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In This Issue

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Distinct roles for VEGF isoforms in bone development. During bone formation, epiphyseal cartilage is avascular until secondary ossification occurs. Vascularization of this maturing tissue relies on angiogenic recruitment from surrounding vessels. VEGF has previously been shown to be critical for metaphyseal bone vascularization and is now implicated as an angiogenic factor for epiphyseal vascularization. By generating mice that express specific splice forms of VEGF, Geert Carmeliet and colleagues determined that the soluble forms of VEGF are indispensable for proper epiphyseal cartilage development and chondrocyte development, as well as survival (pages 188–199). Mice expressing only the matrix-bound form (VEGF188) but neither of the soluble forms (VEGF120 or VEGF164) had increased hypoxia and massive chondrocyte apoptosis in the epiphyseal cartilage, as well as dwarfed skeletal defects. Metaphyseal development appeared normal in these mice, demonstrating that different molecular processes requiring specific VEGF isoforms regulate epiphyseal and metaphyseal vascularization. See figure Impaired inhibition of TGF-β signaling contributes to fibrotic disorders. Although the pathogenesis of scleroderma has not been entirely elucidated, the disease typically results in fibrosis of the skin and internal organs. Hironobu Ihn and colleagues aimed their studies at the TGF-β1 cytokine pathway and showed that cytokine signaling is a key player in the molecular pathogenesis of this fibrotic disorder (pages 253–264). TGF-β1 is regulated by a negative feedback loop whereby an inhibitory […]

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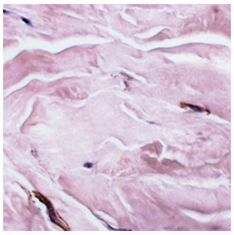
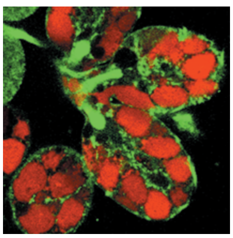
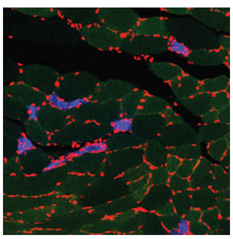


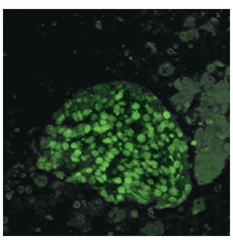
Impaired inhibition of TGF-β signaling contributes to fibrotic disorders. Although the pathogenesis of scleroderma has not been entirely elucidated, the disease typically results in fibrosis of the skin and internal organs. Hironobu Ihn and colleagues aimed their studies at the TGF-β1 cytokine pathway and showed that cytokine signaling is a key player in the molecular pathogenesis of this fibrotic disorder (pages 253–264). TGF-β1 is regulated by a negative feedback loop whereby an inhibitory molecule, Smad7, blocks transcriptional activation in the pathway and promotes degradation of the TGF-β receptor complex. Comparisons between normal and scleroderma fibroblasts reveal that Smad7 expression is elevated in diseased fibroblasts, but its ability to promote degradation of the receptor complex through recruitment of ubiquitin ligases, termed Smurfs, is impaired. These results further implicate autocrine TGF-β signaling in the pathogenesis of scleroderma.



OspC in *B. burgdorferi* guides tick salivary gland invasion. Lyme disease is caused by the bacterium *Borrelia burgdorferi*. When a tick harboring the bacterium engorges, initiating transmission to a new host, *B. burgdorferi* downregulates expression of OspA; this mediates adherence of the spirochete to the tick gut and begins expression of a different outer surface protein, OspC. To determine the function of OspC, Erol Fikrig and colleagues generated a strain of *B. burgdorferi* deficient in OspC (pages 220–230). These spirochetes were able to survive and multiply in feeding ticks; however, they were unable to invade tick salivary glands. The results agreed with their findings that OspC binds to tick salivary gland extracts and that antibody inhibition of OspC reduces the invasion of salivary glands by *B. burgdorferi*. These insights into pathogen transmission might offer new approaches to reducing the incidence of Lyme disease.



Na/Ca exchange by Ncx3 is vital to skeletal muscle physiology. Intracellular calcium levels are essential to physiologic signaling processes such as synaptic transmission in nerve cells and excitation-contraction coupling in muscle. As a Na/Ca exchanger, Ncx3 is able to control calcium levels in the cell by efflux or influx at the plasma membrane. To elucidate the physiologic role of Ncx3 in skeletal muscle, Sophie Sokolow and colleagues generated mice lacking the *Ncx3* gene (pages 265–273). They observed localized muscle fiber necrosis and impaired neuromuscular transmission and attributed this to reduced Na/Ca exchange activity and altered calcium homeostasis in the absence of Ncx3. These defects at the cellular level manifested as muscle weakness and ease in fatigability in $Ncx3^{-/-}$ mice, further emphasizing a key role for Ncx3 in skeletal muscle physiology.



Independent roles for insulin. Cellular proliferation and metabolism are both known to be regulated by insulin, but whether or not these two processes are interdependent has remained questionable. Domenico Accili and colleagues addressed this question by generating mice with variable degrees of cellular mosaicism for null insulin receptor (Insr) alleles (pages 209–219). They characterized strains with 80% (Δ80) and 98% (Δ98) reduction in Insr levels and found that both strains exhibited severely stunted growth. Interestingly, Δ80 mice were hypoglycemic, and Δ98 mice were hyperglycemic. Further analyses enabled them to conclude that growth was more sensitive to Insr depletion than insulin-dependent metabolism and that these two processes are regulated independently. The phenotype of the Δ80 mice modeled a human disorder, known as leprechaunism, caused by Insr mutations, implicating differential insulin receptor sensitivity in various tissues as a contributor to pathogenesis of the disease.