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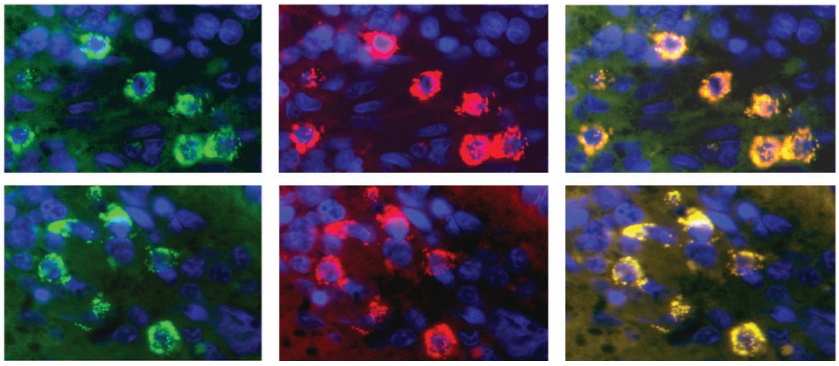

Mechanism of ECMO-related systemic inflammatory response syndrome

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Extracorporeal membrane oxygenation (ECMO) is used in neonates and young children with respiratory failure, congenital heart disease, or overwhelming sepsis. On one hand, the use of ECMO has resulted in a large decrease in mortality. On the other, there is a high incidence of systemic inflammatory response syndrome (SIRS), an uncontrolled inflammatory response that is associated with neutrophil activation, widespread microvascular damage, and multiorgan dysfunction that can last for many days.

Because SIRS is characterized by an inflammatory "storm," McIlwain and colleagues sought to understand the relationship between circulating inflammatory cytokines and SIRS. They originally hypothesized that inflammatory cytokines were produced *de novo* by inflamed tissues. However, surprisingly, their study showed that the increases in plasma tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) were too rapid to be explained by *de novo* synthesis in inflamed tissues. Further work showed that mucosa-associated mast cells were likely to be responsible for the release of pre-formed stores of TNF-α and IL-8 in response to ECMO. The authors' results suggest that plasma inflammatory cytokines might be useful as biomarkers for the severity of SIRS and response to treatment. Furthermore, given that mast cell degranulation appears to lie at the heart of SIRS pathogenesis, drugs that stabilize mast cells or antibodies that neutralize TNF-α could be beneficial in the prevention or treatment of SIRS.

Protection from ischemia by erythropoietin

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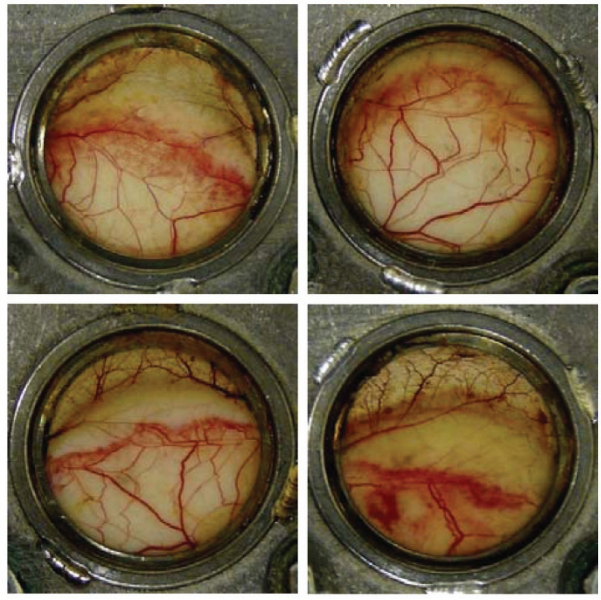
Pathologists are intimately familiar with the toll that ischemic damage takes on soft tissue. Amputations for ischemic limbs and removal of nonviable surgical flaps are far too common, reminding us of the need to address this important clinical problem. There is increasing evidence suggesting that erythropoietin (EPO), the main regulator of erythropoiesis, has tissue-protective properties in a variety of ischemic tissues, including heart, brain, liver, kidney, and skeletal muscle, that are independent of erythropoiesis. Among the possible mechanisms for mediating tissue protection are inhibition of apoptosis, anti-inflammatory effects, increased vascular endothelial growth factor (VEGF), and production of vasodilators such as nitric oxide (NO). To confirm and understand the mechanistic basis of tissue protection by EPO, Rezaeian and co-workers studied how EPO protects musculocutaneous tissues in a mouse model of surgically induced ischemia.

Their study showed that EPO was indeed capable of protecting musculocutaneous tissue from ischemic damage. The effect appeared to be mediated predominantly by microvascular dilatation related to NO production by endothelial NO synthase (NOS). Cotreatment with EPO and L-Name, an NOS antagonist, diminished the benefits of EPO, whereas bevacizumab, an anti-VEGF monoclonal antibody, did not inhibit the protective effects of EPO. Further studies using additional models to explore the efficacy of EPO and further delineate its mode of action in the prevention and treatment of tissue ischemia are clearly warranted.



NKT cell immune suppression by FTY720

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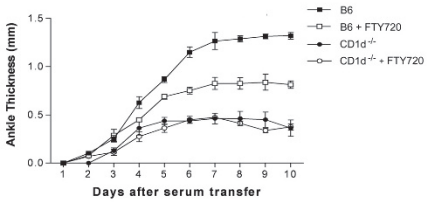

The cellular immune response is complex and orchestrated by different subsets of T cells. NKT cells are a distinct class of T cells that recognize glycolipid antigens complexed with CD1d. Upon activation, they secrete interleukin-4 and interferon-γ, which contribute to the regulation of innate and adaptive immune responses. They play important roles in a variety of immune responses and can promote immune-mediated diseases. Therefore, it would be advantageous to manipulate NKT cell activity. FTY720 is a potent immune suppressant that is phosphorylated *in vivo* and acts as a high-affinity agonist for S1P receptors, which are important for trafficking T and B cells between the lymphoid organs and the circulation. Recent evidence suggesting that S1P receptors play a role in migration and function of NKT cells prompted Hwang and colleagues to explore the effects of FTY720 on NKT cells.

