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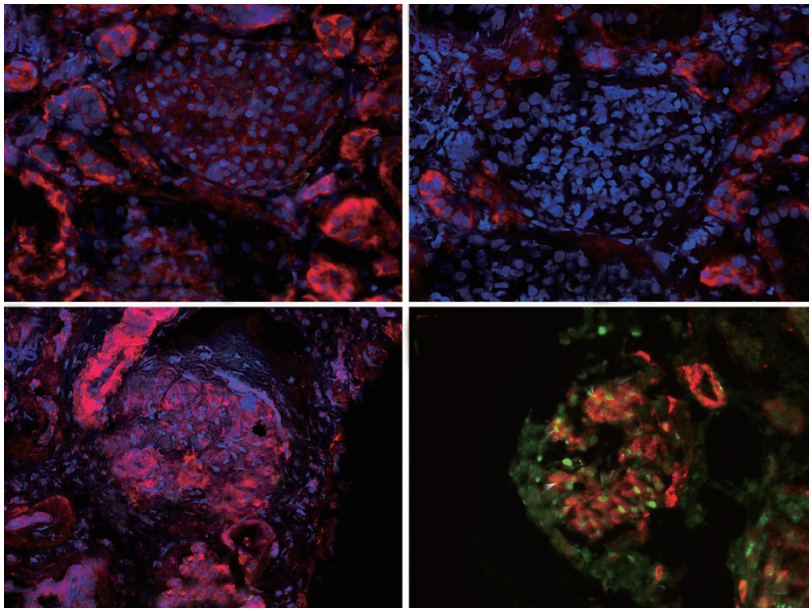

Candidate genes involved in early diabetic glomerulopathy

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Diabetic nephropathy is the leading cause of end-stage renal disease. Podocyte injury appears to be an important initiating event in diabetic nephropathy. Damaged podocytes eventually undergo apoptosis, which results in glomerular damage and subsequent inflammation and tubulointerstitial scarring characteristic of diabetic nephropathy. Alterations in several signaling pathways have been implicated in the molecular pathogenesis of diabetic podocyte injury. To further understand the pathways involved in podocyte injury, Jain and colleagues performed gene expression studies on podocyte cultures that were exposed to high glucose for up to 2 weeks.

The authors identified three genes that showed consistent changes at both 1 and 2 weeks after exposure to high glucose and that had defined annotation information. Follow-up validation studies focused primarily on endothelial lipase, which was transcriptionally upregulated in podocytes after exposure to high glucose. Endothelial lipase is a member of the lipase gene family and an important regulator of high-density lipoprotein (HDL) and inflammation by promoting monocyte adhesion to vascular endothelium. HDL, in particular, is linked to diabetes mellitus and inflammation, suggesting that endothelial lipase–mediated deregulation of HDL may be instrumental in the pathogenesis of diabetic glomerulopathy. Further studies are warranted to define the precise role of endothelial lipase in diabetic glomerulopathy. The authors also detected endothelial lipase in urine samples from patients with diabetic glomerulopathy, suggesting that urine endothelial lipase could be used diagnostically or as a biomarker for following the progression or treatment response of diabetic glomerulopathy.

CD44 exacerbates lethal pneumococcal pneumonia

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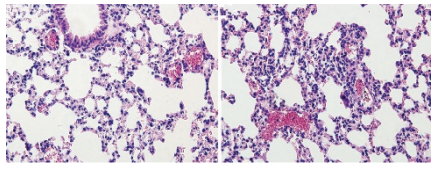
Streptococcus pneumoniae is the organism most commonly responsible for community-acquired pneumonia. With the increasing incidence of antibiotic resistance, it is important to understand the roles of host immune defenses in combating this often lethal infectious disease. CD44 is a transmembrane adhesion molecule that has important functions in innate and adaptive immune responses. It is known to be involved in the (sub)acute inflammatory response to both infectious and sterile pulmonary damage. To elucidate the functions of CD44 during *S. pneumoniae* infection, van der Windt and colleagues infected CD44-deficient knockout mice after infection with *S. pneumoniae*.

The host response to *S. pneumoniae* infection can be broken down into an acute response, which functions to eliminate invading organisms, and a late response, which clears pulmonary inflammation. Surprisingly, the authors found that lethal infections with *S. pneumoniae* were worse in CD44 knockout mice, indicating that CD44 facilitates *S. pneumoniae* infection. CD44 knockout mice infected with lethal amounts of *S. pneumoniae* survived longer than wild-type mice infected with the same dose. Examination of infected mice revealed that



the infection took longer to disseminate to organs beyond the lungs in CD44 knockout mice, which corresponded to increased numbers of pulmonary neutrophils. van der Windt and colleagues also provided evidence that CD44 helped in the late response to clear pulmonary infiltration. Because CD44 is known to bind and internalize hyaluronic acid (HA), which is a proinflammatory molecule, the authors suggested that CD44 clears HA during the resolution of inflammation.

Loss of Vhl decreases pancreatic β-cell mass during aging

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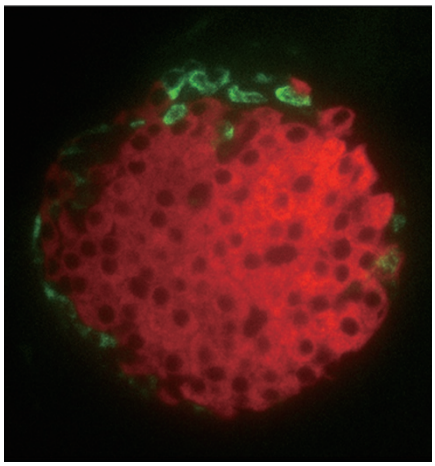
Type 2 diabetes mellitus (type 2 DM) has reached epidemic proportions throughout the world as a result of changes in diet and activity. The two hallmarks of type 2 DM are

insulin resistance and β-cell dysfunction. After development of insulin resistance, β-cells attempt to compensate by increasing β-cell mass. However, increasing insulin resistance can eventually outstrip



the ability of the pancreas to increase its β-cell mass. Previous work showed that β-cell-containing human islets from patients with type 2 DM had a decrease in hypoxia inducible factor (HIF)-1α and HIF-1β expression, suggesting that HIF signaling was impaired in β-cells from patients with type 2 DM. The von Hippel–Lindau tumor-suppressor protein (VHL) is a negative regulator of HIF signaling because it functions to target HIF-1α for proteasomal degradation.

