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INSIDE LAB INVEST

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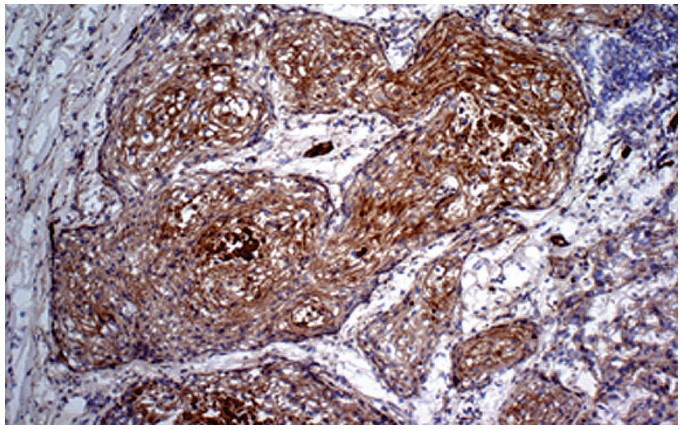

Continuing where a giant left off

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When Noël Bouck and Judah Folkman identified endogenous inhibitors of angiogenesis, the potential for cancer therapy was obvious. Unfortunately, although highly successful in treating tumors in various animal models, efficacy has been less remarkable in human trials to date. An article by Hasina *et al* in this issue may shed some light on that discrepancy. The study of human head and neck squamous cell carcinomas (HNSCCs) found remarkable variability in the expression of angiogenesis-related genes within individual tumors. Further analysis suggested the existence of two potentially distinct pathways of tumor-induced angiogenesis, and this was supported by *in vivo* studies showing that the ability of anti–vascular endothelial growth factor (VEGF) therapy to treat mice implanted with human HNSCC xenografts was directly-related to the amount of VEGF secreted by tumor cells.

These findings underscore the importance of angiogenic heterogeneity and may provide one potential mechanistic explanation for the limited efficacy of anti-angiogenic agents that has been observed. It further underscores the need to prospectively ensure that the specific target of the anti-angiogenic therapy is produced by a given patient's tumor in much the same way that we already prospectively determine the estrogen receptor/progesterone receptor and Her-2 status of breast cancer patients prior to administering adjuvant therapy. As we mourn the loss of Judah Folkman this past January, it is perhaps comforting to remember his legacy, which includes the field of anti-angiogenesis therapy, and recognize that those who stand on his shoulders may yet develop the cures of which he dreamed.

A mouse with pregnancy-associated hypertension as a model of preeclampsia

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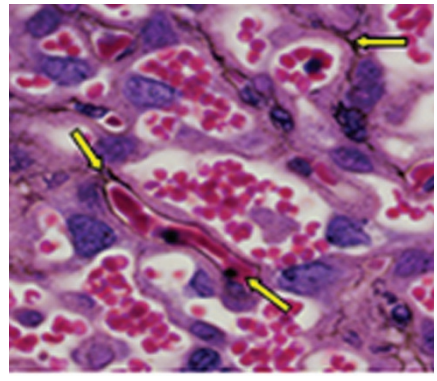
Although preeclampsia has been recognized for centuries, the etiology of the disease remains to be elucidated. Our understanding of the complex pathobiology of preeclampsia is limited by the difficulties in performing studies in pregnant women, and in part to the lack of an animal model that adequately recapitulates the disease. Furuya *et al* had previously generated a pregnancy-associated hypertension (PAH) mouse model by mating females expressing human angiotensinogen and males expressing human renin. The present study analyzed the PAH mouse placenta carefully, from the time of onset of maternal hypertension to delivery. The findings indicate impaired development, maturation, and remodeling of fetoplacental vasculature formation during the second half of gestation as a key anatomic feature of the placenta in these mice. Although it is still unclear



how the findings are directly relevant to clinical preeclampsia, in which the involvement of the renin–angiotensin system is controversial, the PAH mice certainly provide an important insight into how maternal hypertension leads to vasculature changes in placenta.

Islet destruction in diabetes

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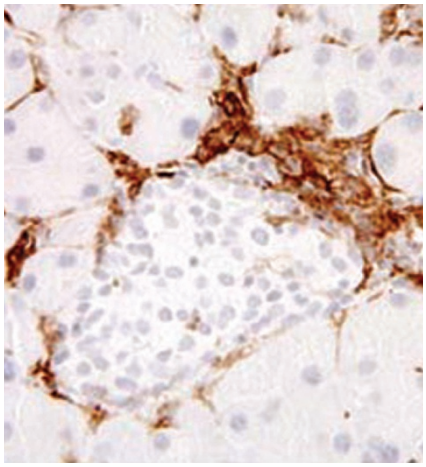
Macrophage-secreted inflammatory cytokines such as interleukin-1β and

tumor necrosis factor-α are known to play a major role in β-cell destruction and ensuing hyperglycemia in type 1 diabetes. The article by Fukuda *et al* provides significant insights into the mechanism by which this process occurs. To test the involvement of the p38 MAPK pathway, which has been implicated in cytokine-islet death, the authors used a mouse deficient in MKK3, a p38 upstream kinase. *Mkk3*$^{-/-}$ mice were susceptible to streptozotocin-induced β-cell apoptosis, but they were protected from islet leukocyte infiltrates and inflammatory cytokine production and did not develop hyperglycemia. Further experiments suggested that MKK3 signaling in damaged islets leads to production of monocyte chemoattractant protein-1, which in turn induces macrophage infiltration and inflammatory cytokine production, causing destruction of the remaining islet cells and resulting in insulin deficiency and hyperglycemia. These results, which should be further validated in an autoimmune setting, contribute to our understanding of chronic inflammatory autoimmune diseases.



