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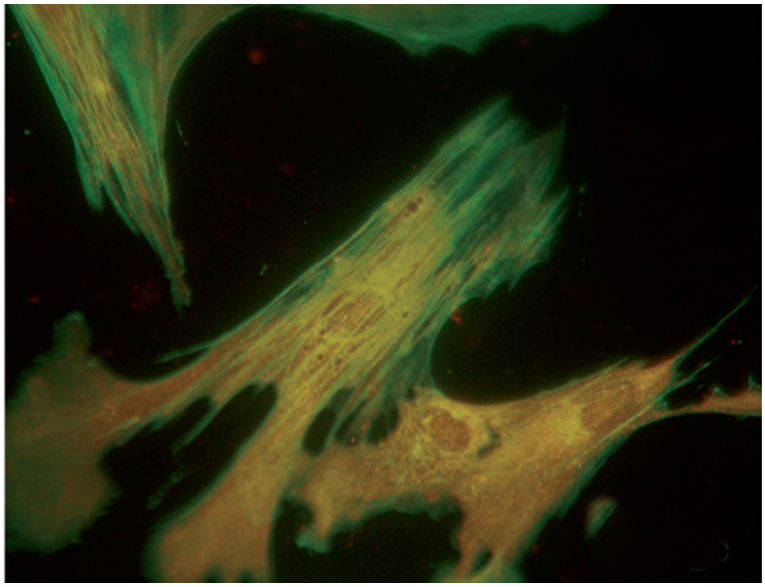

F_2-isoprostanes and thromboxane A_2 receptors on hepatic stellate cells

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Hepatic stellate cells (HSCs) are a major source of collagen biosynthesis during chronic liver injury and contribute to hepatic deposition of fibrous tissue. Activation of quiescent HSCs to become myofibroblasts, proliferate, and produce collagen is promoted, *in vivo*, by pro-inflammatory cytokines such as TGF-α. The process of HSC isolation for *in vitro* culture also leads to their activation. A 2005 publication by Comporti and colleagues demonstrated that F_2-isoprostanes also mediate HSC proliferation and collagen hyperproduction. F_2-isoprostanes are a key indicator of oxidative stress, as they are formed by free radical–catalyzed peroxidation of phospholipid-bound arachidonic acid. The 2005 report supported the concept that such chemicals were also mediators of tissue fibrogenesis. Since F_2-isoprostanes act through a thromboxane A_2 receptor (TxA_2r or TPr), it is now of value to determine whether such receptors are present on HSCs, and whether they mediate the activation process.

Accordingly, in this issue, Gardi *et al*. from the same research group first demonstrated that the F_2-isoprostane, 8-epi-$PGF_{2\alpha}$, and a TxA_2r-specific agonist, I-BOP, both stimulated synthesis of DNA by cultured HSCs, an effect almost completely inhibited by the TxA_2r-specific agonist SQ29548. They further demonstrated that 8-epi-$PGF_{2\alpha}$ stimulated HSC collagen synthesis and, through morphologic, biochemical, and kinetic studies, that a TxA_2r-type receptor was indeed present on activated HSCs. This is the first demonstration of TxA_2 receptors on HSCs. The potent effects of F_2-isoprostanes on HSCs, and the fact that their profibrogenic action can be inhibited by antagonists of TxA_2r receptors, point to a novel mechanism for both hepatic fibrogenesis and its potential treatment.

Molecular interactions of a 'small blue cell' tumor living large

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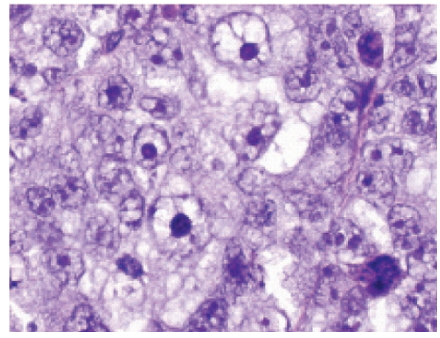
Medulloblastoma, the prototype of central nervous system embryonal neoplasms, is the most common malignant pediatric brain tumor. Arising in the cerebellum, such tumors display locally aggressive growth and a marked tendency to spread via cerebrospinal fluid pathways. Prognosis depends in large part on tumor stage at presentation and histologic subtype. The overall 5-year survival for classic and desmoplastic medulloblastomas is around 70% with current therapy (surgery, radiation therapy, and adjuvant chemotherapy), but histologic variants with poor prognosis are well described. Variants include tumors having 'large-cell/anaplastic' histology, which contrasts with the majority of medulloblastomas that present a 'small blue cell' appearance. While mechanisms of tumorigenesis are poorly understood, one possible clue is provided by studies showing that overexpression or amplification of c-Myc in medulloblastomas is associated with a large-cell phenotype and poor prognosis.



In this issue, Li *et al* present data supporting a functional/molecular interaction of hepatocyte growth factor (HGF)/c-Met signaling and c-Myc in the pathogenesis of large-cell medulloblastoma. These studies were initiated when the authors noticed that HGF-overexpressing DAOY cells (a medulloblastoma cell line) displayed a morphologic appearance that resembled c-Myc-overexpressing DAOY cells. The latter develop a large-cell phenotype that is similar to that of the large-cell/anaplastic human tumor. Using cell lines and primary medulloblastoma cultures, the authors show that c-Myc expression is regulated by HGF and

that HGF induces cell proliferation and apoptosis and regulates cell size in a c-Myc-dependent manner with Cdk2 kinase and Bcl-XL as downstream effectors. These findings provide further insights into medulloblastoma pathobiology, and suggest that an HGF/c-Myc pathway may be exploited in future therapies for this highly aggressive pediatric brain tumor.

