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Pathogenesis of narcolepsy

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Narcolepsy is a debilitating illness characterized by excessive daytime sleepiness, cataplexy (sudden and transient loss of muscle tone triggered by emotions), and abnormal rapid-eye-movement sleep. Narcolepsy with cataplexy is associated with selective loss of hypocretin- (also known as orexin) secreting neurons in the hypothalamus. Given that hypocretins appear to promote wakefulness, loss of hypocretin explains the symptoms associated with narcolepsy. An autoimmune etiology has been suggested to explain the selective loss of hypocretin-secreting neurons due to a tight association between narcolepsy and the HLA-DQB1 0602 allele and an association with the T-cell-receptor α -locus. Recently, Jackson and co-workers reported finding an immunoglobulin G (IgG) antibody in patients with narcolepsy that abolished neuronally mediated colon migrating motor complexes in a bioassay they developed to study narcolepsy.

In the current work, the authors used their whole-colon bioassay system to perform a pharmacological dissection of the mechanism of action of their IgG antibody.

Their work suggests that the narcolepsy-related IgG antibody blocked both excitatory and inhibitory motor neurons, probably by binding to an autoantigen expressed on both populations of neurons. In their future work, the authors plan to focus on the identification of the antigen recognized by their narcolepsy-related IgG, which will require the development of cell-based assays. Identification of the antigen is required for a detailed understanding of the pathogenesis of narcolepsy. Hopefully, their results will stimulate further developments in this field and eventually lead to treatments for this serious disease.

Aurora B kinase and lymphoma

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The Aurora family of serine/threonine kinases, consisting of Aurora A, B, and C kinases, has important roles in mitosis. Aurora A and B are expressed broadly, whereas Aurora C is expressed only in testis and is thought to be involved in spermatogenesis. Given their broad expression patterns and important roles in mitosis, it is not surprising that many studies have found that Aurora A and B kinases are deregulated in a variety of cancers. Because

they are kinases and appear to be important in the pathogenesis of various cancers, they have become attractive targets for small-molecule kinase inhibition-based therapies.

To determine whether Aurora B might be involved in the pathogenesis of non-Hodgkin lymphoma (NHL), Ikezoe and colleagues examined a large collection of NHL samples by immunohistochemistry with antibodies to Aurora B and found that more aggressive NHLs, such as Burkitt's lymphoma (BL), tended to express Aurora B in a larger proportion of their cells than less aggressive NHLs, such as follicular lymphoma. Furthermore, they showed that Aurora B expression correlated with high grade and advanced clinical stage. Treatment of BL cells in culture with an Aurora B-selective inhibitor, AZD1152-HQPA, resulted in reduced proliferation and increased cell death. Additional experiments with vincristine, a

tubulin depolymerizing agent, found that vincristine treatment induced Aurora B kinase expression and that induction was dependent on c-Jun N-terminal kinase. AZD1152-HQPA was found to synergize with vincristine to inhibit proliferation of BL cells, laying the groundwork for a rationale-based approach for the treatment of BL and possibly other high-grade NHLs.

Foxl1 and cholangiocyte proliferation

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Bile duct injury is the hallmark of a number of acquired and genetic diseases collectively known as cholangiopathies. The liver responds to bile duct injury

with biliary hyperplasia. If the injury is not resolved, chronic bile duct injury can result in ductopenia and fibrosis. Therefore, molecular characterization of the response to damage could be instrumental in developing therapies that can enhance liver repair and minimize damage.

