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Editorial

Cancer Prevention Research

Targeting Toll-like Receptors in Cancer Prevention

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Abstract

There is a pressing need for the development of new prevention strategies for the most common worldwide malignancy, nonmelanoma skin cancer (NMSC), as sun protection efforts have not proven to be completely effective. Interestingly, despite the known circumstance that individuals undergoing chronic immunosuppression are at a substantially increased risk for developing NMSC, in this issue of *Cancer Prevention Research*, Blohm-Mangone and colleagues provide new evidence that topical application of the Toll-like receptor 4 (TLR4) antagonist resatorvid may be efficacious as a chemopreventive agent in NMSC specifically via blocking UV-induced inflammatory signaling. These new findings highlight a potentially delicate dichotomy between the role of innate immune receptors in the normal, protective immunosurveillance of damaged cells in the skin and the pathogenic UV-induced overstimulation of cutaneous inflammation that promotes photocarcinogenesis. Given the tremendous cancer burden incurred by NMSC, further exploration of the use of TLR4 antagonists in NMSC chemoprevention strategies is certainly warranted. *Cancer Prev Res; 11(5); 251–4. ©2018 AACR.*

See related article by Blohm-Mangone et al., p. 265

The immune system plays a dichotomous role in cancer. On one hand, the immune system is responsible for immunosurveillance and for orchestrating antitumor immune responses; indeed, much recent attention and effort have been given to developing strategies for harnessing the immune system in tumor-destroying immunotherapy approaches. On the other hand, overstimulation of the immune system can likewise drive tumor initiation and progression, and chronic inflammation is attributed as a causative factor or cofactor in a growing list of cancer types. In many instances, these two attributes of the immune system (both anti- and procarcinogenic) share similar immune pathways, cell types, and even cellular immune receptors.

Toll-like receptors (TLR) serve as an exemplary illustration of the bipolar relationship between the immune system and cancer: TLR agonists are currently in use or under development as immunotherapeutic agents, while TLR antagonists are simultaneously being explored for use in cancer chemoprevention. TLRs are a highly conserved class of innate immune pattern recognition receptors that recognize molecules that are broadly shared by pathogens. For example, TLR4 recognizes lipopolysaccharide (LPS) found in most Gram-negative bacteria. In addition to recognition of microbial components such as LPS, TLR4 is also stimulated by damage-associated molecular patterns, including the nuclear protein HMGB1, certain heat shock proteins (HSPs), oxidized LDL, and fragments of extracellular matrix molecules that are released during noninfectious inflammatory conditions (1). TLR4 stimulation can lead to downstream activation of NF-κB, resulting in the expression of proinflammatory cytokines and type I interferon. TLR4 is expressed on a number of immune cell types, including macrophages and dendritic cells, and is reportedly expressed or has increased expression in a number of cancer types, including head and neck, esophageal, gastric, colorectal, liver, pancreatic, ovarian, cervical, and breast cancer, as well as melanoma (2). TLR expression on cancer cells is thought to facilitate immune evasion, inhibit apoptosis, and promote cell survival and migration (3).

TLR Agonists and Cancer Immunotherapy

Some of the earliest strategies for cancer immunotherapy harness the proinflammatory nature of TLRs. The anticancer agent Coley's toxin, a mix of killed bacteria of species *Streptococcus pyogenes* and *Serratia marcescens*, was later discovered to act via proinflammatory signaling induced by engagement of TLR4 (4). Likewise, Bacillus Calmette-Guérin (BCG) vaccine, commonly used in the treatment of

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bladder cancer, is thought to function in part via activation of TLR4 (5). TLR agonists are likewise commonly used as vaccine adjuvants, and examples include Freunds complete adjuvant, monophospholipid A (MPLA), and Adjuvant System 04 (AS04). Similar TLR agonist strategies are undergoing active exploration as adjuvants to cancer immunotherapies, including in nonmelanoma skin cancer (NMSC). For example, imiquimod (Aldara), a TLR7 agonist, is effectively used to treat genital warts as well as superficial basal cell carcinoma (BCC). The mechanism by which imiquimod acts to eradicate these lesions is proposed to involve heightened immune response that includes activation of antitumor Th1/Th17 cells as well as induced apoptosis of tumor cells (6). The synthetic CpG oligodeoxynucleotide PF-3512676, a TLR9 agonist, has also been shown to demonstrate clinical activity in BCC (7). One important consideration is that all of these TLR agonist immunotherapy strategies are developed for use in the context of eradication of an established cancer.

TLR Antagonists and Cancer Prevention

Although less mature than the use of TLR agonists in cancer therapy, the inhibition of TLRs via the use of TLR antagonists has also been recently explored as a cancer prevention strategy. Much of these efforts have focused on inhibition of TLR4 signaling, as this specific TLR is implicated as a driving factor in many of the most common forms of cancer (8). For example, in preclinical models, TLR4 inhibitors have been shown to inhibit the development and/or migration and invasiveness of colon (9) and breast cancer (10) and have been proposed as a therapeutic strategy in hepatocellular carcinoma (11). Importantly, all of these cancer types have been linked to chronic inflammation as a causative factor or cofactor, indicating that TLR4 may even broadly serve as a major target for the inhibition of inflammation-associated cancers.

In NMSC, TLR4 in particular has been previously demonstrated to contribute to the stimulation of cellular stress in the skin upon UV exposure and may serve as a key driver of cutaneous inflammation (12). Resatorvid is a small-molecule inhibitor of TLR4 and has been previously demonstrated in a clinical trial for use in severe sepsis to have an excellent safety profile (13). In this issue of *Cancer Prevention Research*, Blohm-Mangone and colleagues explore the use of resatorvid as a topical formulation for the prevention of NMSC using *ex vivo* permeability assays and an *in vivo* UV-induced skin tumorigenesis model. The study provides intriguing evidence that blocking TLR4 signaling via pharmacologic TLR4 antagonism by use of topical resatorvid may serve to prevent solar UV-induced skin tumorigenesis. The authors demonstrate that use of resatorvid as a prevention strategy (in conjunction with UV exposure) showed delayed growth of UV-induced cutaneous squamous cell carcinoma and increased survival in high-risk SKH-1 (hairless) mice. Importantly, this same treatment was not effective as an intervention strategy (e.g., use of resatorvid after UV exposure) in this same model. The mechanism of inhibition of tumorigenesis by resatorvid was shown to involve attenuation of UV-induced cellular stress and AP-1 signaling and, importantly, inhibition of epidermal immune cell infiltration. This study by Blohm-Mangone and colleagues provides attractive preclinical evidence for a new NMSC prevention strategy and prompts further exploration of the use of topical resatorvid in the prevention of NMSC.

The skin is the largest organ and an immense epithelial barrier to outside exposure to cancer-inducing insults, such as carcinogens, pathogens, and UV damage. The innate immune system is the responsible guardian of much of this barrier protection, and indeed, immune suppression is globally linked to an increased risk of cancer, including NMSC. Conversely, overstimulation of the immune system, and especially in the form of persistent, chronic inflammation, is a known risk factor for cancer development. Cancer prevention strategies that target the immune system, and specifically key innate immune cell receptors, are certainly warranted and must carefully modulate the delicate balance of immunity that exists at epithelial barriers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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