in environmental or contextual features, suggesting that there are multiple mechanisms by which experiences can be differentiated (*7*, *8*). Small changes in contextual cues result in a change in the correlated neuronal activities ("rate remapping") in the dentate gyrus and CA3, whereas larger changes in contextual information result in the recruitment of different neurons, especially in CA3 ("global remapping") (*8*). McHugh *et al*. observed that rate remapping, but not global remapping, was disrupted in mice genetically engineered to lack NMDA receptors in the dentate gyrus (lack of a functional receptor prevents changes in synaptic strength). This phenotype allowed the authors to assess the role of rate remapping in differentiating between similar experiences.

McHugh *et al*. used a modified fear conditioning paradigm in which one of two experimental contexts to which mice are exposed was paired with the animal receiving a footshock. Although mice lacking NMDA receptors in the dentate gyrus acquired and retained contextual fear conditioning—the animals learned to associate fear with a particular environment—they were slower compared to wild-type littermates in learning to discriminate between two similar contexts. This result is consistent with the idea that synaptic plasticity at entorhinal cortex– dentate gyrus synapses is important when spatial context is used to identify the appropriate memory (receiving a footshock or not), and subsequently for making the appropriate behavioral response (whether or not to become immobile) (*9*). This notion has often been considered in terms of an ability to recall "what" happened "where," and could make a key contribution to episodic memory in humans. The NMDA receptor-mutant mice could, however, acquire spatial memory when learning to navigate a watermaze. The clear implication, therefore, is that NMDA receptor–dependent spatial pattern separation in the dentate gyrus is not required to solve the watermaze. So when is pattern separation a key feature of hippocampal function?

McHugh *et al*. show that subtle changes in the spatial context are sufficient to require pattern separation, but are such context shifts necessary? In a similar study, mice lacking NMDA receptors in the dentate gyrus learned to discriminate between which arms of a radial maze contain food rewards and which arms are not rewarded: They acquired spatial "reference" memory, as did the mice in the watermaze experiment (*10*). However, the mutant mice could not keep track of which arms they had already visited, making more spatial "working" memory errors than wild type mice with intact dentate gyrus physiology. The requirement for spatial pattern separation is the same for both the reference and working memory components of this task. Therefore, impaired spatial pattern separation cannot explain this spatial working memory deficit.

To solve a spatial working memory task, an animal must also process the temporal context associated with an event ("what happened, and when") and record or represent which locations have been visited recently. A role for the hippocampus in encoding temporal sequences in rodents has been demonstrated (*11*). Now, the new studies with genetically modified mice show that NMDA receptor–dependent plasticity at synapses in the dentate gyrus, and the possible subsequent rate remapping of correlated neural activities, contribute to temporal information processing, providing a mechanism by which recent experiences could be represented and thus differentiated.

The development of mice with inactivated or activated genes in specific regions of the hippocampus constitutes a great step forward in our understanding of how the hippocampus works. The challenge now is to understand the roles of individual NMDA receptor subunits, different forms of synaptic plasticity (long-term potentiation, long-term depression, and depotentiation), and the various hippocampal subregions (dorsal-posterior and ventral-anterior) in regulating behavior.

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10.1126/science.1145811

CANCER

Sex, Cytokines, and Cancer

Toby Lawrence, Thorsten Hagemann, Frances Balkwill

A cell signaling protein associated with the innate immune response is linked to a pathway that supports cancer progression.

Cancers are not just malignant cells. More than half of the cancer mass can be made of supporting cells such as fibroblasts, tissue macrophages, and endothelial cells; cancers cannot progress into life-threatening metastatic lesions without them. The process by which normal cells are recruited, expanded, and maintained in cancers is closely related to inflammation and to the remodeling that occurs in tissues as the damage of acute inflammation is repaired (*1*). Two papers in this issue, by Naugler *et al*. on page 121 (*2*) and Rakoff-Nahoum and Medzhitov on page 124 (*3*), advance our understanding of the mechanisms of cancer-related inflammation. They describe an important role for an intracellular signaling protein called MyD88 in the development of experimental liver and colon cancers in mice. MyD88 function has been well characterized in the innate immune response (*4*), relaying signals elicited by pathogen-associated molecules and by the inflammatory cytokine interleukin-1 (IL-1). Its identification in promoting cancer progression reveals a molecular pathway that could be targeted for drug development.