Recently, Sackett and colleagues discovered that Foxl1, a member of the forkhead box family of transcriptional regulators, is upregulated in cholangiocytes in response to bile duct damage. They have now extended this observation to show that mice harboring a germline knockout of Foxl1 (Foxl1^{-/-}) have more extensive liver damage in a bile duct ligation model of obstructive cholestasis than do Foxl1 wild-type littermate controls. Furthermore, Foxl1^{-/-} mice die uniformly within 14 days of bile duct ligation. The researchers found that liver damage in this model is associated with a defect in cholangiocyte proliferation. Interestingly, cholangiocyte proliferation appears to be mediated by Foxl1 through the canonical wnt/ β -catenin pathway. Future studies are planned to perform a detailed molecular analysis of the factors that upregulate Foxl1 and lead to activation of the wnt/ β -catenin pathway. The sonic hedgehog pathway is a leading candidate to activate Foxl1. Overall, these studies help to elucidate how cholangiocyte proliferation mitigates the consequences of bile duct damage; they also provide the framework for a rational understanding of how to prevent end-stage liver damage from chronic bile duct injury.

Fantastic new *in vivo* imaging modality Imagine the ability to image tumor microvasculature both at high resolution and in three dimensions *in vivo* without the aid of exogenous contrast agents. Now imagine the ability to layer the images of the tumor microvasculature onto functional images that measure tumor cell viability. Finally, imagine that all this is possible in a format that allows repeated measurements during therapeutic intervention in mouse models. Actually, there is no need to imagine it because it has already been developed. In a recent technical report in *Nature Medicine*, Vakoc and colleagues describe a technique known as optical frequency domain imaging (OFDI). OFDI takes advantage of newly developed hardware and software to make beautiful pictures of tumor microvasculature with the capability to differentiate capillaries from lymphatics and also to image tissue viability. It is easy to envision how this new technology might enhance the evaluation of various anti-angiogenic cancer therapies.

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Protection of oocytes from chemotherapy-induced death

Ovarian failure and infertility is a common and morbid side effect associated with chemotherapy. Recently, it has been observed that expression of the Tap63- α isoform of p63 (Tap63) is associated with radiosensitivity of oocytes and is essential for their cell death, suggesting that Tap63 may serve as a “guardian” for oocytes. In a recent article in *Nature Medicine*, Gonglioni and colleagues explored the signals that result in Tap63 phosphorylation and resultant oocyte death. They found that c-Abl played an important role in mediating Tap63 phosphorylation. Interestingly, this suggested a possible therapeutic strategy given that imatinib mesylate inhibits c-Abl. The authors found that mice exposed to cisplatin and treated with imatinib had increased fertility in comparison with mice exposed to cisplatin only. These promising results require follow-up in a human clinical trial. Notably, it will be important to demonstrate that imatinib preserves fertility while not affecting the efficacy of cisplatin.

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Susceptibility gene in familial chordoma Chordoma, a rare bone tumor, is believed to arise from notochordal remnants. There are very rare families that develop chordoma in the familial setting. In a recent Brief Communication in *Nature Genetics*, Yang and colleagues describe their use of high-resolution array-comparative genomic hybridization to show that duplication of the *T* gene, which encodes brachyury, a tissue-specific transcription factor

associated with notochord and chordoma, is associated with familial chordoma. Interestingly, because there are no mutations associated with the gene duplication, brachyury was not identified by traditional DNA sequencing. Further studies are necessary to understand how brachyury duplication predisposes to familial chordoma and whether it plays a role in sporadic chordoma.

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Negative regulator of breast cancer metastasis Metastasis contributes greatly to morbidity and mortality, yet it is still poorly understood. Some pathways suppress metastasis whereas others promote it. To identify factors that suppress metastasis, Gumireddy and colleagues, as reported in a recent article in *Nature Cell Biology*, performed a forward genetic screen that took advantage of the inability of 168FARN mouse breast carcinoma cell line to metastasize. They transformed 168FARN cells with a short hairpin RNA (shRNA) library and looked for lung metastasis. Examination of lung metastasis revealed an shRNA to *KLF17*, a member of the Sp/KLF (specificity protein/Krüppel-like factor) zinc-finger protein family of transcription factors. They found that one of the functions of KLF17 was to repress the transcription of *Id1*, which is known to regulate metastasis. Interestingly, expression levels of *KLF17* and *Id1* appeared to predict the ability of human breast cancer samples to metastasize. Further studies will be required to confirm these promising results.

Nature Cell Biology, published online 4 October 2009; doi:10.1038/ncb1974