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# INSIDE THE USCAP JOURNALS

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## MODERN PATHOLOGY

### *MYOD1* mutations in rhabdomyosarcoma

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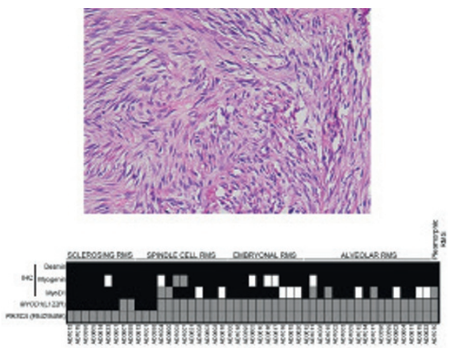


Among the long-recognized embryonal, alveolar, and pleomorphic subtypes, spindle-cell and sclerosing rhabdomyosarcoma are now recognized as specific clinical and molecular subtypes. Rekhi and colleagues demonstrated in a series of 21 sclerosing ($n = 9$) and spindle-cell ($n = 12$) rhabdomyosarcomas that a characteristic *MYOD1* L122R mutation is common: 78% in sclerosing and 25% in spindle-cell. These mutations were not seen in the embryonal ($n = 10$) and alveolar ($n = 17$) subtypes tested or in the single tested pleomorphic rhabdomyosarcoma. The *MYOD1* mutations correlated with more intense MyoD1 expression by immunohistochemistry. Moreover, *MYOD1* L122R mutations in the spindle-cell and sclerosing subtypes are associated with more aggressive behavior compared with these same subtypes lacking the mutations. These results confirm prior smaller studies and clearly delineate sclerosing and spindle-cell rhabdomyosarcoma as distinct from embryonal rhabdomyosarcoma.

### PTEN loss in prostate carcinoma

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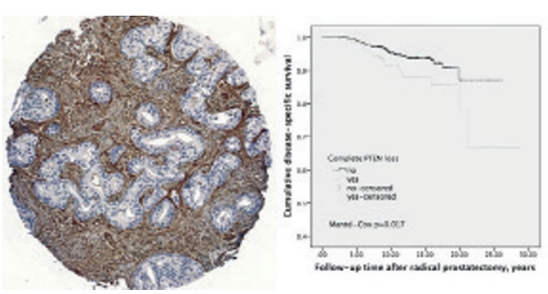


*ERG-TMPRSS2* fusion and loss of PTEN are common genetic alterations in prostate cancer. Lahdensuo *et al* used ERG and PTEN immunohistochemistry as surrogates for these events to investigate two large cohorts of patients with prostate cancer ($N = 815$) for which Gleason score, stage, and other prognostic variables currently provide suboptimal predictive power. The authors found that PTEN loss was associated with poor outcomes and more secondary treatment, particularly in ERG-negative cases. In addition, the absence of both PTEN and ERG stratified Gleason 7 patients into two distinct prognostic groups by outcome and secondary treatments. Patients in whom androgen receptor (AR) showed high immunoreactivity with combined PTEN and ERG absence fared even more poorly. These results suggest that the addition of PTEN and ERG immunohistochemistry to standard AR expression studies can provide significant discriminatory power beyond that of traditional grading, staging, and other prognostic variables.

## LABORATORY INVESTIGATION

### Eating worms to ameliorate fibrosis

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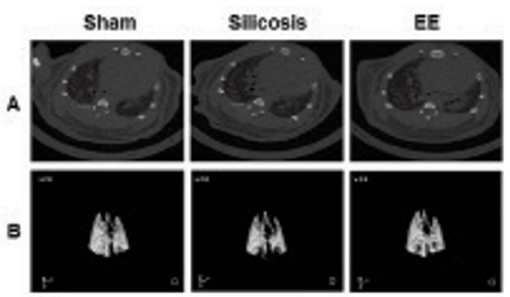


Some of us may have sung from time to time as kids, "Nobody likes me, everybody hates me, I guess I'll go eat worms." This might not a bad idea if you have pulmonary fibrosis, according to recent work by Yang *et al*. Earthworm extract (from the genus *Lumbricus*) has been reported to be protective against inflammation, oxidation, and apoptosis. The best characterized active ingredient is lumbokinase, which has fibrinolytic activity. Using a mouse model of occupational pulmonary fibrosis caused by silica inhalation, the authors demonstrated reduced lung inflammation and fibrosis. In silica-treated cell lines, earthworm extract inhibited oxidative stress, the mitochondrial apoptotic pathway, and epithelial–mesenchymal transition. Mechanistically, they determined that activation of nuclear factor erythroid 2–related factor 2 (Nrf2), a transcription factor that can induce antioxidant pathways, mediates these effects, at least in part. They did not report on the taste quality of earthworm extract in humans.

