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INSIDE LAB INVEST

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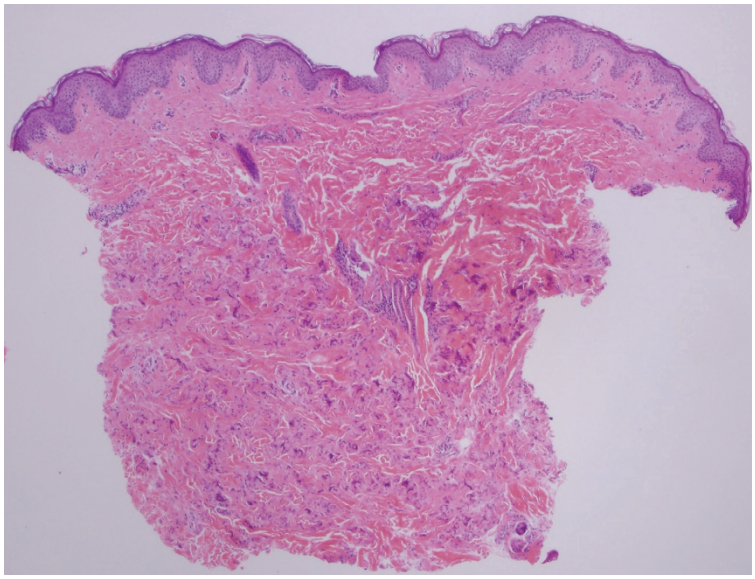

ABC transporters in PXE dermal fibroblasts

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Pseudoxanthoma elasticum (PXE) is a connective tissue disease caused by a deficiency in the *ABCC6* gene, which encodes the multidrug resistance–associated protein 6 (MRP6). *ABCC6* is a member of the large ATP binding-cassette (ABC) transporter superfamily. To date, very little is known about the function of MRP6, except that it is highly expressed in the liver and the kidney, in which it is assumed to serve as an efflux pump transporting intracellular organic anions into the blood. Very low MRP6 levels are found in the tissues directly affected by PXE, such as dermal fibroblasts. Consequently, the causative link between MRP6 deficiency and PXE has not been deciphered.

In this issue, Hendig *et al* hypothesize that compensatory expression of some of the other members of the large ABC transporter family could impair the function of elastic fibers in connective tissues. The authors compared the expression of 47 ABC transporter genes between dermal fibroblasts from PXE patients and healthy controls and found that, in addition to *ABCC6* deficiency, PXE patients exhibit a more than twofold altered expression in eight other ABC transporter genes. siRNA experiments demonstrated that *ABCC6* deficiency was directly responsible for this altered compensatory expression profile of ABC transporter genes. The fact that most of the genes with altered expression due to *ABCC6*/MRP6 deficiency belong to the ABCA subclass points to a role of *ABCC6*/MRP6 in lipid metabolism. These results represent an important step in solving the puzzle of the role of ABC transporters in PXE pathology.

Potential fatty acid oncogenesis in prostate cancer

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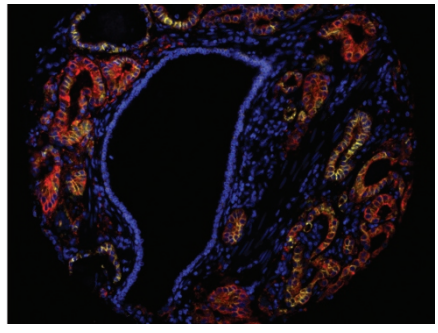
Cancer cells display a metabolic pattern that is more anaerobic than that of normal tissues. In particular, they exhibit increased anaerobic glycolysis, even in the presence of oxygen. The product of anaerobic glycolysis is acetate, which is diverted into fatty acid synthesis through fatty acid synthase (FASN). FASN is minimally expressed in normal human tissues other than the liver and adipose tissue, but upregulation of FASN expression occurs in many cancers. In fact, FASN overexpression is correlated with poorer prognosis in some human malignancies, including prostate cancer, which is itself associated with obesity and the metabolic syndrome. Hence, there is considerable interest in exploring a possible mechanistic role of FASN in prostate carcinogenesis.



