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In This Issue

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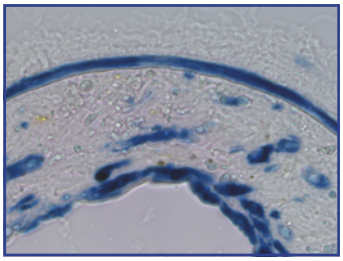
Osteoblast Atf4 in control of energy metabolism Osteoblasts were recently shown to be endocrine cells that affect energy metabolism through secretion of osteocalcin. Yoshizawa and colleagues therefore hypothesized that osteoblasts express a regulatory gene(s), probably one encoding a transcription factor, that controls this osteoblast function (2807–2817). Initial analysis of mice lacking activating transcription factor 4 (Atf4), which is expressed predominantly in osteoblasts, indicated they have lower fat mass and blood glucose levels than control mice. The lower blood glucose levels were due to increased pancreatic β cell area, β cell proliferation, and insulin expression and secretion. Sensitivity to insulin in the liver, fat, and muscle was also enhanced. Several genetic experiments established that lack of Atf4 in osteoblasts was central to the altered metabolic phenotype of Atf4–/– mice. For example, mice with osteoblast-specific deletion of Atf4 exhibited the same altered metabolic phenotype as Atf4–/– mice. Mechanistic analysis in vitro and in vivo indicated that Atf4 controls energy metabolism by binding to the Esp gene promoter, thereby increasing expression of a gene product that decreases osteocalcin bioactivity. As Atf4 in osteoblasts was already known to regulate bone formation and mineralization, the authors conclude that Atf4 regulates many, but not all, osteoblast functions. miR-143/145 micromanage VSMC phenotype VSMCs exhibit phenotypic plasticity, switching from a contractile phenotype to a synthetic phenotype in response […]

miR-143/145 micromanage VSMC phenotype



VSMCs exhibit phenotypic plasticity, switching from a contractile phenotype to a synthetic phenotype in response to environmental cues, many of which (such as hypertension and arteriosclerosis) are associated with human disease. Despite the physiologic and pathologic importance of the VSMC phenotypic switch, the mechanisms that control it have not been well defined. However, Boettger, Beetz, and colleagues have now determined that microRNAs miR-143 and miR-145 regulate acquisition and/or maintenance of the contractile phenotype of VSMCs in mice (2634–2647). Initial analysis indicated that after E8.5, expression of miR-143 and miR-145 became confined to mouse smooth muscle cells. The function of these microRNAs was identified by analyzing miR-143/145–deficient mice, which had dramatically reduced numbers of contractile VSMCs and increased numbers of synthetic VSMCs in the aorta and femoral artery. Mechanistically, miR-143 and miR-145 were found to differentially regulate many VSMC phenotype modulators, including angiotensin-converting enzyme. Thus, their absence resulted in almost complete loss of ligand-controlled arterial smooth muscle contractility in vitro. In vivo, it led to substantially reduced blood pressure and promoted the formation of neointimal lesions. The authors therefore suggest that miR-143/145 might provide new therapeutic targets to enhance vascular repair and attenuate vascular disease.

Maternal immunity not all good for a fetus

A fetus does not mount an immune response to maternal proteins that cross the placenta and is said to exhibit immunologic tolerance. It was therefore assumed that if a fetus was transplanted with non–MHC-matched hematopoietic cells (allogeneic hematopoietic cells) in utero, the cells would not be rejected by the immune system, providing a viable approach for treating congenital hematologic disorders. However, studies in a mouse model of in utero hematopoietic cell transplantation (IUHCT) indicate that most fetal recipients of allogeneic hematopoietic cells lose their transplanted cells 3–5 weeks after IUHCT. In this issue, Merianos and colleagues have identified an immune mechanism responsible for graft failure in this model of IUHCT (2590–2600). Specifically, pups that lost their transplanted cells had a higher frequency of alloreactive T cells than pups that maintained their cells. Surprisingly, however, this fetal alloreactive T cell response was triggered by maternal alloantibodies acquired from breast milk. Further analysis led the authors to conclude that activation of the maternal immune system by IUHCT leads to production of the maternal alloantibodies that ultimately trigger graft rejection. The authors therefore conclude that in the absence of a maternal immune response, a fetus will remain immunologically tolerant of allogeneic transplanted hematopoietic cells, leaving open the door to potential clinical application.

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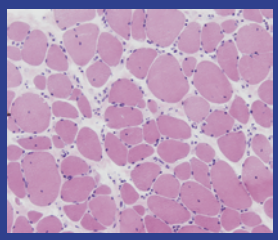
Osteoblasts were recently shown to be endocrine cells that affect energy metabolism through secretion of osteocalcin. Yoshizawa and colleagues therefore hypothesized that osteoblasts express a regulatory gene(s), probably one encoding a transcription factor, that controls this osteoblast function (2807–2817). Initial analysis of mice lacking activating transcription factor 4 (Atf4), which is expressed predominantly in osteoblasts, indicated they have lower fat mass and blood glucose levels than control mice. The lower blood glucose levels were due to increased pancreatic β cell area, β cell proliferation, and insulin expression and secretion. Sensitivity to insulin in the liver, fat, and muscle was also enhanced. Several genetic experiments established that lack of Atf4 in osteoblasts was central to the altered metabolic phenotype of *Atf4*$^{-/-}$ mice. For example, mice with osteoblast-specific deletion of *Atf4* exhibited the same altered metabolic phenotype as *Atf4*$^{-/-}$ mice. Mechanistic analysis in vitro and in vivo indicated that Atf4 controls energy metabolism by binding to the *Esp* gene promoter, thereby increasing expression of a gene product that decreases osteocalcin bioactivity. As Atf4 in osteoblasts was already known to regulate bone formation and mineralization, the authors conclude that Atf4 regulates many, but not all, osteoblast functions.

New gene linked to muscular dystrophy and lipodystrophy



One cause of autosomal-dominant limb-girdle muscular dystrophy is an inherited deficiency in caveolin-3 (CAV3). Caveolin proteins are the main protein components of caveolae, plasma membrane invaginations involved in many cellular processes, although other proteins (including polymerase I and transcript release factor [PTRF]) are thought to be important for caveolae formation and caveolin stabilization. In this issue, Hayashi and colleagues report that five nonconsanguineous Japanese patients with generalized lipodystrophy and muscular dystrophy, whose muscles showed CAV-3 deficiency but no *CAV3* mutations, had *PTRF* gene mutations (2623–2633). Two frame-shift mutations were identified in the five patients, and when the resulting mutant forms of PTRF were expressed in mouse myoblasts, the mutant proteins failed to localize correctly and associate with caveolin proteins. Functionally, this probably causes the reduction in caveolae density observed in biopsied skeletal muscle from the patients. The authors therefore conclude that PTRF is crucial for caveolae formation and proper caveolin localization and that disease in the five patients assessed in the study is likely to be a result of caveolin deficiencies secondary to the *PTRF* gene mutations.