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In This Issue

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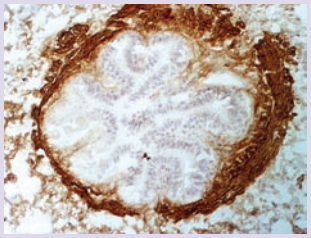
Factoring transcription factors into atheroprotection Despite the presence of systemic risk factors such as hypercholesterolemia, discrete regions of the arterial vasculature remain relatively resistant to the development of atherosclerotic lesions. These regions have distinct hemodynamic properties that appear to be beneficial, but the molecular mechanisms underlying this local protection are not clear. Now, Parmar et al. examine the coordinated regulation of the specific transcriptional programs in the endothelial lining that confer protection against atherogenesis (pages 49–59). The authors show that the transcription factor KLF2 (Kruppel-like factor 2) is selectively induced in endothelial cells by arterial waveforms that mimic the hemodynamic environment present in the atheroprotected regions of the human carotid artery. This flow-mediated increase in KLF2 expression occurs via a MEK5/ERK5/MEF2 signaling pathway. Increased KLF2 activity regulates endothelial transcriptional programs that control inflammation, thrombosis and hemostasis, vascular tone, and angiogenesis. The authors also show that KLF2 modulates endothelial activation. These data suggest that KLF2 acts as a mechanically activated transcription factor that is important for integrating multiple endothelial functions associated with regions of the arterial vasculature that are relatively resistant to atherogenesis. Transplantation patients: enigmas or chimeras? Transplantation medicine is potentially useful in treating a variety of diseases, but the need for life-long immunosuppression limits clinical efficacy. Strategies have been designed to induce transplant-specific immunologic unresponsiveness, but this apparent tolerance […]

Factoring transcription factors into atheroprotection



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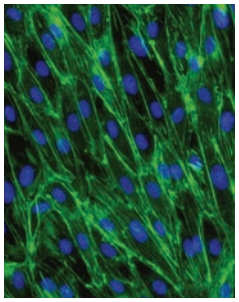
New therapy for asthma is a breath of fresh air

Glucocorticoids are the treatment of choice for many people with asthma. These steroids boost the production of IL-10, an antiinflammatory cytokine with many beneficial actions. But some asthmatic patients are resistant to glucocorticoid therapy because their T cells do not produce IL-10 in response to steroids. Now, Xystrakis et al. investigate IL-10–producing Tregs in the context of human allergic and asthmatic disease (pages 146–155). The authors show that IL-10–secreting Tregs inhibit cytokine production by previously activated allergen-specific Th2 cells. They also show that pretreating T cells with IL-10 or adding vitamin D3 to the cell cultures can reverse the defect and enhance IL-10 production by Tregs from asthmatic patients who were resistant to glucocorticoid therapy. These manipulations increase IL-10 production to levels comparable to those observed in patients who do respond well to therapy. IL-10 increases glucocorticoid receptor expression, and the authors propose that this is the mechanism by which IL-10 overcomes the glucocorticoid-resistant patient defect in IL-10 synthesis. Thus, IL-10–producing Tregs may help treat human allergic diseases and reverse glucocorticoid resistance in asthma.



Transplantation patients: engimas or chimeras?

Transplantation medicine is potentially useful in treating a variety of diseases, but the need for life-long immunosuppression limits clinical efficacy. Strategies have been designed to induce transplant-specific immunologic unresponsiveness, but this apparent tolerance seldom persists long term. Rare cases of stable allograft acceptance after discontinuation of immunosuppression are often accompanied by macro- or microchimerism, defined as greater than or less than 1% donor cells in the blood, respectively. For stable graft acceptance without immunosuppression, donor cell–specific T cell unresponsiveness needs to be maintained long term. In this issue, Bonilla et al. investigate whether persistence of donor cells is the cause or the consequence of long-lasting CTL unresponsiveness (pages 156–162). The authors used an experimental system of lymphohematopoietic engraftment across a minor histocompatibility antigen barrier. They show that donor cell microchimerism drives continuous clonal deletion of graft-specific $CD8^+$ T cells and maintains long-lasting donor cell–specific T cell unresponsiveness in the recipient. These findings provide a strong rationale for induction of lymphohematopoietic donor cell chimerism simultaneously with solid organ engraftment and highlight a need to monitor donor cell microchimerism in transplant recipients.

Standing up to paraplegia with gene therapy

Hereditary spastic paraplegia (HSP) is a neurodegenerative disorder caused by progressive loss of motor and sensory axons and characterized by weakness, spasticity, and impaired function of the lower limbs. HSP sufferers are ultimately confined to a wheelchair, and currently there is no cure for the disease. A proportion of autosomal recessive inherited cases of HSP are due to loss-of-function mutations in the gene encoding paraplegin, a mitochondrial energy-dependent protease. In this issue of the JCI, Pirozzi et al. used a mouse model of HSP to test the ability of adenoassociated viral vectors to deliver paraplegin to spinal motor neurons and to rescue axons from degeneration (pages 202–208). Intramuscular delivery of paraplegin rescued both the neuropathological and the clinical phenotype of the mice for up to 10 months after a single administration. The treatment rescued peripheral nerve mitochondria from the pathology that is characteristic of the disorder and improved motor function. These data show that gene transfer may be useful for patients with axonal neuropathies of the peripheral nerves due to loss of function of a known gene. Further, the data provide strong evidence that adenoassociated virus vectors can be successfully employed for retrograde delivery of an intracellular protein to spinal motor neurons, opening new avenues for several hereditary axonal neuropathies of the peripheral nerves.