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In This Issue

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IGF-binding protein-5 as a growth factor in its own right (See article on pages 73–81.) Growth factors do not typically diffuse freely through intact tissues, but interact with a variety of soluble and insoluble macromolecules in the extracellular space. Binding of these factors to the ECM or to other extracellular proteins can alternately interfere with or potentiate their biological activity, and such interactions provide a reservoir of growth factors that may be released in a regulable manner. The insulin-like growth factors IGF-I and -II bind with high affinity to at least six distinct IGF-binding proteins (IGFBPs). In bone, IGFBP-5 tilts the metabolic balance toward bone formation. Since IGF-I exerts a similar effect, it has been thought that the effect of the binding protein is mediated by one or both of the IGFs, but now, Miyakoshi and colleagues have tested this idea by studying the effects of IGFBPs-4 and -5 in mutant osteoblasts that produce neither of the IGFs. As anticipated, IGFBP-4 inhibits osteoblast function in wild-type but not IGF-deficient cells. Surprisingly, however, these mutant cells respond as robustly as wild-type to added IGFBP-5, promoting cell growth, alkaline phosphatase activity, and osteocalcin expression. Miyakoshi et al. discuss this finding in light of reports that osteoblasts express a receptor for IGFBP-5, which appears to be distinct from the IGF-I receptor. They conclude […]

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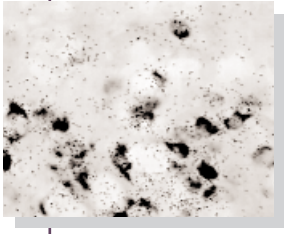
Converging pathways regulate energy metabolism

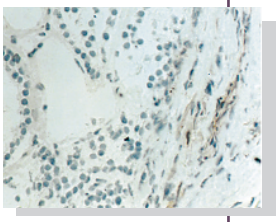
(See article on pages 111–120)

The satiety factor leptin is produced by body fat and acts in the brain to modulate feeding behavior and energy expenditure. Harris et al. have examined the transcriptional regulation of *TRH*, a leptin-sensitive gene whose product, thyrotropin-releasing hormone, ultimately regulates thyroid hormone levels. They argue here that two distinct leptin-dependent signaling pathways activate the *TRH* promoter in the paraventricular nucleus of the hypothalamus (PVH). Leptin was already known to act in the neighboring arcuate nucleus to induce the expression of α-melanocyte stimulating hormone (α-MSH), which acts on the cells of the PVN. In addition, the authors also show that PVH neurons express the leptin receptor and certain downstream signaling molecules that could allow for direct induction of TRH by leptin. Working in heterologous cells, Harris et al. have reconstructed the signaling pathways that lead to TRH induction, and they show that both direct leptin effects and α-MSH–mediated effects converge on the *TRH* promoter. Leptin- and α-MSH–dependent signals act at distinct promoter elements, which can be mutated to block either the direct or the indirect pathway. The authors also show that thyroid hormone can suppress the production of TRH, at least in cultured cells, establishing yet another class of stimulus that might act on the *TRH* promoter, which must integrate the various signals to modulate energy metabolism.



Chemokines and angiostasis

(See article on pages 53–63)



Chemokines were originally defined by, and are still best known for, their ability to activate the motility of leukocytes. Still, certain other cell types can bind these factors, and there are hints that chemokines can regulate other cellular functions. In particular, various members of the CXC family of chemokines can activate or suppress angiogenesis through signaling pathways that are not yet well described. Romagnani et al. report here that human microvascular endothelial cells from a variety of normal tissues express the chemokine receptor CXCR3, several of whose ligands are strongly angiostatic. Interestingly, cultured endothelial cells are heterogeneous with respect to CXCR3 expression. The authors show that these cells fail to express the CXCR3 mRNA while they remain in the G0 or G1 phases of the cell cycle, but that the receptor is induced in parallel with the cell cycle regulator cyclin A. In vivo, the proportion of CXCR3-positive cells is generally low and increases during inflammation, when the normally quiescent endothelial cells enter the cell cycle. This cell cycle dependence is not seen in other cell types that express the CXCR3 receptor. Because endothelial cells induce receptor expression in this manner, they become sensitive to the antiproliferative effect of specific chemokines precisely when they are dividing or preparing to divide. Presumably, this pathway provides an additional mechanism for the physiological control of angiogenesis, one that might be exploited to block tumor angiogenesis.