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INSIDE LAB INVEST

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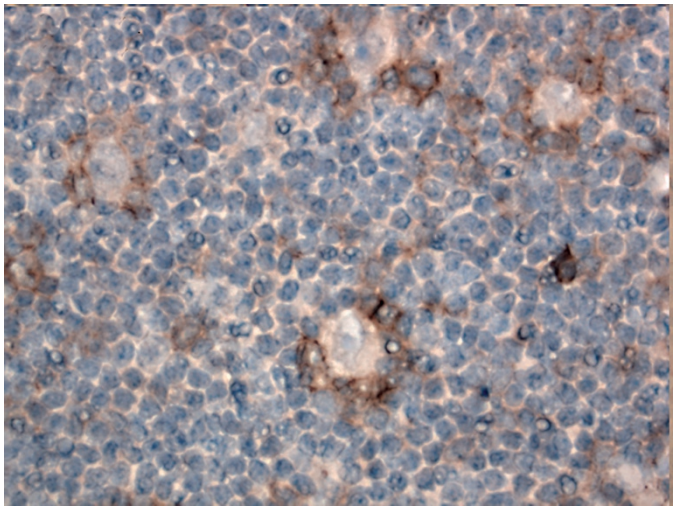

Further characterization of nodal CD4$^+$ T cells in classical Hodgkin's lymphoma

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There is good evidence that chemokines produced by the malignant cells of classical Hodgkin's lymphoma (cHL) attract reactive lymphocytes. These lymphocytes (mostly CD4$^+$) also secrete cytokines that may play a role in the proliferation of the malignant lymphoma cells. Reed–Sternberg cells in cHL often have CD4$^+$CD26$^-$ T cells attached to their surface, forming characteristic rosettes. The nature of these CD4$^+$CD26$^-$ T cells is not well understood. CD26 is an activation molecule involved in costimulation of T cells. In contrast to normal T cells, CD26 is not expressed in CD4$^+$ cells in cHL, even after stimulation. To further investigate the nature and function of these distinctive T lymphocytes in cHL, Ma *et al* analyzed the gene expression patterns of CD4$^+$CD26$^-$ and CD4$^+$CD26$^+$ T-cell subsets isolated from cell suspensions, obtained from either cHL or reactive lymph nodes, and either unstimulated or stimulated *in vitro*.

The results show that the CD4$^+$CD26$^-$ T-cell subset in cHL displays a distinct set of genes corresponding to a regulatory T-cell phenotype. Of interest, in contrast to T cells with the same phenotype obtained from reactive lymph nodes, the CD4$^+$CD26$^-$ cells of cHL appear to be anergic, since mRNA levels of most cytokine genes are not upregulated when the cells are stimulated *in vitro*. This cellular unresponsiveness may play an important role in the impaired immune response observed in cHL.

Diabetic nephropathy in the lepr$^{db/db}$ eNOS$^{-/-}$ mouse

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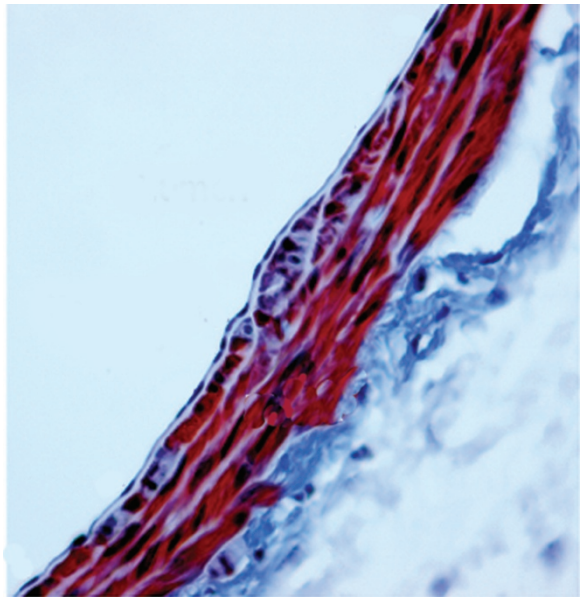
Our understanding of the mechanisms of diabetic nephropathy has been impaired by the lack of a good animal model. Previous work has shown that eNOS-deficient mice that develop either type 1 or 2 diabetes also develop renal lesions that mimic human diabetic nephropathy. A study by Mohan *et al* used a well-characterized model of type 2 diabetes, the lepr$^{db/db}$ mouse, and confirmed that eNOS deficiency resulted in diabetic nephropathy. More importantly, they showed that the macro- and microvasculature was differently affected. Atherogenic lesions in the aorta were observed only in response to mechanical injury and were associated with poor re-endothelialization. In contrast, spontaneous renal microvascular lesions developed in the double-deficient mice (lep$^{db/db}$ eNOS$^{-/-}$) in spite of fasting plasma glucose levels that were lower than those in lepr$^{db/db}$ mice. This indicates that eNOS is a critical determinant of hyperglycemia-induced organ-specific complications and their severity in diabetes The mechanism(s) by which the chronic hyperglycemia associated with eNOS deficiency leads to more severe effects in the glomerular microvasculature than in the aorta remains to be determined. This lepr$^{db/db}$ eNOS$^{-/-}$ mouse offers an excellent opportunity to explore these mechanisms and is a promising model with which to assess therapeutic interventions.



