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Modern Pathology

Not just another gene deficiency in imatinib-resistant GIST

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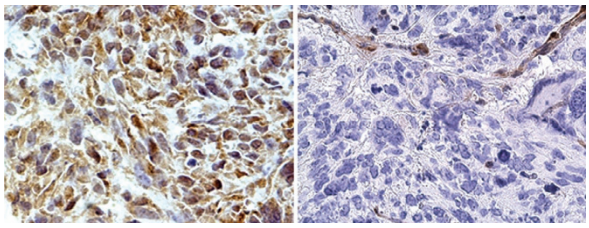

Long a poster child of successful targeted therapy against mutant protein, treatment of gastrointestinal stromal tumor (GIST) with imatinib mesylate is initially gratifying, but with time, resistance emerges. Secondary mutations in the kinase domain of the KIT receptor that prevent binding of the inhibitory drug often underlie resistance. However, diverse mechanisms are involved. Quattrone *et al* found that *PTEN*2 loss is more common in GISTs that have developed imatinib resistance than in naive GISTs, and that the mechanism appears to be genomic loss (often monoallelic) rather than point mutations or promoter hypermethylation. As expected, experimentally induced loss of *PTEN* in GIST cell lines was linked to increased signaling through the PI3K/AKT pathway. In line with previous studies, *PTEN* loss appeared to be a late event in tumor progression and associated with poor outcome. The study also suggests that this event could be selected for via imatinib treatment as a mechanism of resistance.

This is not your daddy's urothelial neoplasm

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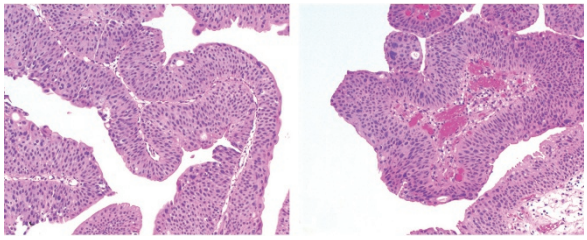

Papillary urothelial neoplasms occur most commonly in male adults. Mutations in *FGFR3* and loss of heterozygosity at 9p21 are common in noninvasive and low-grade papillary urothelial tumors, and mutations in *TP53* are more typical of higher-grade and invasive urothelial carcinomas. Both mutations are probably pathogenic drivers. In children and young adults, urothelial neoplasia—both benign and malignant—is rare and poorly understood. Pediatric cases are thought to be less aggressive than their adult counterparts. Williamson *et al* studied 17 urothelial neoplasms, primarily carcinomas, from patients aged 6 to 26 years. None of these tumors harbored mutations in either *FGFR3* or *TP53*; 9p21 loss was seen in two tumors, and gains or losses of chromosomes 7 or 17 in 3 tumors. Pediatric urothelial neoplasia is distinct from that in adults, perhaps partially in its pathogenesis; for example, local bladder mutagens are presumably less prevalent in children.

Laboratory Investigation

Frontotemporal dementia: relief with bone marrow transplant?

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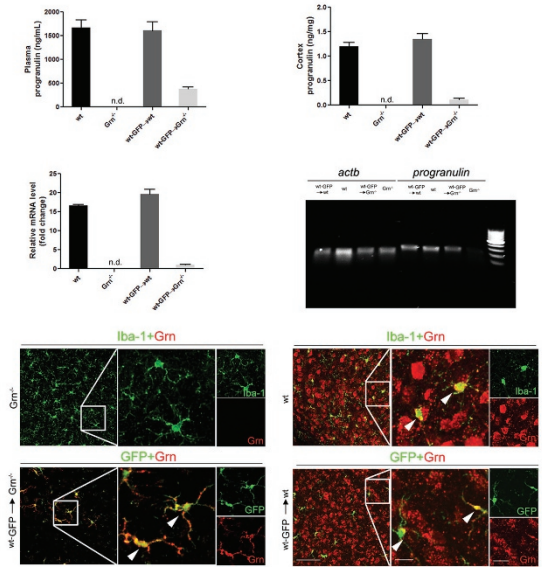

The most common cause of the inherited form of frontotemporal dementia, a neurodegenerative disease that devastates behavior control and social function, is mutation of the progranulin gene (*GRN*). The encoded progranulin is proteolytically cleaved to granulin; both proteins regulate innate immunity and neurotropism via autocrine and paracrine effects, but they tend to have opposite effects. Mice with homozygous deletion of *Grn* show increased innate immune activity, behavior abnormalities, and neuropathology reminiscent of human disease. The authors transplanted bone marrow from a mouse with two intact alleles of *Grn* labeled with green fluorescent protein. Cells derived from the bone marrow

migrated to the central nervous system, adopted a microglial phenotype, and partially normalized progranulin levels and control of innate immune pathways. Thus, bone marrow–derived cells may be able to deliver progranulin to the brain to prevent or delay the onset of frontotemporal dementia.

