Hepatocellular Carcinoma (HCC) is a major cause of cancer-related death worldwide. The development of HCC usually takes 10 to 30 years; however, it is a terminal event in most cases. The common denominator underlying HCC carcinogenesis is the persistence of chronic inflammation. Once cancer is established in the liver, the host's innate and adaptive immune system still persistently attempts to eradicate the tumor. Current chemotherapy and radiation therapies for hepatocellular carcinoma (HCC), which causes 500,000 deaths per year worldwide, are not very effective. The recently approved multikinase inhibitor Sorafenib modestly improves survival by a few months. The common denominator underlying HCC carcinogenesis is inflammation, a form of host immune defense. It is most obvious in the setting of viral hepatitis, especially hepatitis C viral infection, resulting in lasting inflammatory response in the liver. The latent period from the original disease to the development of HCC usually ranges from 10 to 30 years; this long window of time provides an opportunity for investigating cancer development and designing strategies for intervention.

To achieve this end, a better understanding of the mechanisms by which HCC develops and progresses is critically important. The common denominator underlying HCC carcinogenesis is inflammation, a form of host immune defense. It is most obvious in the setting of viral hepatitis, especially hepatitis C viral infection. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade the host's innate and adaptive immune system and establish persistence. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade the host's innate and adaptive immune system and establish persistence. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade the host's innate and adaptive immune system and establish persistence.

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# Notes

The authors report no conflicts of interest.

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Current chemotherapy and radiation therapies for hepatocellular carcinoma (HCC), which causes 500,000 deaths per year worldwide, are not very effective. The recently approved multikinase inhibitor Sorafenib modestly improves survival by a few months in some patients with advanced cancer (1). Surgical resection and liver transplantation can be performed in less than 20% of patients. Thus, development of novel diagnostic and prognostic approaches and therapeutic modalities for HCC is urgently needed. The common denominator underlying HCC carcinogenesis is inflammation, a form of host immune defense. It is most obvious in the setting of viral hepatitis, especially hepatitis C viral infection. Hepatitis C virus is the major etiological factor for HCC in most developed countries. Hepatitis C virus has an ability to evade its host's innate and adaptive immune system and establish persistent infection, resulting in lasting inflammatory response in the liver (3). Although the detailed molecular cascades are not entirely known, there is no doubt that inflammation can cause genetic and epigenetic dysregulation in hepatocytes and, eventually, cell transformation. Once cancer is established in the liver, the host's innate and adaptive immune system still persistently attempts to eradicate or slow the cancer cell growth. Recent studies have demonstrated...
that the vigor and breadth of the immune system play a critical role in the outcome of HCC (4,5). However, the mechanism of how various components of the immune system interact with HCC remains a mystery.

The innate immune response against cancer is important because it not only directly attacks cancer cells but also primes specific and long-lasting adaptive immune response. In HCC patients, antigen-specific T cells are detectable, which indicates that both innate and adaptive immune responses are operative in HCC. Despite this immune response, cancer still prevails. One explanation for the insufficient immune surveillance is that immunosuppressive function mediated by regulatory T cells and myeloid-derived suppressor cells is upregulated in HCC patients (6–8). The increased infiltration of these immunosuppressive cells creates an immunosuppressive milieu in tumor tissue, which is associated with a bleak clinical prognosis. Studies showed that modulation of regulatory T cells improved overall antitumor immunity (9,10). Whether this strategy can be successfully used in HCC immunotherapy remains to be investigated. In addition, there are many other immune cells that infiltrate HCC cancer tissue, such as natural killer (NK) cells, macrophages, and different subsets of T and B cells. These cells can produce numerous cytokines that are almost certain to affect the tumor microenvironment. Moreover, HCC cells are capable of making molecules that counter the host immune response (10). Understanding the tumor microenvironment will undoubtedly help us figure out how to shift a tumor-friendly environment to a host-friendly one.

When discussing inflammatory reactions, a well-known pro-inflammatory family of proteins cannot be ignored. Initially considered key receptors to sense pathogens and activate the innate immune response against bacterial, viral, and fungal infection, Toll-like receptors (TLRs) have been recently recognized to play a role in cancer (11). Expression of different members of TLRs have been reported in a number of human cancers (12). However the functional role of TLRs is much more complicated. Both protumor growth and antitumor activities were reported (13). Clearly more experiments are needed to unravel the biological role of TLRs in cancer. More important, we need to find out how to use the knowledge for cancer therapy because multiple TLR agonists have been developed (14).