Detailed analysis of 17q12 amplicons in breast cancers

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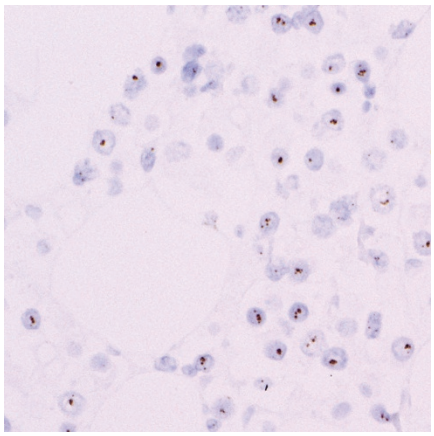

Breast cancers often harbor amplification of the epidermal growth factor receptor type 2 gene (*HER2,* also referred to as *HER2/neu*), which is considered a critical factor in predicting their prognosis and responsiveness to chemotherapy. Of interest, an adjacent gene on chromosome 17q12, the topoisomerase IIα gene (*TOP2A*), is similarly amplified in some cases. The *TOP2A* amplification appears to be relevant to poor sensitivity to anthracyclines (topoisomerase inhibitors). In this issue, Arriola *et al* describe a detailed genetic analysis of *HER2* amplicons in *HER2*-amplified and *HER2/TOP2A*-co-amplified breast cancers, using both *in situ* hybridization and *BAC*-based microarray approaches. The study refined the regions of the amplicons and identified other genes that are co-amplified and overexpressed with *HER2* or *HER2/TOP2A*. Although the *HER2/TOP2A* amplification in breast cancers has been described for years, this refining of amplicons through systematic analysis of a large number of cases provides important information about the variability in amplifications. New opportunities may thus arise for furthering understanding of breast cancer biology and development of better therapeutic strategies.

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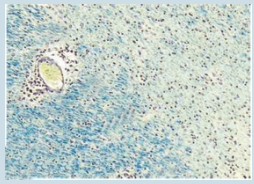
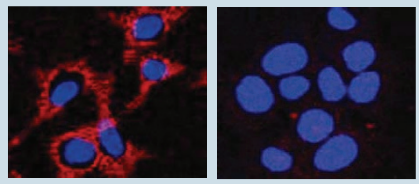
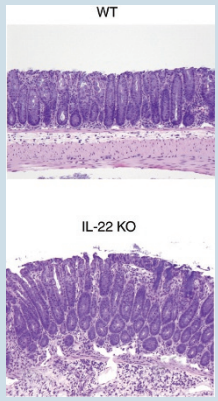


The plot thickens: role of coagulants in multiple sclerosis A clearer picture of the various stages of multiple sclerosis (MS) is necessary to better understand its pathogenesis and develop more effective treatments. A new study published in *Nature* has overcome discrepancies between mRNA and protein expression by using laser-capture microdissection and proteomic analyses to study lesions from three distinct pathological stages of MS: acute plaque, chronic active plaque, and chronic plaque. The data implicate tissue factor and protein C inhibitor in the chronic active plaque stage of the disease, suggesting the importance of coagulation dysregulation in MS. Consistent with this, a mouse model of MS showed evidence of reduced inflammation and disease severity when hirudin, an anticoagulant, was administered. In addition to shedding light on mechanisms of MS pathogenesis, this study demonstrates the utility of proteomic approaches using anatomic pathology specimens.
Nature 2008; 451:1076–1081; doi:10.1038/nature06559



HIF-1α puts a metastatic TWIST on hypoxia Hypoxia has been associated with tumor metastases, but the signaling pathways involved in this relationship are still being defined. A recent study in *Nature Cell Biology* has linked the hypoxia-induced transcription factor HIF-1α to TWIST, a transcription factor implicated in epithelial-mesenchymal transformation (EMT) and metastasis. HIF-1α upregulates TWIST expression, which ultimately drives conversion to the more invasive mesenchymal phenotype. Short interfering RNA knockdown of TWIST prevented the effects of hypoxia on TWIST expression, EMT, and metastasis. Conversely, co-expression of TWIST, HIF-1α, and Snail, another HIF-1α-induced regulator of EMT, correlated with cancer dissemination and poor prognosis. Thus, in many cases, the de-differentiated mesenchymal phenotype that pathologists recognize as a poor prognostic marker reflects expression of TWIST and Snail.
Nature Cell Biology 2008; 10:295–305; doi:10.1038/ncb1691

Genome-wide association studies provide triple threat for prostate cancer Three prostate cancer genome-wide association studies published in the March issue of *Nature Genetics* have identified candidate genes that could act as biomarkers of cancer risk. In addition to validating five previously identified risk loci, these studies found 10 additional loci associated with common single-nucleotide polymorphisms (SNP)s. Two studies implicated SNPs located near the *MSMB* gene on chromosome 10. This locus in particular seems to have a role in prostate cancer pathogenesis; the corresponding protein, β-microseminoprotein, is not expressed in androgen-insensitive cancer and shows promise as a biomarker for early stages of disease. Together with the discovery of additional variants, these studies provide a new, detailed picture of the effects of genetic variation on prostate cancer risk.
Nature Genetics 2008; 40:281–283; doi:10.1038/ng.89; *Nature Genetics* 2008; 40:310–315; doi:10.1038/ng.91; *Nature Genetics* 2008; 40:316–321; doi:10.1038/ng.90



Not just from memory, innate defenses of IL-22 fight intestinal bacteria Attaching and effacing bacterial pathogens such as *Escherichia coli* pose a major threat to human health. A study in *Nature Medicine* illustrates how the innate defenses of interleukin-22 protect the body from systemic infection. Using *Citrobacter rodentium* as a mouse model of enteropathogenic *E. coli* infection, animals deficient in T and B cells were found to be less susceptible to disease than IL-22 knockout mice. Dendritic cells acted as an essential source of this cytokine, explaining the nonessential nature of T and B cells in the response to this pathogen. Because IL-22 is widely expressed at mucosal surfaces, it may play a general role in the defense against bacterial pathogens at these sites.
Nature Medicine 2008; 14:282–289; doi:10.1038/nm1720