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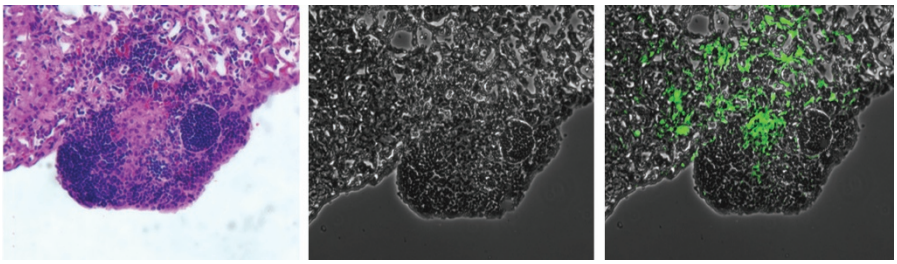

Coordination of granuloma formation by hemoxygenase-1

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Mycobacterium avium is a nontuberculous mycobacterial infection that can infect patients with underlying pulmonary conditions or immunodeficiency. It has been identified as an important human pathogen related to infection of AIDS patients. In response to mycobacterial infection, granulomas are formed that limit dissemination to multiple organs. Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that breaks down heme. HO-1, which is induced by a variety of stimuli, is known to be upregulated in lungs following mycobacterial infection.

To investigate the role of HO-1 in the host response to mycobacterial infection, Regev *et al* used a germline HO-1$^{-/-}$ knockout mouse. The mice that had been infected with *M. avium* failed to develop organized granulomas and had more severe and disseminated disease than did wild-type controls. Mechanistic studies revealed that monocytes produce HO-1 in response to *M. avium*. HO-1 expression regulates monocyte chemoattractant protein-1 (MCP-1) and expression of its receptor, chemokine receptor 2 (CCR2). MCP-1 is responsible for creating a chemoattractant gradient for immune cells from the periphery to the site of infection in order to develop functional tight granulomas to contain the infection. In the absence of HO-1, the immune response is disorganized and fails to produce tight granulomas. It is not clear whether HO-1 plays a role in granuloma formation in other diseases characterized by an immune response that generates granulomas. The HO-1$^{-/-}$ mouse model described by Regev *et al* should be of great importance in answering this question. It could also serve well as a model with which to study aspects of mycobacterial dissemination and therapeutic interventions.

Disruption of tight junction organization in cystic fibrosis

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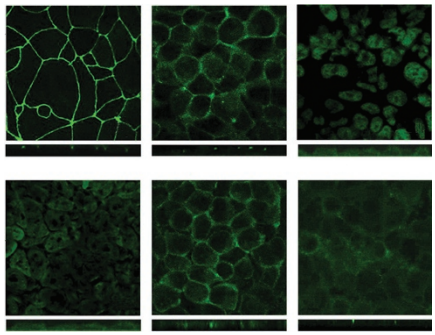

The genetic basis of cystic fibrosis (CF) is loss-of-function mutations in *CFTR* (cystic fibrosis transmembrane conductance regulator), which encodes a chloride channel. The pathological hallmark of CF is mucous plugs in several organs; these are thought to be due to a defect in mucociliary clearance and resultant opportunistic bacterial infections. The inflammatory response, which results in local destruction of vital tissues, is characterized predominantly by polymorphonuclear neutrophils (PMNs). NHERF1 (Na^+/H^+ exchange regulatory factor 1) interacts with CFTR through its PDZ (postsynaptic density 95/disc-large/zona occludens)-interacting domain. The most common *CFTR* mutation—a deletion of phenylalanine at amino acid 508 (F508del CFTR)—results in an improperly folded protein that is unable to reach the cell membrane, which is critical to normal function. Overexpression of NHERF1 leads to proper localization and chloride-channel function of F50del CFTR by tethering it to the cell membrane.

