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In This Issue

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Hormonal regulation of hepatic glucose production by fat cells (See article on pages 1875–1881.) Since the discovery of the satiety factor leptin, it has been clear that fat should be regarded not solely as a storage site for lipids, but also as an endocrine tissue. The discovery of resistin and Acrp30 extended this finding and showed that multiple hormones secreted by adipocytes can profoundly alter energy metabolism in various tissues. Here, Combs and colleagues elucidate the primary metabolic effect of the latter hormone, also known as adiponectin. From earlier work, it appears that Acrp30 can sensitize animals to insulin's effects on the liver and muscle; Combs et al. now find that when healthy mice are maintained for short periods at constant blood glucose and insulin levels, the presence of exogenous Acrp30 decreases hepatic glucose production. In particular, the authors show that glucose-6-phosphatase (G6Pase), an enzyme critical for hepatic glucose release, is less active in animals treated with exogenous Acrp30. At least during the 90-minute test period, this hormone has no appreciable effect on other aspects of energy metabolism, such as the rate of glucose consumption. Interestingly, Combs et al. show that mRNAs for G6Pase and a related gluconeogenic enzyme decline in the liver of Acrp30-treated animals. However, the effect on G6Pase activity seen in their physiological measurements probably occurs too […]

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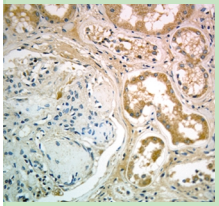
Glomerular fibrosis now all the RAGE

(See article on pages 1853–1863.)

Oldfield et al. have identified a crucial pathological role for the multifaceted receptor RAGE — the receptor for advanced glycation end products (AGEs). AGEs form spontaneously when reducing sugars react with lysine residues on extracellular proteins. Even in healthy individuals, they accumulate inexorably during aging, but this progression is particularly swift in diabetics, reflecting the higher glucose levels in their tissues during periods of hyperglycemia. Activation of RAGE by these ligands is associated with several disorders, and Oldfield and colleagues now propose that tubulointerstitial disease, a form of diabetic nephropathy, should be added to this list. The cell-type transformation, or trans-differentiation, of normal kidney epithelial cells to collagen-secreting myofibroblasts is thought to drive this disease process. The authors show that RAGE signaling is required to induce trans-differentiation in cultured kidney cells and rat kidney tissue, and probably also in the diabetic human kidney. In the rat system, a drug that removes sugar adducts on proteins prevents trans-differentiation. This treatment also limits the secretion of TGF-β, which appears to mediate the effects of RAGE signaling on the phenotype of kidney cells. Consistent with this model, Oldfield et al. note that another inhibitor of AGE formation has also been reported to suppress RAGE-dependent activation of TGF-β in diabetic animals.



MPO generates nitrotyrosine in the subendothelial space

(See article on pages 1759–1770.)

Inflamed vascular tissue provides another example of a pathological form of protein modification occurring outside the cell. Vascular ECM components, particularly the prominent interstitial protein fibronectin, readily undergo tyrosine nitration during the inflammatory process. Still, as Baldus et al. note, the mechanism of this post-translational modification and the basis of its localization have been uncertain. Striking images in their present report show that the oxidative enzyme myeloperoxidase (MPO) colocalizes with fibronectin in inflamed vessels. This finding provides a ready explanation for the specific accumulation of nitrotyrosine residues in the subendothelial space, but it also raises the question of how an enzyme produced in the lumen of the vessel by activated neutrophils can then traverse the endothelium. Baldus et al. show that following degranulation of neutrophils, MPO associates with endothelial heparan sulfate proteoglycans and is transcytosed to the basolateral side of cultured endothelial cells (and to the corresponding ablumenal face of the endothelium in vivo). There, MPO, activated by peroxide, oxidizes free nitrite, which can then modify neighboring ECM proteins. Whereas nitrotyrosine has previously been thought to form spontaneously in the presence of the peroxynitrite radical (itself a secondary product of the simple signaling molecule NO), the present work places a new emphasis on MPO as a mediator of tyrosine nitration. Indeed, the authors show that, following treatment to provoke systemic inflammation, the liver of animals lacking MPO is significantly poorer in protein nitrotyrosine adducts than wild-type liver. The physiological significance of MPO transcytosis remains unresolved, but the MPO knockout mouse may provide a useful system for testing the role of localized protein nitration in the onset, progression, or termination of vascular inflammation.