Modern Pathology (2015) 28, 1284–1285

INSIDE THE USCAP JOURNALS

doi:10.1038/modpathol.2015.107

MODERN PATHOLOGY

Clinical NGS in colon cancer

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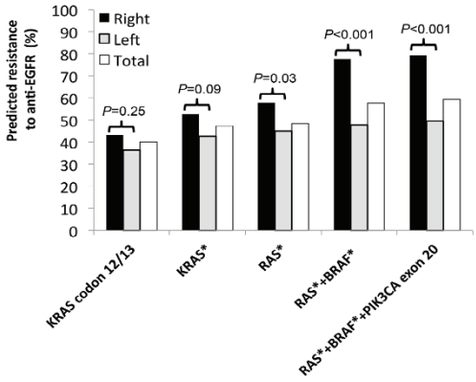

The epidermal growth factor receptor (EGFR) pathway is a key regulator of both the RAS/RAF/ERK and PI3K/AKT pathways. It is a target for colon cancer treatment, but additional mutations in the two downstream pathways can confer resistance to anti-EGFR therapy. In a retrospective examination of 310 colon cancer specimens tested using a clinical next-generation sequencing (NGS) panel, Haley *et al* correlated activating mutations in *KRAS*, *NRAS*, *BRAF*, and *PIK3CA* with resistance to EGFR therapy. Resistance to EGFR treatment can be better elucidated via both examination of a higher number of relevant genes in the downstream pathways and broader sequencing of individual genes, i.e., expanding beyond codons 12 and 13 of *KRAS* to include exons 3 and 4. In addition, left-side colonic carcinomas showed a significantly lower incidence of mutations in *KRAS*, *NRAS*, *BRAF*, and *PIK3CA* than right-side tumors. These results demonstrate the clinical utility of NGS when broad examination of genes is needed.

BAP1 in mesothelial effusions

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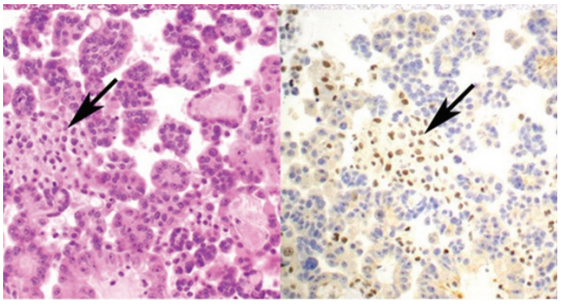
Although mesothelioma commonly presents with pleural effusion, it is debatable whether it can be diagnosed with confidence based on effusion cytology. *BRCA-1 associated protein* (*BAP1*) is a tumor-suppressor genes shows biallelic loss in about half of mesotheliomas. Loss of BAP1 protein in the nucleus can be demonstrated by immunohistochemistry. Andrici *et al* performed BAP1 immunohistochemistry on effusion-sourced cell blocks. As expected, 43 of 74 (57%) mesothelioma cases showed loss of BAP1. Of 57 patients in whom atypical mesothelial cells were present, 8 showed BAP1 loss and all 6 of the



patients with follow-up were subsequently diagnosed with mesothelioma. Analysis of 100 consecutive benign fusions revealed that virtually all had intact nuclear reactivity, but identifying a positive internal control was critical. Forty-seven lung adenocarcinomas showed intact BAP1. As with other immunohistochemical tests, loss of BAP1 must be interpreted within the broader clinical context but it is strongly suggestive of mesothelioma. However, intact staining does not exclude this diagnosis.

LABORATORY INVESTIGATION

Protecting against tacrolimus-induced kidney injury

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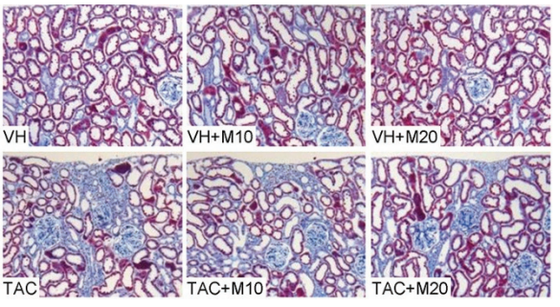

Glucagon-like peptide 1 (GLP-1), which is secreted by the gut, is well known to reduce blood glucose levels, but it also protects against kidney injury. Tacrolimus is a maintenance immunosuppressive drug that is commonly used in the setting of renal transplant. Unfortunately, treatment with tacrolimus has a direct nephrotoxic effect that leads to progressive renal failure with underlying interstitial fibrosis, tubular atrophy, inflammation, and afferent arteriole hyalinosis. Dipeptidyl peptidase (DPP) IV inhibitors are a new class of antidiabetes drugs that extend the effects of a variety of incretin hormones such as GLP-1. Using a rat model of tacrolimus-induced

nephrotoxicity, Lim *et al* found that treatment with the DPP IV inhibitor MK0626 was associated with increased blood GLP-1 levels and attenuated renal dysfunction and injury. Perhaps the renoprotective effects of GLP-1 as modulated by DPP IV can be useful in prevention of tacrolimus-associated renal toxicity