Because barrier function of epithelial cells is disrupted in CF, Castellani *et al* asked whether NHERF1 overexpression might correct abnormal barrier function in bronchial epithelial cells expressing F50del CFTR. They found that the tight junction (TJ) proteins were located predominantly in the nucleus and cytoplasm, in contrast to CFTR wild-type cells, in which the TJ proteins were localized to the cell membranes. Overexpression of NHERF1 corrected the localization defect in TJ proteins. Further analysis revealed that a multiprotein complex that was formed among CFTR, NHERF1, ezrin, and actin maintained TJ organization and barrier function. The authors suggest that defects in barrier function might be involved in facilitating access to organ-destructive PMNs.

Role of angiopoietin-like protein 2 in acute inflammation

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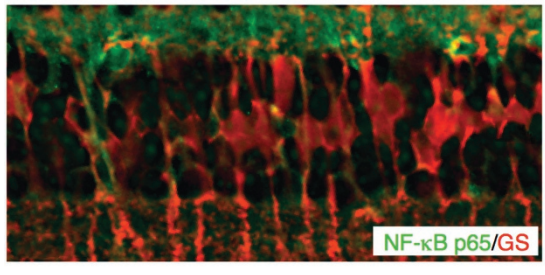
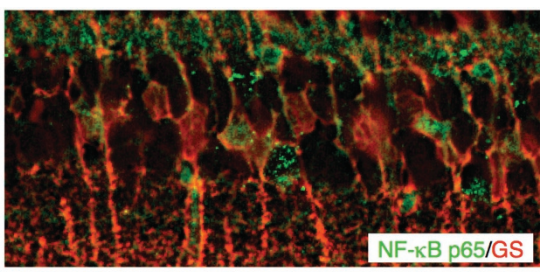
Acute inflammation is a primitive defense mechanism that lies at the heart of the early response to infection and tissue injury. Repeated or overly severe acute inflammation can result in excessive



tissue damage and has been implicated in the pathogenesis of a variety of diseases, including Behçet's disease, a rare systemic vasculitis involving mucous membranes that results in ulcers as well as in ocular impairment leading to uveitis. Endotoxin-induced uveitis is a bacterial endotoxin lipopolysaccharide (LPS)-induced model that is useful for studying uveitis. Angiopoietin-like protein 2 (Angptl2), which has roles in endothelial cell sprouting and vascular development, has recently been shown to be involved in chronic inflammation in the eye via signaling in endothelial cells. However, little is known about the role of Angptl2 in acute inflammation.

Kanda *et al* used EIU to discern the role of Angptl2 in acute inflammation in the eye. They demonstrated that Angptl2 is strongly and ubiquitously expressed in the retina and that LPS significantly induced expression of *Angptl2*. *Angptl2*$^{-/-}$ mice had blunted acute inflammation characterized by decreased leukocyte adhesion and infiltration. Mechanistic studies showed that acute inflammation mediated by Angptl2 signaled through α5β1 integrin, a receptor for Angptl2, which led to NF-κB activation through the canonical NF-κB pathway, resulting in transcription of several proinflammatory cytokines. Because it is difficult to target NF-κB directly, targeting Angptl2 might be useful in the treatment of disorders characterized by Angptl2-mediated acute pathologic inflammation. Further studies are required to determine whether Angptl2 plays a prominent role in mediating acute inflammation in other settings and diseases.



