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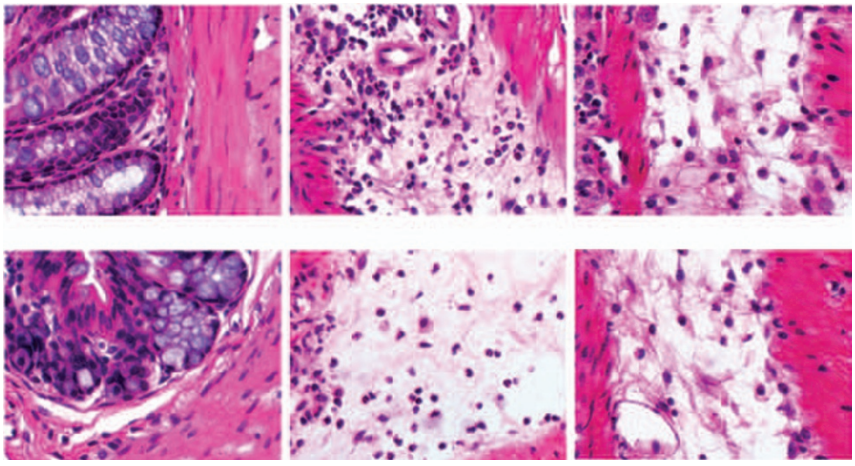

Novel experimental therapy inhibits colitis

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Inflammatory bowel disease (IBD) is a group of chronic intestinal diseases that includes ulcerative colitis and Crohn's disease. IBD has an autoimmune etiology and is characterized by uncontrolled inflammation. The p38 mitogen–activated protein kinase (MAPK) pathway is an important signal-transduction pathway that promotes inflammation in IBD. MAPK-activated protein kinase-2, known as MAKAP kinase-2 or Mk2, is a substrate of p38 MAPK that is known to regulate the production of proinflammatory cytokines by controlling macrophage migration.

Cannabinoid (CB) 1 and CB2 receptors in the gastrointestinal tract are thought to play roles in antagonizing intestinal inflammation. CB antagonists increase inflammatory responses in several intestinal inflammation models whereas CB agonists decrease inflammation. WIN55,212-2 (WIN55) is an aminoalkylindole derivative and a potent nonselective CB1 and CB2 receptor agonist. To test the efficacy of WIN55, Li *et al* used a mouse dextran sodium sulfate (DSS) model in both wild-type and *Mk2* knockout mice.

They found that, as compared with wild-type mice, *Mk2* knockout mice had decreased colitis after drinking DSS, supporting the prior work indicating that the MAPK pathway—specifically Mk2—promotes IBD. When they treated wild-type and *Mk2* knockout mice with WIN55, the severity of DSS-induced colitis was reduced. This correlated with decreased proinflammatory cytokines, demonstrating a direct effect on cytokine production. The effects of WIN55 and Mk2 loss were additive, suggesting that combining a MAPK inhibitor with WIN55 would be effective in treating IBD. Further studies are indicated to elucidate the relationship between the CB receptor anti-inflammatory pathway and the MAPK proinflammatory pathway in the pathogenesis of IBD.

Targeting c-MET sensitizes brain metastasis to radiotherapy

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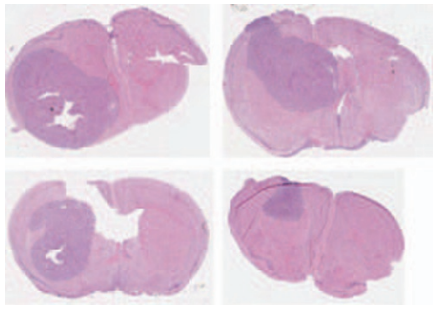

Metastasis is the most important factor in overall survival in cancer patients. Brain metastasis is an especially adverse prognostic factor. Standard treatment options for brain metastasis include surgery, radiosurgery, and whole-brain radiotherapy (WBRT) in various combinations. WBRT, the gold standard for treatment of multiple brain metastases, results in prolonged overall survival. However, because attempts to control the metastatic burden can result in brain damage, including cognitive deficits, WBRT treatments involve quality-of-life considerations. Given the general efficacy of WBRT, there has been great interest in radiosensitization agents that would allow lower doses while still maintaining control over metastatic burden.

c-MET has drawn attention from metastasis researchers because it is associated with epithelial-to-mesenchymal transition and a stem cell phenotype. Recently, c-MET signaling was demonstrated to be increased after irradiation. These results suggested to Yang *et al* that inhibition of c-MET might sensitize brain metastasis to radiation therapy. Utilizing both orthotopic and brain metastatic breast cancer models, they demonstrated that inhibition of c-MET either genetically or pharmacologically sensitized both primary and metastatic tumors to radiation therapy. Mice treated with a combination of radiotherapy and c-MET inhibition survived longer than those treated with either modality alone. Combination therapy was also associated with a higher level of apoptosis, indicating that the survival benefit was due to more extensive tumor cell death. It will be interesting to see in future experiments whether lower doses of irradiation can be used in combination with c-MET inhibition, and whether this results in better preservation of brain function after therapy.

