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# In This Issue

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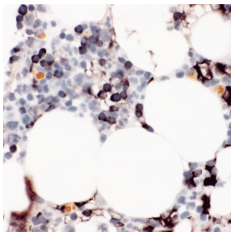
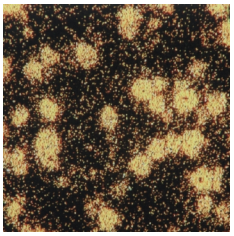
**In this issue**

Getting more mileage out of cord blood. Human cord blood contains hematopoietic precursor cells that can rapidly proliferate and mostly immature lymphocytes that are less likely to trigger graft-versus-host disease after transplantation into HLA-mismatched recipients. One obstacle to using cord blood more routinely as a source of stem cells in transplantation patients is the amount of blood required. Clinical trials have established that higher numbers of nucleated and CD34+ cells are associated with improved transplantation outcome. However, the amount of blood collected from cords is often not sufficient for an adult recipient. On pages 1165–1174, Irwin Bernstein and colleagues report their success in expanding cord-blood-derived precursors in vitro under defined conditions. Exposing cord blood progenitors to immobilized Delta-1 ligand in cytokine-containing serum-free cultures induced a 100-fold increase in CD34+ cells as well as high numbers of other myeloid and lymphoid precursors. The resulting cell populations exhibited enhanced repopulation ability in the marrow or thymus of immune-deficient mice, suggesting that similar strategies could enhance the utility of cord blood as a source for hematopoietic stem cell transplantation in humans.pH-specific receptors mediate acid-evoked pain in humans. Local infection, muscle ischemia, and inflammation evoke pain in humans concurrent with local tissue acidosis. This drop in extracellular pH is believed to activate specific nociceptors: proton-sensitive vanilloid receptor subtype-1 (VR1) and acid-sensing ion channels (ASICs) […]

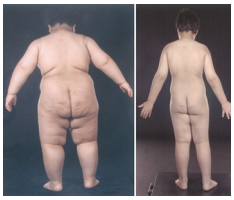




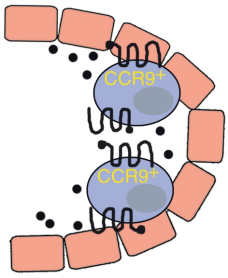
**Getting more mileage out of cord blood.** Human cord blood contains hematopoietic precursor cells that can rapidly proliferate and mostly immature lymphocytes that are less likely to trigger graft-versus-host disease after transplantation into HLA–mismatched recipients. One obstacle to using cord blood more routinely as a source of stem cells in transplantation patients is the amount of blood required. Clinical trials have established that higher numbers of nucleated and $CD34^+$ cells are associated with improved transplantation outcome. However, the amount of blood collected from cords is often not sufficient for an adult recipient. On pages 1165–1174, Irwin Bernstein and colleagues report their success in expanding cord-blood-derived precursors in vitro under defined conditions. Exposing cord blood progenitors to immobilized Delta-1 ligand in cytokine-containing serum-free cultures induced a 100-fold increase in $CD34^+$ cells as well as high numbers of other myeloid and lymphoid precursors. The resulting cell populations exhibited enhanced repopulation ability in the marrow or thymus of immune-deficient mice, suggesting that similar strategies could enhance the utility of cord blood as a source for hematopoietic stem cell transplantation in humans.



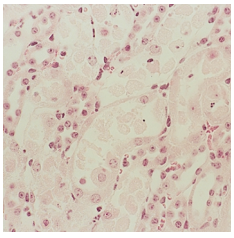
**pH-specific receptors mediate acid-evoked pain in humans.** Local infection, muscle ischemia, and inflammation evoke pain in humans concurrent with local tissue acidosis. This drop in extracellular pH is believed to activate specific nociceptors: proton-sensitive vanilloid receptor subtype–1 (VR1) and acid-sensing ion channels (ASICs) — the main detectors of pain-producing stimuli. In vitro experiments reveal that activation of the VR1 channel requires severe acidification, below pH 6.0, suggesting that another sensor may be involved in nociception at less acidic levels. On pages 1185–1190, Shinya Ugawa and colleagues investigate the effects of ASIC inhibitor amiloride and VR1 inhibitor capsazepine on acid-evoked pain at various pH levels. After direct infusion of acidic solution (pH 6.0) into human skin, amiloride potently blocked proton-induced pain, while capsazepine did not. At lower pH, amiloride was less effective in reducing pain and capsazepine had a partial blocking effect. These results suggest that ASICs are the leading acid sensors in human nociception, while VR1 mediates nociception during severe acidification.



**Human leptin-replacement therapy.** The leptin-deficient *ob/ob* mouse presents with a multitude of phenotypic abnormalities including severe obesity, infertility, immune system dysfunction, and limited growth — all reversible following subcutaneous leptin administration. Much less is known about human leptin deficiency. I. Sadaf Farooqi and colleagues previously reported on two children with congenital leptin deficiency suffering from hyperphagia and severe obesity. These conditions were reduced following one year of subcutaneous recombinant human leptin therapy in the older subject. The authors now report (pages 1093–1103) on the status of these two children, as well as a third, after up to 50 months of chronic r-metHuLeptin therapy. Treatment induced a decrease in caloric intake and fat mass (while lean mass increased in keeping with increased linear growth). Surprisingly, the basal metabolic rate in all subjects remained unchanged and allowed appropriately timed pubertal development. Reversal of severely impaired lymphocyte function suggests that leptin is a key molecule in both $CD4^+$ T cell development and function, and raises the possibility of leptin-replacement therapy for other immunodeficiencies.




**Selective recruitment of lymphocytes to the gut.** Given the continuous exposure of the intestine to foreign antigens, it is not surprising that large numbers of T lymphocytes are recruited from the blood to the intestine. In addition to lymphocytic expression of adhesion molecules that direct lymphocyte migration from the blood into intestinal tissues, evidence is mounting that chemokines and their receptors may also be involved. On pages 1113–1121, William Agace and colleagues demonstrate that expression of the chemokine receptor CCR9 is selectively maintained on $CD8\alpha\beta^+$ T cells activated in murine gut-associated lymphoid tissues and that neutralization of the CCR9 ligand CCL25 with a blocking antibody inhibits the accumulation of these cells in the small intestinal epithelial compartment. These results provide direct in vivo demonstration of a functional role for a chemokine/receptor pair in lymphocyte localization to the intestinal mucosa.



**Not just neutrophils responsible for IL-18–mediated renal failure.** Acute tubular necrosis is the predominant pathological process in animal models of ischemic acute renal failure (ARF) and in post-transplantation ARF in humans. Caspase proteases are involved in apoptotic as well as necrotic cell death, and several lines of evidence suggest that caspases play a role in ischemic ARF in mice. Charles Edelstein and colleagues have previously shown that mice lacking proinflammatory caspase-1 are protected from ischemic ARF and that this is (at least in part) due to lack of caspase activation of IL-18. Caspase-1 knockout mice also show less neutrophil infiltration. In a new set of experiments (pages 1083–1091), the researchers tested the potential of a new caspase inhibitor to protect against ischemic ARF and further examined the role of neutrophils in damage to the kidney. The experiments demonstrated efficacy of the drug in mice and revealed a novel mechanism of IL-18–mediated renal toxicity that acts independently of neutrophils.