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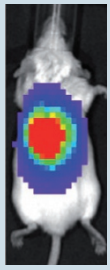
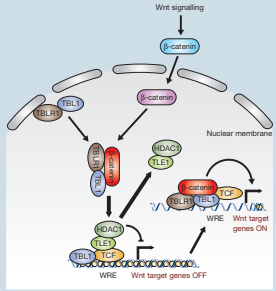


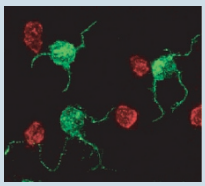
Go big or go micro? Expression of the microRNA miR10b has been implicated in breast cancer invasion and metastasis. A new study has shown that two additional microRNAs—miR-373 and miR-520c—also stimulate cancer cell migration and invasion *in vitro* and *in vivo*, and that in some cases miR-373 is required for efficient cell migration. Remarkably, array studies showed that CD44, a surface protein known to act as a metastasis suppressor in colon and prostate cancer, is a critical target of miR-373 and miR-520c; expression of these microRNAs suppressed CD44 expression. Please look for more about microRNA functions in an upcoming Pathobiology in Focus article.

Nature Cell Biology 2008;10:202–210; doi:10.1038/ncb1681

Wnt brings up new recruits Aberrant Wnt signaling plays a role in numerous human cancers by promoting β-catenin translocation to the nucleus and in turn activating transcription of Wnt target genes. Despite progress in understanding the role of β-catenin as a transcription co-activator, the mechanism of β-catenin recruitment is poorly defined. A recent study in *Nature Cell Biology* describes roles for transducin-like protein 1 (TBL1) and TBL1-related protein (TBLR1), proteins previously shown to participate in nuclear receptor co-repressor exchange, ubiquitination, and p53-mediated β-catenin degradation. The new data demonstrate that Wnt signaling causes β-catenin to interact with TBL1-TBLR1. This protein complex displaces resident co-repressors and stimulates transcription of Wnt target genes. Consistent with this, TBL1–TBLR1 depletion inhibited Wnt-β-catenin-induced oncogenic growth *in vivo*. Activity of TBL1-TBLR1 in human cancers remains to be defined.



Nature Cell Biology 2008;10:160–169; doi:10.1038/ncb1684



NKG2D and cancer immunosurveillance The mechanisms underlying tissue immunosurveillance remain poorly-understood. A recent study in *Nature Immunology* has demonstrated that the upregulation of NKG2D ligands alone can trigger immunosurveillance without the detection of foreign or inflammatory "danger" signals. Using a transgenic mouse that expresses the murine NKG2D ligand Rae-1 independent of tumor and inflammatory dysregulation, the data show reorganization of tissue-resident intraepithelial T cells and Langerhans cells as well as epithelial infiltration of unconventional T cells. Rae-1-activated local T cells suppressed carcinogenesis, but, unexpectedly, activated Langerhans cells seemed to promote neoplasia. These data have widespread implications linking immune regulation and carcinogenesis at many epithelial surfaces.

Nature Immunology 2008;9:146–154; doi:10.1038/ni1556

SNPing away at the genome Recent studies evaluating disease on a genome-wide scale have proved instrumental in identifying genetic risk factors for complex diseases. Genome-wide association studies evaluate genetic variation on a genomic level by looking at thousands of single-nucleotide polymorphisms (SNPs). A series of recent studies published in *Nature Genetics* used this approach to identify genes associated with complex multigenic diseases without the need for familial linkage analyses. For example, several studies have associated specific SNPs with serum lipids and coronary artery disease.[1–3] Another study has discovered new genetic variants that could have a role in SLE,[4] and a study in *Mucosal Immunology* has expanded on past genome-wide association studies of inflammatory bowel diseases using a new gene-centric approach.[5] Perhaps most remarkable is recent work that demonstrated correlations between SNPs in flanking sequences and gene expression or isoform selection.[6] These new technologies are accelerating our ability to unravel complex diseases and reveal unanticipated regulatory effects of genetic variation in human populations. An upcoming Pathobiology in Focus article will discuss genome-wide association studies in further detail.

[1]*Nature Genetics* 2008;40:149–151; doi:10.1038/ng.2007.61; [2]*Nature Genetics* 2008;40:161–169; doi:10.1038/ng.76; [3]*Nature Genetics* 2008;40:189–1971; doi:10.1038/ng.75; [4]*Nature Genetics* 2008;40:204–210; doi:10.1038/ng.81; [5]*Mucosal Immunology* 2008;1:131–138; doi:10.1038/mi.2007.15; [6]*Nature Genetics* 2008;40: 225–231; doi: 10.1038/ng.2007.57