Early experiments demonstrated the need for inflammatory cytokines such as tumor necrosis factor–α (*5*), and inflammatory cells such as macrophages (*6*), in the development and spread of some experimental tumors. More recently, activation of the transcription factor nuclear factor κB (NF-κB), which is critical in cellular responses to TLR ligands and IL-1, was implicated in the innate immune response promoting murine hepatocellular and colon carcinoma (*7*, *8*). The conclusion from Naugler *et al*. and Nahoum and Medzhitov is that MyD88 may function upstream of NF-κB in cells

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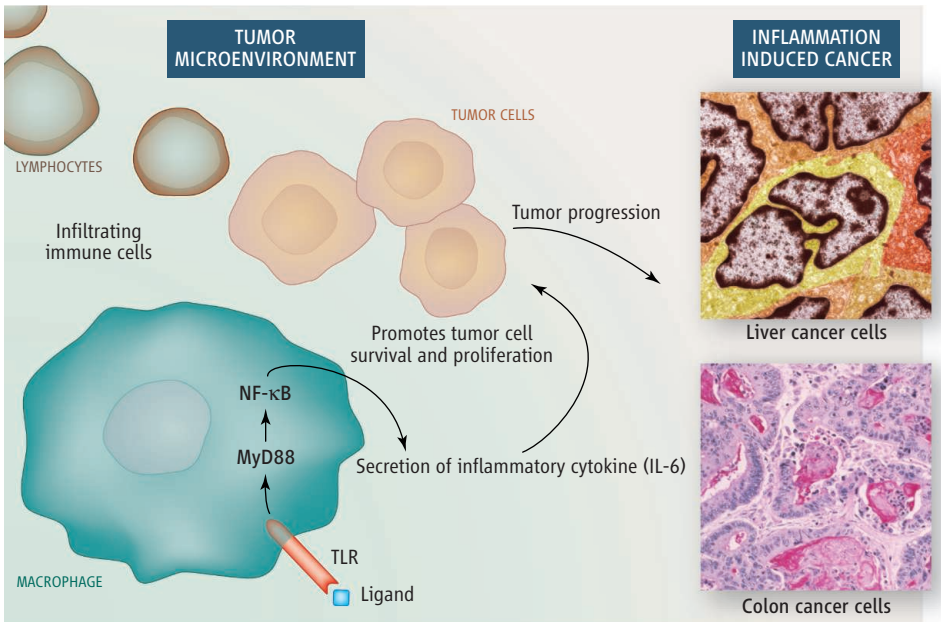
involved in inflammation-associated cancer (see the figure).

A key finding of Naugler *et al*. is that chemically induced liver damage in mice leads to the MyD88-dependent induction of IL-6 production. In this liver cancer model, IL-6, made by liver macrophages (Kupffer cells), promotes tumor progression. By specifically eliminating NF-κB activation in macrophages, this group previously established that during the development of liver cancers, IL-6 secreted by Kupffer cells requires NF-κB activity. MyD88 is required for both TLR and IL-1 to activate NF-κB in the innate immune response (*4*). The data of Naugler *et al*. suggest that TLR ligands (or IL-1β released by dead hepatocytes) could drive NF-κB activation in Kupffer cells through MyD88. However, the selective ablation of MyD88 in Kupffer cells is required to firmly establish this link. Ablation of specific TLRs or the IL-1 receptor would also reveal whether inhibition of these receptors could protect against liver tumor development.

