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In This Issue

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The explosive effects of nitroglycerin in Asians Glyceryl trinitrate (GTN), also known as nitroglycerin, is often used to treat angina and heart failure. Recently, mitochondrial aldehyde dehydrogenase-2 (ALDH2) was shown to be responsible for the formation of NO, a vasorelaxing metabolite required for GTN efficacy. In this issue, Li et al. show that a common G-to-A polymorphism in exon 12 of ALDH2, which results in a Glu504Lys replacement, virtually eliminates ALDH2 activity and subsequent NO production, especially in Asian populations (pages 506–511). This polymorphism is associated with a lack of efficacy of GTN. Following this lead, the authors found that the catalytic efficiency of GTN metabolism of the Glu504 protein is approximately10-fold higher than that of the Lys504 enzyme. The authors conclude that the presence of the Lys504 allele in Asians is, in part, responsible for the failure to respond to nitroglycerin. This factor may warrant consideration when administering nitroglycerin to Asian patients, 30–50% of whom possess the inactive ALDH2 allele. Taxing the esophagus with eotaxin-3 Eosinophilic esophagitis (EE) is an emerging worldwide disease with symptoms similar to those of gastroesophageal reflux disease (GERD), with vomiting, abdominal pain, and failure to thrive in children, but EE patients do not respond to anti-GERD therapy. While the disorder has been linked to allergy, there is a paucity of information concerning its pathogenesis […]

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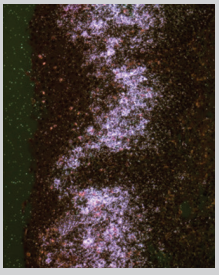
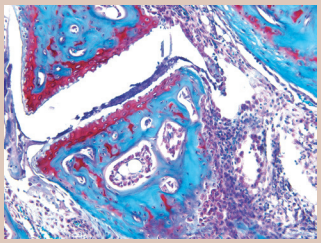
Taxing the esophagus with eotaxin-3

Eosinophilic esophagitis (EE) is an emerging worldwide disease with symptoms similar to those of gastroesophageal reflux disease (GERD), with vomiting, abdominal pain, and failure to thrive in children, but EE patients do not respond to anti-GERD therapy. While the disorder has been linked to allergy, there is a paucity of information concerning its pathogenesis and diagnosis. In their current study, Blanchard and colleagues took an empiric approach involving DNA microarray analysis to identify an EE gene–expression profile that would distinguish EE patients from healthy controls and individuals with non-EE chronic esophagitis (pages 536–547). The resulting profile was remarkably conserved between EE patients despite their age, sex, and atopic status. The authors discovered that the most induced transcript in the EE patients was eotaxin-3, a potent eosinophil chemoattractant and activating cytokine. Levels of esophageal eotaxin-3 mRNA and protein strongly correlated with disease severity. Furthermore, a single nucleotide polymorphism in *eotaxin-3* conferred disease susceptibility. The importance of this pathway was demonstrated in mice harboring a genetic deletion in the eotaxin receptor (CCR3), as the *Ccr3*$^{-/-}$ mice were protected from experimental EE. Taken together, the results of this study strongly implicate eotaxin-3 as a critical effector molecule and genetic risk factor for EE.





Arthritis wagers on T-bet

Inflammatory arthritis results as the consequence of systemic autoimmune responses arising from both the adaptive and innate immune systems. Wang and colleagues now report an essential role for the adaptive immune system transcription factor T-bet in directing DCs during the development of collagen antibody–induced arthritis (pages 414–421). Given the prominent role of T-bet in directing Th1 differentiation, a contribution of T-bet to adaptive immune system–mediated autoimmunity was expected. However, the authors found that the primary site for T-bet activity in controlling inflammation occurred early and resided in the DC population. Mice lacking T-bet had markedly reduced joint inflammation at both early and late time points, and mice deficient in T-bet without T or B cells (*Rag2*$^{-/-}$ mice) were essentially resistant to disease. Adoptive transfer of WT DCs, but not *T-bet*$^{-/-}$ DCs, into the protective environment of a *Rag2*$^{-/-}$*T-bet*$^{-/-}$ host restored inflammatory arthritis. These studies show that both proinflammatory mediators secreted by DCs and the ability of DCs to prime naive T cells were compromised in the absence of T-bet. Therefore, T-bet plays a vital function in DCs and links innate and adaptive immunity to regulate inflammatory responses. T-bet could provide an attractive new target for therapy in inflammatory arthritis.

Tlx: the new angiogenic fulcrum

A delicate balance of pro- and antiangiogenic activities regulates the formation of vascular networks. While hypoxia-inducible factors (HIFs) act as the primary proangiogenic switches, not much is known about other players — especially those that regulate formation of matrix scaffolds that can promote adhesion and migration of endothelial cells. Uemura et al. now identify a new signaling pathway underlying the proangiogenic switch in the mouse retina (pages 369–377). The authors start with the observation that expression of glial fibrillary acidic protein (GFAP), a marker for astrocyte-lineage cells that is regulated by HIF, is suppressed in proangiogenic retinal astrocytes. They then describe how Tlx, a transcriptional repressor of GFAP, plays an indispensable role in maintaining proangiogenic activity. Tlx expression by retinal astrocytes is controlled by oxygen concentration and is rapidly downregulated upon contact with blood vessels. In *Tlx*$^{-/-}$ mice, retinal astrocytes maintain VEGF expression; however, the extracellular assembly of fibronectin matrices is severely impaired, leading to defective scaffold formation and a complete failure of normal retinal vascular development. Based on these findings, the authors propose that Tlx is a new molecular angiogenic switch whose expression rapidly evokes a series of cellular responses against hypoxia.