In this issue of the Journal, Chew et al. present their intriguing study on the role and the underlying mechanism of TLR3 in HCC (15). This study brings attention to the effect of innate immunity on HCC progression and its clinical outcome. The investigators examined the expression levels of TLR3 in 172 human liver cancer tissues from predominantly female (82%) patients and found that increased TLR3 expression is positively correlated with a longer survival for HCC patients. Using immunohistochemical staining, they identified TLR3 overexpression in both HCC cancer cells and tumor-infiltrating NK cells and, independently, that higher expression of TLR3 on either cell population is associated with longer survival. The investigators then performed a series of experiments to demonstrate that activation of TLR3 by polyinosinic:polycytidylic acid (poly I:C) caused apoptosis of the TLR3-positive HCC cell lines, whereas similarly activated TLR3 promoted NK cell proliferation and increased NK cell antitumor activity. The investigators further examined the impact of TLR3 activation on cancer cells and immune cells in mouse models. Similar to the in vitro observation, they found that both T cells and NK cells proliferated upon poly (I:C) treatment, whereas in vivo the HCC cells exhibited fourfold lower proliferation and an 11-fold increase in tumor cell apoptosis. The findings suggest that effects of TLR3 are quite different in immune cells and in cancer cells. The tantalizing questions are how TLR3 knows how to act differently in normal and cancer cells and what the downstream signaling molecules are.

Chew et al. also examined the effect of TLR3 activation in murine HCC models (15). When mice with endogenous HCC were treated with poly (I:C), there was increased expression of Ccl5 and CXCL9 in both the HCC cancer cells and tumor-infiltrating leukocytes. NK cell numbers also increased; these cells appeared to be activated in the tumors. The authors further demonstrated in a transplant HCC mouse model that the expression of Ccl5 and CXCL9 increased tumor-infiltrating lymphocytes and suppressed the tumor growth. The data seem to suggest that TLR3 may function through induction of these two cytokines. This interpretation may be an oversimplification of a much more sophisticated process. It is well known that TLR3 can activate interferon regulatory factor 3 (IRF3) and induce abundant production of type 1 interferons. One has to wonder what happens to interferons in the tumor and what role interferons play. It is a relevant question because interferons have an antitumor effect on many types of human cancers, including HCC, as well as an immune regulatory effect.

One of the most interesting findings from this study is the demonstration of the multiple functions of TLR3: slowing cancer cell proliferation, increasing apoptosis, and attracting NK cells and T cells and enhancing their proliferation and antitumor effect. These functions are all beneficial for fighting cancer, at least in HCC. It is not surprising that TLR3 can cause HCC apoptosis because it has been shown before that TLR3 and IRF3 activation induces the production of tumor necrosis factor–related apoptosis-inducing ligand (16). The puzzle is why this TLR3-mediated pathway does not act earlier to stop the cancer in the first place. Because hepatitis C virus has an ability to interfere with TLR3 signaling (17), it is possible that cancer cells can act similarly.

Although the molecular mechanisms remain to be defined, activation of TLR3 appears to be beneficial for HCC patients and raises the hope that TLR3 can be used as a target for immunotherapy. The use of TLR3 agonists in this study provides proof of concept. However, the immune system can be a double-edged sword, and we must proceed carefully with experimental therapy. The challenge is how to kill cancer cells without causing damage to noncancerous hepatocytes. The nontumor liver tissue has its own unique microenvironment created by interaction between viruses and immune responses, and we should focus on how to selectively turn on TLR3 in cancer tissues but not in the whole liver or the whole body. The timing, intensity, and location of certain immune functions are paramount to maintain homeostasis while fighting off disease. Understanding how TLRs or other innate immune components operate in the cancer microenvironment will certainly enhance our ability to fine-tune the immune system to fight cancer.

References
An Aspirin a Day: The Allure (and Distraction) of Chemoprevention

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Controlling cancer by using one or more chemical compounds to prevent its occurrence has held tantalizing promise for decades (1). Nearly 30 years ago, when the research community was exploring the potential of ascorbic acid and \( \alpha \)-tocopherol, proponents observed that chemoprevention had a solid theoretical base and examples of protection from neoplasia in experimental animals had been documented (2). Subsequently, chemoprevention trials have shown mixed results. Studies have disappointed for the effects of \( \beta \)-carotene, \( \alpha \)-tocopherol, retinol, retinyl palmitate, \( N \)-acetylcycteine, and isoretinoin on lung cancer (3), one of the more intensely studied organ systems. On the other hand, use of selective estrogen receptor modulators, such as tamoxifen, has been shown to reduce the incidence of breast cancer in high-risk women (4), and dutasteride in cancer: a double-edged sword for defense and offense. Arch Pharm Res. 2012;35(8):1297–1316.

Evidence has now accumulated that daily aspirin reduces the long-term risk of death due to cancer too (8,9). However, although aspirin has been shown to reduce incidence of colorectal cancer, the effects on incidence of other cancers are essentially unknown (9). Meanwhile, other nonsteroidal anti-inflammatory drugs (NSAIDs) have also shown promise in cancer chemoprevention. COX2 inhibitors, which slow the cyclooxygenase enzymes involved in the synthesis of prostaglandins, appear to prevent colon and breast cancer (10). In this issue of the Journal, Sahasrabuddhe et al. (11) examine the preventive benefits of NSAIDs for primary hepatocellular cancer (HCC) and the presumed intermediate surrogate of chronic inflammatory liver disease. The investigators make the promising observation that, in a large, prospective, cohort study, use of aspirin and other NSAIDs was associated with lower risk of death due to chronic inflammatory liver disease, and aspirin use was linked to reduced risk of developing HCC. Although the emerging research findings on cancer impacts have not yet translated into clinical recommendations such as those for prevention of vascular disease by the use of daily aspirin, the hype is building. A Google search of