Fiorentino *et al* generated immortalized prostate epithelial cells overexpressing FASN. Radiolabeled palmitate, generated *in situ* by FASN from ^{14}C-acetate, was found to be incorporated into Wnt-1. The overexpression of FASN also caused membranous and cytoplasmic accumulation and activation of β-catenin; knockdown of FASN expression reduced the extent of β-catenin activation. Orthotopic transplantation of these immortalized cells resulted in invasive tumors overexpressing β-catenin. The authors then examined 862 cases of human prostate cancer and found a strong, significant association between FASN expression and immunostaining for cytoplasmic β-catenin. The authors propose that cytoplasmic stabilization of β-catenin through palmitoylation of Wnt-1 and activation of the Wnt pathway is a potential oncogenic mechanism in prostate cancer.

The origin of Ewing's family tumors

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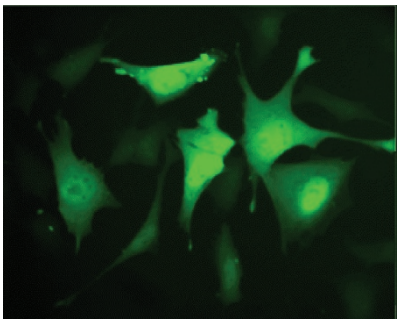
Ewing's family tumors (EFTs) are recurrent tumors that exhibit chromosomal translocations that produce chimeric fusions between the *EWS* gene and one of five ETS transcription factors, most often EWS/FLI1. EFTs remain a mysterious set of malignancies because their cell of origin is unknown, possibly lying between mesenchymal progenitors and neuroectodermal cells. The high incidence

of chimeric fusions between the *EWS* gene and ETS transcription factors implicates this fusion protein as playing a critical role in their etiology. However, mechanisms regarding how the fusion protein causes EFTs, such as via activation of downstream target genes, remain largely unidentified, partly because expression of the fusion protein is often toxic in primary cells.

Potikyan *et al* have taken a unique approach to solving these unsolved mysteries. First, to gain an insight into the cellular origin of the tumors, they silenced the *EWS/FLI1* fusion gene in EFT cell lines and, using a computer database, compared subsequent cellular gene expression profiles with those of various tissue types. The authors expected that, by inhibiting EWS/FLI1, the cells might



regain the genetic characteristics of the originating cells that gave rise to EWTs. The study revealed a similarity of the "silenced" EWT cell line gene expression profiles with that of a cell line with mesenchymal origin, human fetal fibroblasts (IMR-90 cells). Accordingly, they transfected the *EWS/FLI1* gene into IMR-90 cells and found that this gene was not toxic, unlike the toxic outcome of such transfection into other cell types. Instead, partial transformation of the IMR-90 cells occurred, with enhanced expression of genes reported to be targets of EWS/FLI1. Although the data presented here do not provide a definitive answer for either the origin of EFTs or the role played by EWS/FLI1, the unique approach introduced in this study might prove very useful for studies of other cancers of uncertain origin.

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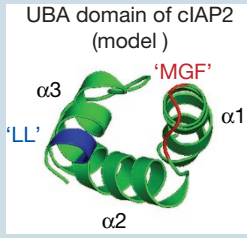
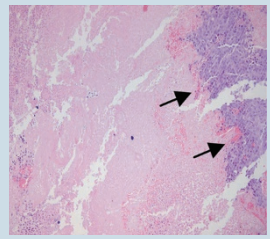
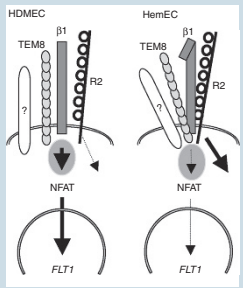