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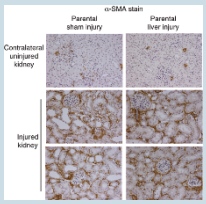
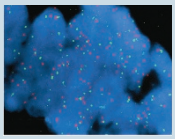
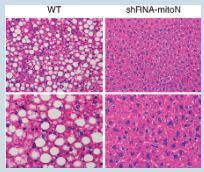


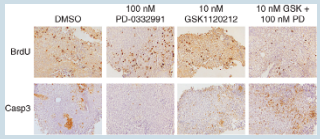
Epigenetic inheritance of resistance to hepatic fibrosis Although many patients with chronic liver disease have the potential to progress to cirrhosis, only a small percentage do so, which suggests that genetic factors influence the response to liver injury. Because epigenetic mechanisms have the potential to control adaptive mechanisms to hepatic fibrosis and are heritable through meiosis, Zeybel *et al*, as described in a recent article in *Nature Medicine*, asked whether environmentally induced adaptive traits could be transmitted between generations through heritable epigenetic signatures. Using a mouse model of carbon tetrachloride–induced fibrosis, they found that treated mice were able to transmit resistance to fibrosis through epigenetically controlled alterations in hepatic gene expression. Interestingly, their data suggest that hepatic myofibroblasts secrete factors that alter sperm to deliver the epigenetic reprogramming to offspring.
Nature Medicine 2012;18:1369–1377; doi:10.1038/nm.2893



SOX2 amplification in small-cell lung cancer Advances in high-throughput technologies used to characterize the genomic landscape of cancer genomes are yielding a breathtaking amount of data. In a recent letter in *Nature Genetics*, Rudin *et al* describe comprehensive genomic analysis of small-cell lung cancer (SCLC) via exome capture sequencing, chromosomal copy-number analysis, and RNA sequencing. Of particular note was the finding that several mutations clustered in the SOX family of transcription factors. Additionally, *SOX2* was amplified in ~27% of the SCLC samples. Knockdown of *SOX2* in two cell lines with strong SOX2 expression reduced cell proliferation. Finally, four gene fusions were identified involving kinase genes (*NPEPPS-EPHA6*, *SKP1-CDKL3*, *NEK4-SFMBT1*, and *ZAK-RAPGEF4*). These are particularly interesting because of the therapeutic potential of targeting oncogenic kinase fusions. Further work will be required to determine the significance of targeting these kinase fusions.
Nature Genetics 2012;44:1111–1116; doi:10.1038/ng.2405



MitoNEET preserves insulin sensitivity in obesity To investigate the relationship between mitochondrial function, obesity, and type 2 diabetes mellitus (T2DM), Kusminski *et al*, as described in recent article in *Nature Medicine*, exploited the protein mitoNEET, which controls mitochondrial iron content. Using genetically engineered mouse models, they were able to manipulate the expression of mitoNEET in white adipose tissue. Overexpression of mitoNEET resulted in decreased mitochondrial function and increased adipose tissue accumulation. Paradoxically, the increased adipose tissue proved to be an adaptive response to preserve insulin sensitivity. This study highlights how recent advances in understanding cellular metabolism are leading to profound insights into diseases such as T2DM and cancer. It is only a question of time before these insights can be leveraged therapeutically to treat, and possibly even cure, these diseases.
Nature Medicine 2012;18:1539–1549; doi:10.1038/nm.2899



Indirect targeting of NRAS signaling in melanoma Approximately 15–20% of melanomas harbor activating *NRAS* mutations, making targeting of NRAS a viable therapeutic strategy. However, direct targeting of NRAS has proven difficult. Using genetically engineered mouse models and a systems-biology approach, as described in a recent article in *Nature Medicine*, Kwong *et al* demonstrated that simultaneously targeting both mitogen-activated protein kinase and cyclin-dependent kinase 4 (CDK4) achieved results comparable to those with genetic ablation of *NRAS*. They developed a gradient model to explain this result. Their model postulates that canonical NRAS-MAPK signaling regulates its two major downstream phenotypes—cell survival and proliferation— at different thresholds. Targeting MAPK inhibits cell survival, but it fails to inhibit proliferation, which occurs at a higher threshold. Inhibition of proliferation is achieved by adding a CDK4 inhibitor. The conceptual and experimental framework described in this paper will be invaluable in developing targeted cancer therapies.
Nature Medicine 2012;18:1503–1510; doi:10.1038/nm.2941