as mice, it might go far toward explaining the consistently poorer survival rates after a heart attack for men, relative to women who either produce or receive estrogen.