Preventing apoptosis drives MALT Overexpression of inhibitor of apoptosis (IAP) proteins is common in neoplasia, has been implicated in tumorigenesis and chemoresistance, and correlates with poor patient survival. Besides regulating caspases and apoptosis, IAPs enhance cell survival via NF-κB activation. This is demonstrated most effectively by MALT lymphomas, in which a cIAP2–MALT1 fusion protein drives constitutive NF-κB activation and B-cell transformation. The authors of a recent letter in *Nature Cell Biology* have identified a ubiquitin-associated domain within IAPs that is necessary to prevent TNF-induced apoptosis. Consistent with the critical role of this domain, it is present in nearly all cIAP2–MALT1 fusion proteins.
Nature Cell Biology, published online 19 October 2008; doi:10.1038/ncb1789

New determinants for indeterminate colitis Several Crohn's disease–associated genes have been identified in recent years, and some of these are also associated with ulcerative colitis. A recent letter in *Nature Genetics* provides an analysis of genes associated specifically with ulcerative colitis. Remarkably, interleukin-10, an immunosuppressive cytokine that has been studied extensively in the context of intestinal inflammation, is strongly associated with ulcerative colitis but only weakly with Crohn's disease. This observation will significantly bolster efforts to understand the mechanisms of ulcerative colitis as well as the pathogenic differences between Crohn's disease and ulcerative colitis.
Nature Genetics 2008;1319–1323; doi:10.1038/ng.221



A master switch in prostatic neoplasia? MicroRNA (miRNA), the discovery of which was recognized with the 2008 Lasker Award, is composed of small, noncoding, single-stranded RNAs that posttranscriptionally repress gene expression binding to the 3′ untranslated region (UTR) of target mRNAs and thereby regulate cell proliferation, migration, and apoptosis. A recent letter in *Nature Medicine* has directly demonstrated a critical role of miRNAs miR-15a and miR-16-1 as tumor suppressors in prostate cancer. The study demonstrates that these miRNAs target *CCND1* (which encodes cyclin D1), *WNT3A*, and *BCL2* and that, in advanced prostate cancers, reduced miR-15a and miR-16-1 content correlates with increased expression of cyclin D1, WNT3A, and BCL2. *In vivo* knockdown of miR-15a and miR-16 induced hyperplasia of normal prostate and caused untransformed prostate cells to become tumorigenic. Conversely, expression of miR-15a and miR-16-1 induced apoptosis and regression of prostate tumor xenografts. These data provide new insight into prostatic carcinogenesis and may lead to novel treatments for prostate cancer.
Nature Medicine, published online 19 October 2008; doi:10.1038/nm.1880



Suppression causes hemangioma growth Infantile hemangiomas are inapparent at birth but grow rapidly over the first 6–10 months of life as a result of disorganized angiogenesis. A recent letter to *Nature Medicine* sheds light on the mechanisms of hemangioma growth. Excessive activation of the vascular endothelial growth factor (VEGF) receptor VEGFR2 triggers a signaling cascade that induces expression of VEGFR2 targets, including VEGF, and, in turn, drives endothelial cell proliferation and migration. The exuberant VEGFR2 activation is due to reduced expression of the high-affinity decoy receptor VEGFR1 (encoded by the gene *FLT1*), which normally binds VEGF to limit VEGFR2 activation. Further data, including the identification of mutations in hemangioma endothelial cells, suggest that a complex containing VEGFR2, β1 integrin, and the integrin-like protein TEM8 is abnormal in hemangioma endothelial cells and that this suppresses the NFAT transcription factor that drives *FLT1* transcription. Thus, these data unravel a complex signaling pathway and indicate potential sites at which therapeutic intervention to limit hemangioma growth may be possible.
Nature Medicine, published online 19 October 2008; doi:10.1038/nm.1877