They discovered that although FTY720 decreased the production of cytokines from NKT cells, it had a minimal effect on NKT cell migration. This is in contrast to the effect on T cells; FTY720 decreases T-cell migration. Because NKT cells are involved in immune-mediated diseases, the authors investigated the effect of FTY720 on NKT cells in antibody-induced joint inflammation in a rodent serum transfer arthritis model. They showed that NKT cells migrated into the joint normally but produced fewer cytokines, resulting in suppression of arthritis. These results support the use of FTY720 or other NKT-cell inhibitors in the treatment of NKT-cell immune-mediated disorders.

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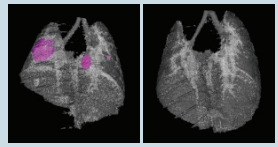
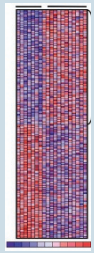
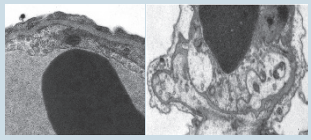


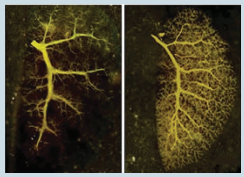
NF-κB in pulmonary adenocarcinoma Lung cancer is the leading cause of cancer deaths worldwide in both men and women; adenocarcinoma is the most common subtype. Approximately 20–30% of pulmonary adenocarcinomas harbor oncogenic Kras mutations, while approximately 50% of non-small-cell lung carcinomas have inactivating mutations in p53. Overexpression of oncogenic Ras is known to activate NF-κB, while p53 antagonizes NF-κB signaling. In a recent letter in *Nature*, Meylan and colleagues hypothesized that activation of endogenous Kras through oncogenic activation or deletion of p53 might activate NF-κB signaling. They demonstrated that oncogenic activation of Kras cooperated with loss of p53 to activate NF-κB signaling both *in vitro* and *in vivo*. Furthermore, inactivation of NF-κB inhibited both tumor initiation and tumor maintenance. These results suggest that targeting the NF-κB signaling pathway could be a useful strategy in the treatment of pulmonary adenocarcinoma with activated RAS and loss of p53.
Nature 2009;462:104–107; doi:10.1038/nature08462



TBK1 is required for *KRAS*-activated cancers Oncogenic activation of *KRAS* is common in a wide array of aggressive human cancers. Unfortunately, targeting *KRAS* therapeutically has been largely ineffective. In a recent letter in *Nature*, Barbie and colleagues took a synthetic lethal approach with RNA interference libraries to identify other proteins in *KRAS*-driven cancers that might be useful as therapeutic targets. Using this approach, they showed that *KRAS*-driven cancers depend on TBK1 for their survival. Given that TBK1 is a noncanonical IκB kinase, this suggested that TBK1 acted through NF-κB signaling, which was confirmed by gene-expression signature analysis in *KRAS*-activated cell lines and *KRAS*-activated human cancer specimens. Inhibition of NF-κB signaling by IκBα super-repressor induced cell death specifically in cells containing mutant *KRAS*. Together, these data indicate that TBK1 and NF-κB signaling proteins are high-priority therapeutic targets in *KRAS*-driven cancers.
Nature 2009;462:108–112; doi:10.1038/nature08460



Important role for histones in the pathogenesis of sepsis Recombinant human activated protein C (APC) is approved by the US Food and Drug Administration for the treatment of severe sepsis. To understand the mediators of sepsis, Xu and colleagues, as described in a recent letter in *Nature Medicine*, examined the media of lipopolysaccharide (LPS) and interferon-γ-activated macrophages that had been treated with APC. They identified cleaved histones within the media of APC-treated macrophages but not in untreated controls. They found that histones H3 and H4 were highly toxic to endothelium but that the toxicity could be relieved by APC. Injection of histones into mice resulted in death at a high dose or a sepsis-like clinical picture at a lower dose. Cotreatment of mice with LPS and antibody to H4 rescued the mice from the effects of LPS, suggesting that anti-histone antibodies might be therapeutically useful in the treatment of sepsis.
Nature Medicine 2009;15:1318–1321; doi:10.1038/nm.2053



Notch3 signaling and pulmonary hypertension Pulmonary arterial hypertension (PAH) is characterized by extensive remodeling of small pulmonary arteries and arterioles, resulting in obliteration of the pulmonary arterial tree and leading to elevated pulmonary arterial pressure, right ventricular failure, and eventually death. Adult vascular smooth muscle cells (vSMCs) lie at the heart of the pathogenesis of PAH. Because Notch3 signaling has been implicated in controlling vSMC proliferation, Li and co-workers explored the roles of Notch3 in the pathogenesis of PAH in a recent article in *Nature Medicine*. They observed that NOTCH3 protein levels were elevated in human PAH patients and in rodent models of PAH. Furthermore, the levels of PAH correlated with disease progression. Finally, *Notch3*$^{-/-}$ knockout mice failed to develop PAH under hypoxic conditions in comparison with wild-type mice and *Notch3*$^{+/-}$ heterozygotes. This important study highlights the potential of Notch3 signaling for therapeutic intervention in PAH.
Nature Medicine 2009;15:1289–1297; doi:10.1038/nm.2021