Epigenetic research identifies a potential tumor suppressor gene in gastric cancer

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CpG-enriched regions, called CpG islands, are often found at the proximal promoter regions of protein-encoding genes. These CpG islands, which are usually free from DNA methylation, are thought to play an essential role in maintaining active genes or those competent for transcription. Some cancer cells demonstrate aberrant increases in DNA methylation at such CpG islands, leading to silencing of the genes. When this happens to tumor-suppressor genes, cancer obtains a growth advantage.

In this issue, Jung *et al* demonstrate that the *TSPYL5* gene that encodes testis-specific Y-like protein 5 would fit into this category in gastric cancers. The *TSPYL5* gene has a typical CpG island between its proximal promoter region and the first exon, which is not methylated in normal gastric tissues. However, in both gastric-cancer cell lines and primary gastric tumors, the CpG island of the *TSPYL5* gene is often hypermethylated, and its gene expression is silenced.

Moreover, the authors demonstrate that the gene had a growth-inhibitory effect on gastric-cancer cell lines, as seen with other tumor-suppressor genes. These indicate that the *TSPYL5* gene is a tumor-suppressor candidate in gastric cancer. Clearly, further studies are necessary to demonstrate that the loss of *TSPYL5* gene expression by aberrant DNA methylation is indeed critical for progression of gastric cancer.

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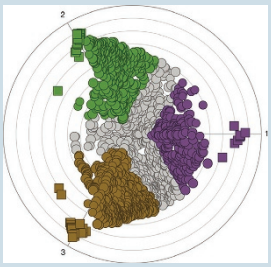
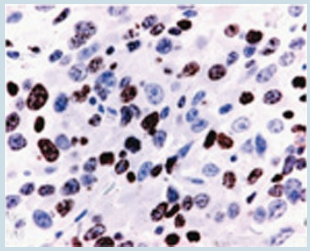
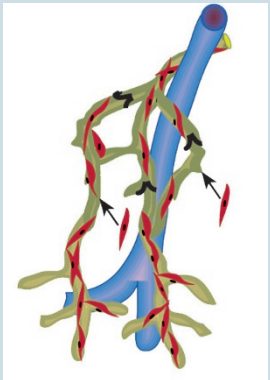


The malaria transcriptome reveals new insight into physiology Infection with *Plasmodium falciparum* results in a spectrum of disease that is partly dependent on host factors. However, variables in parasite behavior have been studied less. A recent report assessed transcriptional profiles of *P. falciparum* isolated from human samples. Computational analysis and comparison with previously described yeast expression profiles revealed three distinct *P. falciparum* physiological states characterized by glycolytic growth, a starvation response, or an environmental stress response. This improved understanding of the physiological diversity of the parasite may help to explain the range of outcomes after infection and lead to novel therapeutic approaches.
Nature 2007;450:1091–1095; doi:10.1038/nature06311

Keeping cancer in check Collaboration between American and Australian pathologists has provided a new understanding of the role of adaptive immunity in preventing expansion of occult cancers. Using a mouse model of chemical carcinogenesis, the group found that tumors are maintained at a small size by a variety of immune effectors via processes distinct from elimination and escape. The data suggest that the stable lesions, which consist of slowly proliferating transformed cells, escape to form large lesions only after they became less immunogenic as a result of editing. While fascinating from a pathogenic perspective, this study may also lead to an improved understanding of the interface between immune cells and tumors, as well as to new approaches to inducing tumor dormancy.
Nature 2007;450:903–907; doi:10.1038/nature06309



Promoter polymorphisms may provide clues to lupus pathogenesis A recent study has uncovered a genetic regulatory element that confers susceptibility to systemic lupus erythematosus (SLE). Analyzing both family-based and case–control study information, the group discovered a haplotype upstream of the *TNFSF4* gene that increases transcription and surface expression of the encoded protein, also known as OX40 ligand, on peripheral blood lymphocytes. OX40 ligand interactions with its receptor, *OX40* or *TNFRSF4*, are known to produce a co-stimulatory signal for $CD4^+$ T cells. Thus, increased OX40 ligand expression could contribute to SLE pathogenesis by increasing T cell–APC interactions or by altering the consequences of T-cell activation via *OX40*.
Nature Genetics, published online 2 December 2007; doi:10.1038/ng2007.47



Growth factors encourage lymphatic vessel maturation Radiation and surgical treatments for metastatic cancer often damage lymph nodes and vessels, causing lymphedema and leaving the patient without the protection of the lymphatic circulation against cancer recurrence. A paper published recently in *Nature Medicine* shows that treatment of mice with vascular endothelial growth factor-C (VEGF-C) and VEGF-D can induce lymphatic capillary growth following lymph node excision. After progressive remodeling and differentiation, these capillaries matured into functional collecting lymphatics. VEGF therapy also enhanced the effects of lymph node transplantation, including reconstitution of the immunological barrier against metastasis. Thus, VEGF-induced maturation of lymphatic vessels holds promise in enhancing tumor surveillance and therapy for lymphedema.
Nature Medicine 2007;13:1458–1466; doi:10.1038/nm1689