To investigate the dependence of pancreatic β-cells on HIF signaling, Choi and colleagues created a mouse model in which *Vhl* was specifically deleted in pancreatic β-cells. They hypothesized that enhanced HIF-1α stabilization and HIF signaling would enhance β-cell mass and improve glucose homeostasis. Contrary to what they expected, they found that β-cell mass decreased with age in their mouse model and that this was associated with loss of GLUT2 expression. They were able to improve glucose tolerance by treatment with exogenous erythropoietin, which restored GLUT2 expression. These results suggest that erythropoietin therapy may be of use in the treatment of type 2 DM.

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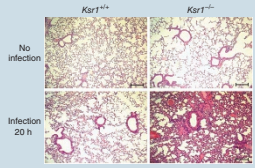
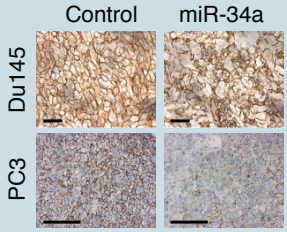
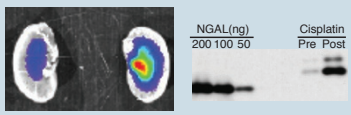


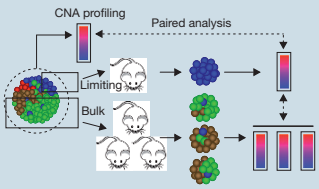
Kinase suppressor of Ras-1 plays a critical role in protection against pulmonary *Pseudomonas aeruginosa* infection *Pseudomonas aeruginosa*, a Gram-negative opportunistic pathogen, causes severe respiratory infections in immunocompromised patients. Kinase suppressor of Ras-1 (Ksr1) is a serine–threonine kinase that has important functions in many cellular contexts. Importantly, Ksr1-deficient mice fail to clear *P. aeruginosa* infections. In a recent article in *Nature Medicine*, Zhang *et al* investigated the mechanism by which Ksr1 clears *P. aeruginosa* infections. They demonstrated that Ksr1 enhances nitric oxide (NO)-activated killing of *P. aeruginosa* through the assembly of a protein complex including Ksr1, inducible NO synthase (iNOS), and heat shock protein-90. This result argues against the previous assumption that iNOS is activated primarily at the transcriptional level. Further studies are necessary to determine whether Ksr1 plays a role in protection against other pathogenic bacterial species.
Nature Medicine, published online 6 February 2011; doi:10.1038/nm.2296



miR-34a dictates metastatic phenotype in prostate cancer Eradication of cancer stem cells (CSCs) is crucial to cancer therapy because CSCs have been implicated in therapeutic resistance and metastasis. CD44 is enriched in tumor-initiating and metastatic prostate cancer cells and is considered a CSC marker. To determine whether CD44 is controlled by microRNAs (miRNAs), Liu *et al*, as described in a recent letter in *Nature Medicine*, compared miRNA expression in $CD44^+$ and $CD44^-$ prostate cancer cells. They found that miR-34a was underexpressed in $CD44^+$ prostate cancer cells, which suggests that CD44 might repress miR-34a expression. Expression of miR-34a in $CD44^+$ prostate cancer cells inhibited tumor formation and metastasis whereas knockdown of miR-34a in $CD44^-$ prostate cancer cells had the opposite effects. These results suggest that miR-34a might be useful in the treatment of prostate cancer.
Nature Medicine 2011;17:211–215; doi:10.1038/nm.2284



Evaluation of Ngal as a biomarker of acute renal injury using an Ngal reporter mouse Currently, the diagnosis of acute kidney injury (AKI) relies on the measurement of serum creatinine (sCr), a method that has several drawbacks. Seeking to validate a more useful marker of AKI, Paragas and colleagues, in work described in a recent technical report in *Nature Medicine*, developed an ingenious mouse model that expresses a luciferase-2 and mCherry fusion from the endogenous neutrophil gelatinase–associated lipocalin (Ngal) promoter. Their rigorous methodology clearly indicates that quantification of urine Ngal is likely to accurately reflect the extent of AKI. Furthermore, this study serves as a model that can be used in the validation of other disease-associated biomarkers.
Nature Medicine 2011;17:216–222; doi:10.1038/nm.2290



Therapeutic implications of tumor heterogeneity in leukemia-initiating cells in acute lymphoblastic leukemia The cancer stem cell and clonal evolution models offer competing views of how tumor cells evolve to generate tumor heterogeneity. To evaluate which model predominates in Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph^+ ALL), Notta *et al*, as reported in a recent article in *Nature*, integrated functional assays with genetic analysis to determine whether tumors contain genetically distinct clones of tumor-initiating cells. They demonstrated that Ph^+ ALL could be divided into two subgroups based on functional properties and specific genetic alterations. Subclone analysis indicated that progression could occur through linear or branching evolution. Their results suggest that cancer stem cell and clonal evolution models may eventually be combined into a single, more complex model that more accurately reflects the evolution of tumor heterogeneity. This has profound implications for cancer therapy.
Nature 2011;469:362–367; doi:10.1038/nature09733