The liver on a Western diet

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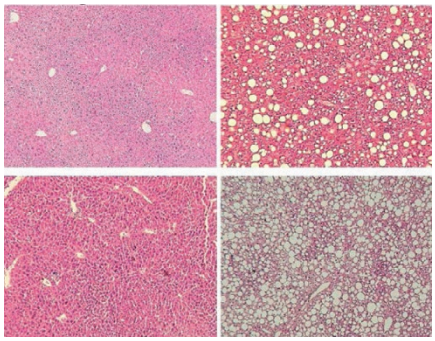

An association has been observed between nonalcoholic fatty liver disease and cardiovascular disease and atherosclerosis. Kampschulte and colleagues examined this correlation by studying hepatic pathology in a mouse model of atherosclerosis. Male mice with knockout of both apolipoprotein E and low-density lipoprotein receptor given a Western-style diet high in fat and cholesterol are particularly susceptible to atherosclerosis. The authors found that these mice developed both hepatic inflammation and dyslipidemia along with spontaneous hepatic tumors in the setting of nonalcoholic fatty liver disease. Underlying these changes were aberrations in the NF-κB, Stat3, JNK, and AKT pathways. Interestingly, micro–computed tomography was able to distinguish tumor neovascularization from the vascularization of nonneoplastic liver undergoing inflammation or regeneration. The authors suggest that signaling pathways associated with liver damage and compensatory regeneration might combine with elevated inflammation to produce a protumorigenic environment.

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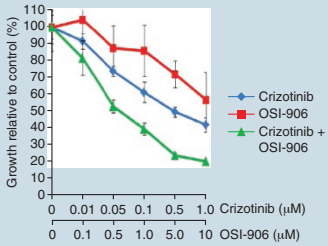
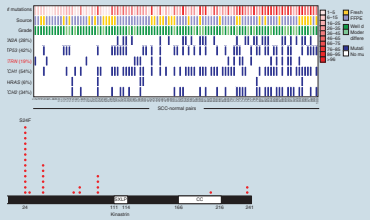
Better ALK targeting in the lung



Lung carcinomas with anaplastic lymphoma receptor tyrosine kinase (ALK)-translocations, which have a low incidence, respond to the tyrosine kinase inhibitor crizotinib. Although responses to this inhibitor can be gratifying, the initial responses are variable and resistance invariably develops. To investigate the underlying mechanism, Lovly *et al* studied an exceptional responder with lung cancer to an antibody inhibitor of the insulin-like growth factor 1 receptor (IGF-1R). In models of ALK inhibition, resistance can be mediated by activation of the IGF-1R pathway. The authors observed that knockdown of insulin receptor substrate 1 (IRS-1), a mediator of the IGF-1R pathway, enhanced the efficacy of ALK inhibition. Biopsy samples from the ALK-rearranged lung cancer patient, who was progressing on crizotinib, showed increased levels of IGF-1R and IRS. This careful study of a single exceptional responder suggests that combined targeting of both the ALK and IGF-1R pathways in ALK-rearranged lung carcinomas should be considered for clinical application.

Nature Medicine 2014;20:1027–1034; doi:10.1038/nm.3667*

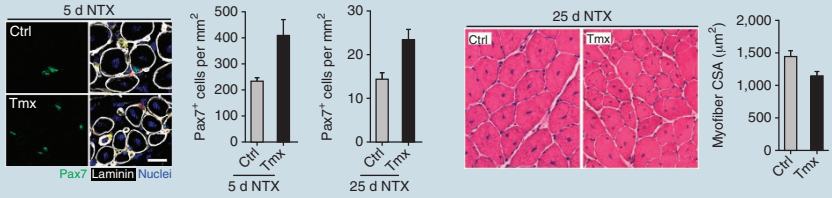
New recurrent mutation in cutaneous squamous cell carcinoma



Cutaneous squamous cell carcinoma is believed to be driven by mutations promoted by ultraviolet radiation damage to keratinocytes. In *Nature Genetics*, Lee and colleagues recently reported recurrent hotspot mutations in a kinetochore gene, *KNSTRN*, showing an ultraviolet signature in both actinic keratosis and cutaneous squamous cell carcinoma. Mutations in *NOTCH* genes, *CDKN2A*, and *TP53* were also common. *KNSTRN* encodes a kinetochore-associated protein that regulates the onset of anaphase and chromosome segregation during mitosis. Loss of this gene is associated with aneuploidy, and loss of function of *TP53* could prevent apoptosis in this context. Transduced expression of the common S24F mutant *KNSTRN* results in disrupted sister chromatid adhesion in primary human keratinocytes, demonstrating a mechanism for aneuploidy. *KNSTRN* appears to be a newly recognized oncogene associated with tumor progression in cutaneous squamous cell carcinoma.

Nature Genetics 2014;46:1060–1062; doi:10.1038/ng.3091

Skeletal muscle repair—stat!



Some of the loss of regenerative capacity in muscle seen with aging and disease is mediated by a decline in both the number and functionality of satellite cells that contribute progeny to muscle repair. The molecular mechanisms regulating the number and function of satellite cells are largely unknown. Inflammatory cytokines, including interleukin-6 (IL-6) and its downstream effector Stat3, are elevated in age- and disease-related muscle atrophy. The authors of a letter in *Nature Medicine* found that this pathway regulates stem cells in muscle and other tissues. Stat3 activation promoted myogenic lineage progression mediated by Myod1. In a mouse model, conditional ablation of *Stat3* in satellite cells expressing Pax7 increased expansion of a satellite cell population during regeneration, at the expense of myogenic differentiation. The Stat3 pathway is potentially regulated by cytokines such as IL-6 in the maintenance of muscle satellite cells. Pharmacologic manipulation of Stat3 might therefore be useful to slow or prevent loss of muscle-regenerating capacity.

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*This article includes a USCAP member as an author.