Contribution of B-cell-activating factor to NAFLD/NASH

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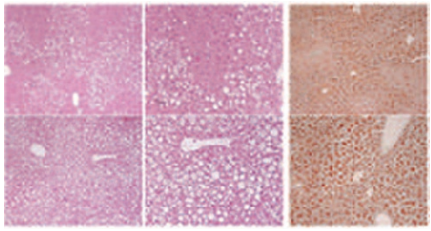
Recent studies have demonstrated that B cells are important effectors in metabolic



syndrome. B-cell-activating factor (BAFF; CD257) belongs to the tumor necrosis factor ligand family. BAFF promotes the expansion and differentiation of the B-cell population, leading to increased serum immunoglobulin (Ig) levels. It was recently reported that serum BAFF levels were increased in a high-fat-diet (HFD) mouse model of nonalcoholic fatty-liver disease (NAFLD). BAFF was preferentially expressed by visceral adipose-tissue cells in this model. Furthermore, patients with nonalcoholic steatohepatitis (NASH) have been found to have higher serum BAFF levels than patients with simple steatosis. Overall, these results suggest a relationship among obesity, BAFF levels, and inflammation. They also suggest that BAFF might be involved in the progression from NAFLD to NASH. To test this hypothesis, Kawasaki *et al* used a BAFF receptor (BAFF-R)$^{-/-}$ knockout mouse.

When the investigators placed BAFF-R$^{-/-}$ mice on an HFD, they found that their serum IgG levels were lower than those in wild-type mice, indicating a smaller number of B cells in the BAFF-R$^{-/-}$ mice. BAFF-R$^{-/-}$ mice also demonstrated increased insulin sensitivity, supporting the concept that B-cell-mediated inflammation contributes to liver-function deficits in the HFD NAFLD model. Surprisingly, they discovered that hepatic fat deposition was increased in BAFF-R$^{-/-}$ HFD mice. This correlated with expression of genes associated with fat transportation and biosynthesis. Overall, the results of this study suggest that early in NAFLD, BAFF protects liver cells from increased hepatic fat deposition through suppression of lipogenic genes in liver cells. Subsequently, BAFF contributes to NAFLD and NASH by increasing inflammation and the number of B cells.

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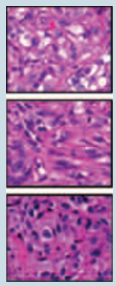
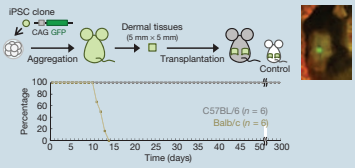


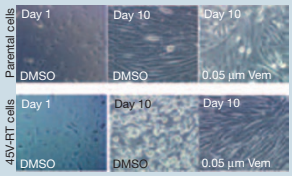
Epigenetic expansion of VHL-HIF signaling drives metastasis in renal cancer Inactivation of the von Hippel–Lindau tumor suppressor gene, *VHL*, is the tumor-initiating event, and it also mediates metastasis in clear-cell renal-cell carcinoma (RCC). However, loss of *VHL* alone does not predict metastasis, whereas activation of hypoxia-inducible transcription factor (HIF)-driven chemokine (C-X-C motif) receptor 4 (CXCR4) does. In a study recently reported in *Nature Medicine,* Vanharanta *et al* discovered that *CXCR4* and other metastasis genes downstream of VHL-HIF were activated by epigenetic events in metastatic subpopulations of renal cells. Specifically, they demonstrated that liberation from repressive chromatin modifications and DNA methylation activated a subprogram directed by VHL-HIF in metastatic cells. These findings highlight the interplay between genetic and epigenetic mechanisms in the evolution of metastatic traits in RCC.

Nature Medicine 2013;19:50–56; doi:10.1038/nm.3029



Negligible immunogenicity of iPSCs after transplantation Induced pluripotent stem cells (iPSCs) hold incredible promise for treating a vast array of human maladies. They are particularly attractive in comparison to embryonic stem cells (ESCs) because of ethical issues involved in generating ES cell lines. One factor that might limit the use of iPSCs is the possibility that iPSCs elicit immunogenic responses after transplantation. As recently described in a letter in *Nature,* Araki *et al* investigated this question. Because the future of iPSC therapy lies in transplanting terminally differentiated cells such as keratinocytes to skin or bone marrow cells to bone marrow, the authors sought to determine whether terminally differentiated iPSCs or ESCs provoke an immune response. They were unable to identify immunogenic responses or differences between the iPS and ES cell lines, suggesting that iPSCs and ESCs may be equally useful in treating human disease.

Nature, published online 9 January 2013; doi:10.1038/nature11807



Vemurafenib resistance creates vulnerability in melanoma Vemurafenib is a small-molecule BRAF inhibitor that is effective in treating melanoma cells harboring BRAF V600E mutations. However, the rapid emergence of vemurafenib resistance has limited its usefulness. To better understand vemurafenib resistance in melanomas with BRAF V600E mutations, Das Thakur *et al* modeled vemurafenib resistance in human xenograft models, as described in a recent letter in *Nature.* In a major conceptual breakthrough, they demonstrated that the fitness of vemurafenib-resistant tumor cells depended on ongoing treatment with vemurafenib, such that a 'sweet spot' of BRAF activity caused tumor cells to proliferate. This suggested a treatment approach in which drug treatment was periodically interrupted to delay the occurrence of resistant tumors; the strategy was successful. These data support a human clinical trial to test whether what worked in mice will also work in humans.

Nature, published online 9 January 2013; doi:10.1038/nature11814

Novel germline mutations in colorectal adenoma and carcinoma patients To identify germline mutations in patients with multiple or large colorectal adenomas or early-onset colorectal carcinomas, Palles *et al* performed whole-genome sequencing. As recently reported in *Nature Genetics*, they identified germline *POLE* mutations that encode POLE L424V enzymatically defective DNA polymerase ε molecules with a proofreading deficiency that leads to increased mutations. In addition, they identified germline *POLD1* mutations that encode POLD1 S478N enzymatically defective DNA polymerase δ proteins that also promote a mutator phenotype. The *POLD1* mutations also predispose to endometrial carcinoma. These results emphasize a critical role of DNA replication errors and coupled repair of mutations in predisposition to colorectal and endometrial cancers.

Nature Genetics 2013;45:136–144; doi:10.1038/ng.2503