Although the study by Naugler *et al*. implies that IL-1 or ligands for TLRs may trigger MyD88 activity and an innate immune response in liver cancers, it is likely that activation of MyD88 in spontaneous colon carcinogenesis, as described by Rakoff-Nahoum and Medzhitov, is driven by commensal bacteria that encounter intestinal macrophages. These authors crossed MyD88-deficient (*Myd88*$^{-/-}$) mice with mice that spontaneously develop intestinal tumors due to a mutation in the adenomatous polyposis coli (*APC*) gene (ApcMin/+). Mortality of the resulting mice was reduced by more than 60%. Although the absence of MyD88 did not affect initiation of malignancy, microscopic tumors failed to progress, and production of many inflammatory and tissue-remodeling factors (including IL-6) decreased. This study did not determine the role of MyD88 or NF-κB signaling in the intestinal macrophages of the ApcMin/+ mice. However, Greten *et al*. (*7*) have shown that ablation of NF-κB activation in macrophage cells protect mice from chemically induced colon carcinomas.

It's important to note that NF-κB also has cytoprotective and anti-apoptotic functions in malignant cells (*7*, *9*). However, neither of these phenotypes appears to be MyD88 dependent, suggesting that MyD88 is only responsible for inflammation-associated tumor promotion by NF-κB.

Another key finding of Naugler *et al*. relates to the gender differences in liver cancer susceptibility. In their model, the actions of IL-6 were only seen in male mice. Male mice—and men—are three to five times as likely to develop liver cancer as females because estrogens are key inhibitors of IL-6 production. At all ages, women are less likely than men to develop colon cancer (*10*). Estrogen hormone replacement therapy also reduces the incidence of colorectal cancer in postmenopausal women, and in several murine colon cancer models, females have fewer colon tumors than males. These estrogen-related gender differences may well extend to other cancers.



Inflammation spurs cancer progression. Immune cells infiltrate the microenvironment of a tumor. Naugler *et al*. and Rakoff-Nahoum and Medzhitov suggest that the development of liver and intestinal cancers in mice may depend on a signaling pathway in infiltrating immune cells that involves the protein MyD88, the transcription factor NF-κB, and the pro-inflammatory cytokine IL-6. Shown are images of human cancers.

However, MyD88 seems to have a wider role in malignancy than regulation of IL-6 production. Although Rakoff-Nahoum and Medzhitov do not specify the age and sex characteristics of the mice used in their experiments, they present no evidence that only males were protected from colon cancer when MyD88 was deleted. In ApcMin/+ mice (presumably both male and female), MyD88 induced the expression of factors (the enzymes COX-2 and MMP-7, and IL-1) that not only enhance tumor progression, but also are involved in tissue repair. It seems that MyD88 regulates a tissue-repair pathway that both promotes, and is triggered by, growing malignancy.

Do these experiments in mice have any relevance to cancer prevention and therapy? As suggested by Naugler *et al*., estrogen mimetics that inhibit excessive IL-6 production might prevent chronic liver disease in men. Certainly, TLR ligands are possible targets for cancer therapeutics, but their inhibition could severely compromise immune responses. The findings of Naugler *et al*. and Rakoff-Nahoum and Medzhitov strengthen the rationale for inhibiting inflammatory cytokines in cancer. IL-6 is implicated in the progression of several other human cancers including multiple myeloma, prostate cancer, and ovarian cancer. Antibodies that inhibit IL-6 action are safe and active in rheumatoid arthritis patients (*11*). They are also highly effective in the IL-6–driven myeloproliferative disorder Castleman's disease and are currently in Phase I/II clinical trials in other advanced cancers (*12*). But will these agents work best in males and postmenopausal women?

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10.1126/science.1146052

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Sex, Cytokines, and Cancer

Toby Lawrence, Thorsten Hagemann and Frances Balkwill (July 6, 2007)

Science **317** (5834), 51-52. [doi: 10.1126/science.1146052]

Editor's Summary

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