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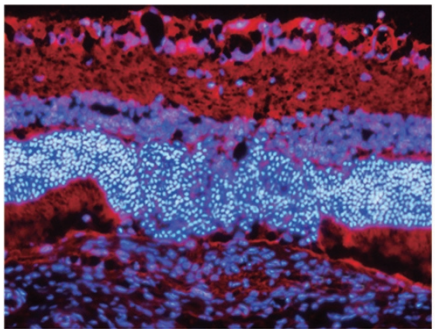

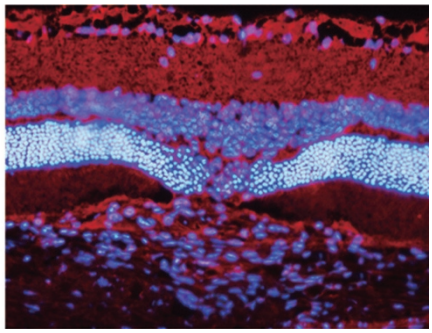

NSAIDs for the treatment of choroidal neovascularization

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Ocular angiogenesis, which is common to many ocular diseases, is a cause of severe vision loss. Recently, anti–vascular endothelial growth factor (anti-VEGF) antibody-based therapy has been used successfully to treat ocular diseases that are characterized by neovascularization, such as age-related macular degeneration (AMD). However, some concerns have arisen about long-term use of anti-VEGF antibodies. Long-term treatment with VEGF may induce retinal damage because it is a neurotrophic factor and plays important roles in retinal development and neuroprotection. Reports have emerged showing that complete blockade of VEGF causes retinal degeneration in animal models, and some AMD patients have developed unexplained retinal atrophy after several years of anti-VEGF therapy. As a result of these findings, Yoshinaga *et al* explored the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of ocular angiogenesis.

Using models of choroidal neovascularization (CNV), the authors found that bromfenac, an NSAID formulated for topical application for ocular inflammation, reduced macrophage infiltration and VEGF levels and diminished the size of CNV lesions in a rat model. Studies of the mechanism of action demonstrated that bromfenac activates NF-E2-related factor 2 (Nrf2), a transcription factor that controls an antioxidant program. Heme oxygenase (HO)-1, an antioxidant protein that is under Nrf2 control, appeared to play a prominent role as application of stannic mesoporphyrin, an HO-1 inhibitor, interfered with the effects of bromfenac. These results suggest that NSAIDs such as bromfenac may play a role in the treatment of ocular diseases characterized by neovascularization.

Contribution of *NPM1* heterozygosity to NPM-ALK-induced lymphomagenesis

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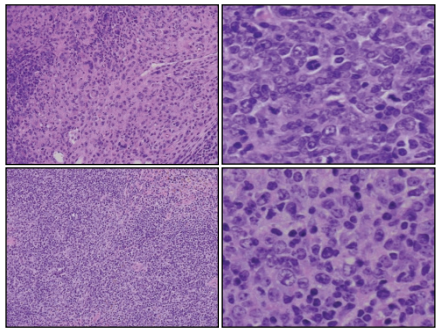

Nucleophosmin (NPM) is a ubiquitously expressed protein that plays key roles in control of cell growth and proliferation. A t(2;5) translocation resulting in fusion of the *NPM1* gene, which encodes NPM, to *ALK*, which encodes ALK tyrosine kinase, is characteristic of anaplastic large-cell lymphoma. As a result of the t(2;5) fusion, one copy of the *NPM1* gene is lost, which could contribute to lymphomagenesis. There is evidence that *NPM1* can act as a tumor suppressor as well as an oncogene. Mice with heterozygous loss of *Npm1* develop a myelodysplastic syndrome. Furthermore, *Npm1* heterozygosity accelerates lymphoma formation in *Eμ-Myc* mice.

To determine whether *NPM1* heterozygosity contributes to NPM-ALK-induced lymphomagenesis, McDuff and colleagues interbred transgenic mice harboring an *Npm-Alk* fusion transgene under the control of the T-cell lineage–specific CD2 promoter with $Npm1^{+/-}$ mice to generate cohorts of mice that possessed the *Npm-Alk* fusion and either one or two copies of *Npm1*. Contrary to what might be expected, they found that *Npm1* heterozygosity did not collaborate with the *Npm-Alk* fusion transgene in their model. The tumor spectrum and incidence were essentially the same between *Npm-Alk* mice with one copy and those with two copies of *Npm1*. This is perhaps not very surprising because *ALK* is occasionally fused to other gene partners besides *NPM1* in anaplastic large-cell lymphoma. However, the clinicopathological features of these cases are identical. Thus, the *Npm-Alk* fusion gene acts as a dominant oncogene without the need to collaborate with loss of *Npm1* in this model.

Therapeutic targeting of inflammatory hypoxia in IBD

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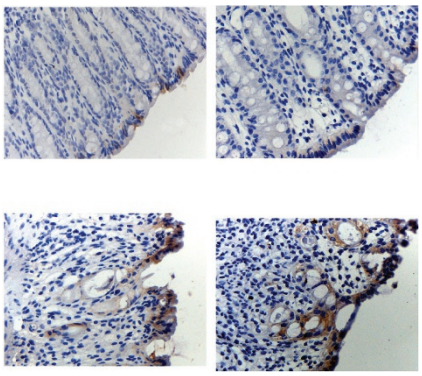
Tissue hypoxia has recently garnered attention in studies of the pathogenesis of inflammatory bowel disease (IBD). Mucosal colonocytes, which play an important role in mucosal barrier function, are extremely sensitive to low oxygen levels. Low oxygen levels decrease proliferation and increase apoptosis of colonocytes. Furthermore, they promote the release of inflammatory

cytokines such as tumor necrosis factor-α. Hyperbaric oxygen therapy has been shown to be beneficial in animal models of IBD. However, hyperbaric oxygen is expensive and has potentially dangerous side effects.