## PKC in the pathogenesis of bullous pemphigoid

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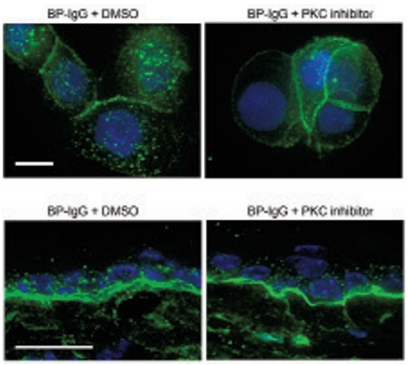


Bullous pemphigoid is a chronic inflammatory subepidermal blistering disorder. Immunoglobulin G (IgG) autoantibodies to an intracellular component of the hemidesmosome, type XVII collagen, mediate the disease. When keratinocytes are exposed to IgG from bullous pemphigoid patients, they internalize collagen 17 (COL17) decorated with IgG via macropinocytosis. This process, which depletes local stores of COL17, is part of the pathogenesis of bullous pemphigoid. Iwata *et al* discovered that they could partially disrupt macropinocytosis by inhibiting the small GTPase family members Rac1, Cdc42, and Rho. Internalization of COL17-IgG complexes was also associated with increased intracellular calcium levels and rapid phosphorylation of COL17 by protein kinase C (PKC). This phosphorylation of the intracellular tail of COL17 by PKC seems to be required for COL17 internalization, as inhibiting PKC also prevented internalization. PKC could thus play an important, previously unrecognized role in the pathogenesis of bullous pemphigoid.

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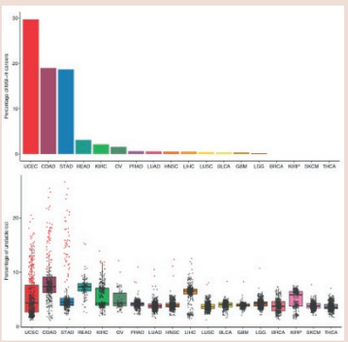
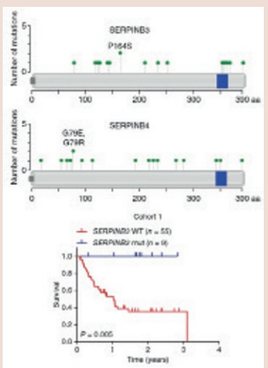
### Microsatellite instability across 18 TCGA cancer types



Microsatellite instability (MSI) is common in colorectal and endometrial carcinomas but seen at lower levels in other tumors. Cancers with MSI often have different clinical properties; recently, MSI colorectal carcinomas were shown to respond dramatically to immune checkpoint inhibitors in contrast to microsatellite stable colorectal tumors. In standard DNA-based testing for MSI, a few of the many genomic microsatellites (stretches of mono- or dinucleotide repeats) that are altered in size when DNA mismatch repair proteins are deficient. This handful of microsatellites (usually 5 to 12 sites are tested) is optimized for colorectal samples. Hause *et al* used TCGA data from 18 cancer types (5,930 exomes). They examined more than 200,000 microsatellites per case and demonstrated varying degrees of MSI in 14 cancer types. Pertinent for clinical molecular testing, specific microsatellites showing MSI varied across cancer types, suggesting that colorectal consensus microsatellites may not be appropriate for all cancer types. This has important implications for oncologists screening cancers for immunotherapy trials dependent on MSI.

*Nature Medicine*, published online 3 October 2016; doi:10.1038/nm.4191

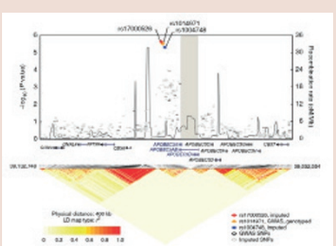
### Recurrent mutations in immunotherapy response




Immune checkpoint inhibition has transformed treatment paradigms for metastatic disease in several cancer types. Little is understood of the discrete molecular determinates of response. Mutational loads, immune microenvironmental constituent cells, and expression of immune checkpoint proteins all appear to have some influence. As recently reported in *Nature Genetics*, Riaz *et al* found that somatic mutations in *SERPINB3* and *SERPINB4* were associated with survival following treatment with anti-CTLA4 immunotherapy in two large cohorts of melanoma patients. Mutations in these two genes correlated somewhat with total mutational loads, although they were more discriminatory for response than mutational load. The mutations remained predictive in settings of relatively low mutational loads. Intriguingly, serpin proteins are associated with autoimmunity. A single mutation so strongly associated with immune checkpoint response will certainly evoke additional mechanistic characterization.

*Nature Genetics*, published online 26 September 2016; doi:10.1038/ng.3677

### Germline influences on APOBEC-signature mutations in cancer



Several mutational signatures have been defined in cancers, some with clear etiologies such as aging, smoking, and other environmental influences. A less-understood signature is associated with activity of the AID/APOBEC (apolipoprotein B mRNA editing enzyme, catalytic-peptide-like) family of cytodine amidases. Some researchers suggest that this signature is related to viral infection or tissue inflammation, although mechanistic understanding is lacking. This APOBEC signature is present in more than 20 cancer types and is particularly prevalent in cervical and bladder cancers. Middlebrooks *et al* explored the role of two common changes in various *APOBEC3* region genes. Using the genotypes for 5,832 bladder cases and 10,791 controls from the NCI-GWAS1 and 2 studies, the single-nucleotide polymorphism rs1014971 was associated with not only bladder cancer risk but also increased *APOBEC3B* expression and APOBEC-signature mutations. Another germline *APOBEC3* variant was associated with breast cancer risk and APOBEC signatures. This suggests tissue specificity for the oncogenic triggers of these mutational signatures.

*Nature Genetics*, published online 19 September 2016; doi:10.1038/ng.3670

Russell Broaddus and Emma Judson contributed to these reviews.