Endoplasmic reticulum stress linked to EMT and apoptosis

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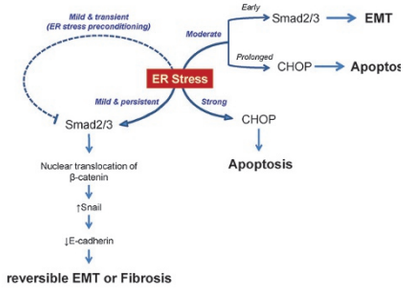

Peritoneal dialysis is known to induce both epithelial-to-mesenchymal transition (EMT) and apoptosis of peritoneal mesothelial cells, leading to perineal fibrosis. Shin *et al* examined the effects of endoplasmic reticulum (ER) stress on EMT. The ER stress inducers tunicamycin (TM) and thapsigargin (TG) induced EMT with Smad 2/3 phosphorylation, nuclear accumulation of β-catenin, and Snail expression, and higher concentrations led to apoptosis of mesothelial cells. Transforming growth factor-β1 (TGF-β1) induced EMT as expected, but this effect was blocked by taurine-conjugated ursodeoxycholic acid, which prevents ER stress. Interestingly, ER stress preconditioning with low levels of TM or TG prevented TGF-β1-mediated EMT. This suggests that ER is an adaptive response that initially protects mesothelial cells but reaches a tipping point at which it leads to EMT and apoptosis. Modulation of ER stress could be contemplated as a therapeutic intervention to prevent peritoneal dialysis–induced fibrosis..

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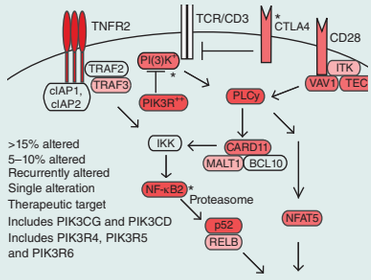
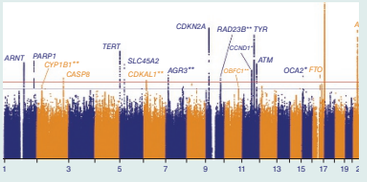
Genomic landscape of mycosis fungoides



The genetic basis of mycosis fungoides and Sézary syndrome is poorly understood. As reported in *Nature Genetics*, Ungewickell and colleagues performed whole-exome sequencing on 11 mycosis fungoides and Sézary syndrome samples. Using these data, they selected 494 genes for deep sequencing in an additional cohort of 91 patient samples and cell lines. The tumor-suppressor genes *MLL3* (aka *KMT2C*; 26%) and *TP53* (13%) were the two most commonly mutated genes. The authors discovered recurrent point mutations and genomic gains of *TNFRSF1B* encoding the tumor necrosis factor receptor THFR2 in 18% of patients, with 38% demonstrating mutations in TNFR2-related T-cell signaling pathways. A recurrent *CTLA4–CD28* gene fusion was also noted. The resulting activation of the THFR2 pathway led to enhanced noncanonical nuclear factor–κB signaling that could be inhibited by the proteasome inhibitor bortezomib. This study defines the genomic landscape of mycosis fungoides and suggests potential novel therapies for this challenging disease.

Nature Genetics 2015;47:1056–1060; doi:10.1038/ng.3370

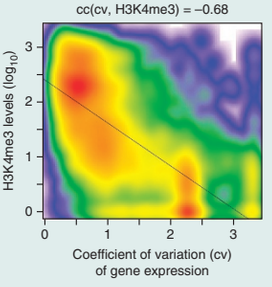
New genetic susceptibility loci for melanoma



Thirteen common susceptibility loci have been reliably associated with cutaneous melanoma. In *Nature Genetics*, Law *et al* report an international two-stage meta-analysis of cutaneous melanoma genome-wide association studies (GWAS) encompassing 11 GWAS studies (5 previously unpublished). The studies came from Europe, the United States, and Australia. In aggregate, the data were from 15,990 patients with cutaneous melanoma and 26,409 controls. All 13 previously reported and confirmed susceptibility loci were found, along with 2 previously reported but unreplicated loci and 5 additional new loci. The newly discovered susceptibility loci include potential melanocyte regulatory elements and a determinant of telomere biology. An example is *HERC2* at the 15q13.1 locus, which is the major determinant of eye color in Europeans; eye color is an established risk factor for cutaneous melanoma. This study provides important new leads for further studies of the genetic basis of melanoma predisposition.

Nature Genetics 2015;47:987–995; doi:10.1038/ng.3373

Histone modifications in developmentally regulated genes



Various histone modifications can have positive or negative regulatory effects on gene expression. Knowledge of the presence and absence of the various positive and negative histone marks within regulatory regions can be addressed in computational models that often show excellent predictive accuracy. These posttranslational histone marks provide a blueprint governing gene differential expression that is evolutionarily conserved and presumably critical for development and tissue- and cell-type maintenance. In *Nature Genetics*, Pérez-Lluch *et al* demonstrate that in fly and worm development temporally regulated gene expression occurs in the absence of the histone marks usually associated with active genes. In mammals, there is an association of histone marks with stable gene expression rather than rapid fluctuations. The model that this work suggests is that chromatin marking is associated with stable RNA production whereas dynamic changes during development may be more closely associated with unmarked chromatin, on which transcription factors might have more influence. Given that developmental pathways are often hijacked by cancer, these results might have relevance in this arena as well.

Nature Genetics, published online 17 August 2015; doi:10.1038/ng.3381