Seeking a better way to deliver oxygen to the bowel in IBD, Hindryckx *et al* explored oxygen delivery using oxygenated perfluorodecalin, an organic compound with high solubility for oxygen. Oxygen is released to ischemic tissues along an oxygen gradient. The authors demonstrated that oxygenated perfluorodecalin decreased the severity of IBD in a mouse model when used in a preventive setting and decreased healing time in a treatment setting. Furthermore, oxygenated perfluorodecalin stimulated colonocyte proliferation while simultaneously decreasing apoptosis, thus preserving barrier function. Interestingly, nonoxygenated perfluorodecalin exhibited anti-inflammatory activity on its own, but the authors did not elucidate the mechanism of action. Although it was not the subject of this work, the authors noted that perfluorodecalin can be used as a delivery vehicle for a variety of biological agents that might cooperate with the delivery of oxygen, enhancing its therapeutic potential. Clearly, these results suggest that oxygenated perfluorodecalin may be a useful therapeutic modality in the treatment of IBD. Its clinical use for this purpose warrants further study.

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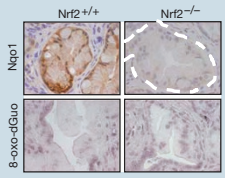
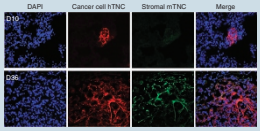
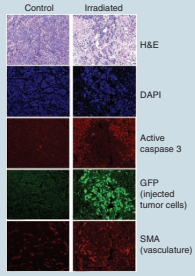


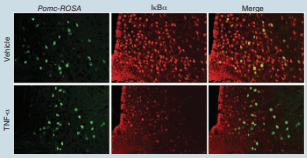
ROS detoxification promotes tumorigenesis Reactive oxygen species (ROS) levels are normally controlled by an inducible antioxidant program under the control of Nrf2, a transcription factor, and its repressor Keap1. Recently, Keap1 mutations that stabilize Nrf2 have been identified in cancer, suggesting that suppressing ROS is advantageous to cancer cells. As reported in a recent letter in *Nature,* DeNicola and colleagues examined the role of ROS in cellular transformation and tumorigenesis. They found that oncogenic K-Ras, B-Raf, and Myc increased *Nrf2* transcription, resulting in decreased intracellular ROS *in vitro*, and that Nrf2 levels were elevated in mouse and human cancers *in vivo*. Observations following deletion of *Nrf2* in mouse models of pancreatic and lung cancer harboring oncogenic K-Ras suggested that Nrf2 plays an important role in initiation and proliferation of preneoplastic cells. These results indicate that modulation of ROS levels may represent a therapeutic opportunity in cancer.
Nature 2011;475:106–109; doi:10.1038/nature10189



Breast cancer cells produce tenascin C to facilitate metastasis The recent work of Oskarsson *et al*, as described in an article in *Nature Medicine*, sheds some light on the long-standing seed-versus-soil debate regarding cancer metastasis. In their previous work, the group identified *TNC*, which encodes tenascin C (TNC) in a set of genes whose expression in breast cancers is associated with lung metastasis. TNC is present in stem cell niche regions and in tumor-associated connective tissue, suggesting that cells that express TNC might have a selective advantage in colonizing metastatic sites. The authors demonstrated that TNC modulates stem cell signaling to promote proliferation and survival without controlling proteins involved in determining stem cell phenotype or pluripotency. Thus, their results favor the "seed" side of the seed-versus-soil debate.
Nature Medicine 2011;17:867–874; doi:10.1038/nm.2379



Unexpected role of caspase 3 in accelerating cancer cell repopulation during radiotherapy The presence of cleaved caspase 3, an undisputed hallmark of apoptosis, is generally thought to correlate with therapeutic success. However, in a recent article in *Nature Medicine,* Huang *et al* report a surprising role for caspase 3 as a promoter of therapeutic resistance. They found that activation of caspase 3, in either tumor cells or tumor cell stroma, resulted in activation of calcium-independent phospholipase A_2, group 6, in turn resulting in activation of arachidonic acid and its downstream product prostaglandin E_2 (PGE_2). Because PGE_2 is a key regulator of tumor growth, tumor cells or stromal cells that express caspase 3 contributed to radiotherapy resistance. These results indicate that caspase 3 is both a marker for resistance to radiotherapy and a therapeutic target to enhance its efficacy.
Nature Medicine 2011;17:860–866; doi:10.1038/nm.2385



Molecular mechanism of obesity-associated hypertension It has recently been shown that IκB kinase-β (IKK-β) and nuclear factor-κB (NF-κB) are activated in the hypothalamus under obesogenic conditions to promote an imbalance in energy, body weight, and glucose. In a recent letter in *Nature Medicine*, Purkayastha *et al* describe their investigation into whether inhibition of IKK-β and NF-κB could uncouple the effects of obesity and hypertension. They demonstrated that IKK-β and NF-κB were activated specifically in pro-opiomelanocortin (POMC) neurons within the mediobasal hypothalamus. Using mice with a POMC lineage–specific *Ikkb* deletion, they were able to uncouple obesity from hypertension in mice fed a high-fat diet. POMC neurons express tumor necrosis factor (TNF)-α receptor 2, which appears to mechanistically link obesity-related inflammation to hypertension through TNF. These results suggest that treatment of obesity-related hypertension need not be predicated on weight reduction, which is good news for individuals with obesity-related hypertension.
Nature Medicine 2011;17:883–887; doi:10.1038/nm.2372