

Cancer Immunoprevention: A New Approach to Intercept Cancer Early

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Abstract

Cancer immunoprevention refers to the modulation of the host immune response to control the initiation or development of cancer. The significant role of host immunity in early tumorigenesis has only recently been confirmed, as a better understanding of the mechanisms, molecules and cells involved in tumor immunology have been elucidated over the past two decades. Of utmost importance, preclinical and clinical evidences have demonstrated that early neoplastic cells (transformed cells that initiate cancer formation) express antigens that allow the immune system to distinguish them from normal cells. Furthermore, recognition of the aberrant cell by the immune cells activates a complex interaction of mutual modulation between the immune cells, the tumor and the tumor microenvironment that may result not only in inhibition but also promotion of cancer. The deepening understanding of cancer-related immunologic processes, properties, and components has spawned exploration of more rational, mechanism-based immunologic strategies (using vaccines, antibodies, and immune modulators) for cancer prevention. This introduction to the *Cancer Prevention Research* immunoprevention series will attempt to review the basics of the immune response modulation as a basis for potential application to cancer immunoprevention strategies with an emphasis on vaccines. Recognizing the fast-paced research in immune response modulation, the series will cover current understandings and future directions of cancer immunoprevention research.

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Mechanistic Bases of Immunoprevention: A Primer

Innate versus adaptive immunity

The concept of cancer immunomodulation is based on the physiologic immune response during the natural course of disease (1–3). The immune response has been historically divided into two types: innate and adaptive (4, 5). The innate immune response provides immediate, short-term protection against a variety of nonspecific antigens. In contrast, adaptive immune responses develop over a longer period of time, are specific, and provide long-term protection. Activation of innate and subsequent adaptive immunity is fundamental to effective immunologic eradication of exogenous and endogenous pathogens and undesirable endogenous cells (e.g., cancer cells).

The essential components of each type of immunity differ, but their activities overlap. The elements of the innate immune system are (i) epithelial barriers, (ii)

phagocytic leukocytes, (iii) dendritic cells (DC), (iv) natural killer (NK) cells, and (v) circulating plasma proteins. Elements of the adaptive immune system fall into two functional categories: humoral immunity, mediated by the antibodies produced by B lymphocytes, and cellular immunity, mediated by T lymphocytes (6). DCs are one of the major sentinels of both innate and adaptive immune responses.

During the innate response, DCs scan for potential pathogens using Toll-like receptors (TLR), which are pattern recognition receptors. Once the TLR recognizes and then processes, it activates NF- κ B cells and MAPK signal transduction pathways, which play a large role in initiation and regulation of innate immune responses (7–9). Modulation of TLR immune responses are being pursued as potential therapeutic targets for various inflammatory diseases and cancer.

The adaptive or acquired (specific) immune response is much more complex than the innate (nonspecific) response as it continually adapts to new pathogenic signals (i.e., infections or tumor antigens). Upon encountering an antigen presented on DCs or other antigen-presenting cells (APC), this plastic system undergoes somatic hypermutations in the B-cell receptors leading to high-affinity immune responses, producing antibodies with increased highly specific antigen-bonding capacity and durability (5, 10). With each repeated antigen encounter, more of the same

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Table 1. Similarities and differences between innate and adaptive immune responses

Innate immune response	Adaptive immune response
Immediate response	Delayed response
Short-term memory	Long-term memory
Nonspecific response	Specific to antigens
No antigen needed	Antigen required
DCs, NK cells, neutrophils, macrophages	DCs, T cells, B cells

NOTE: DCs—a link between the innate and adaptive systems.

antibodies are produced. This process conveys the long-term memory of the adaptive immune system, which can be elicited by both tumor-specific antigens and oncogenic infectious agents. Thus, both B and T memory cells can respond quickly to subsequent challenges by the same antigen. Conversely, in later stages of carcinogenesis and chronic inflammation, regulatory T cells (T_{reg}) and myeloid-derived suppressor cells (MDSC) are invoked, which subdue the immune response (see Table 1; ref. 11).

Cancer Immunosurveillance and Immunoediting

More recently, the immune response to cancer has been termed "immunoediting," which expands upon "immunosurveillance," a hypothesis that was introduced by Burnet and Thomas in the mid 20th century (12–14). However, much later in the century, with the availability of novel molecular techniques, the hypothesis was pursued (Fig. 1).

The immunoediting hypothesis proposes that both the innate and adaptive immune systems provide an immunosurveillance function, which inherently identifies and eliminates aberrant cells and builds a durable specific defense against them. This hypothesis also explains how tumors are able to escape from the antitumor immune responses (15). For instance, sarcomas from immunodeficient mice were significantly more immunogenic than tumors from wild-type mice that arose in the presence of an intact immune system (16), indicating that immune response is sculpting the tumors' ability to be recognized by the immune system. Recently, the presence, location, and density of T cells and cytokines within colorectal tumors was shown to have a better prognosis, hence emphasizing that the ability of immune response to maintain a subclinical tumor in an equilibrium state (17). However, in the setting of late stages of cancer, these mechanisms are often coopted to favor the tumor, in which they collectively carry out "immunoediting," manipulating their microenvironment by expression of inhibitory chemokines and cytokines as well as recruitment of immunosuppressive cells such as MDSCs and T_{reg} s (2, 3).

Immunology of Vaccines against Oncogenic Infectious Agents

Both innate and adaptive immune responses play important roles in the battle against oncogenic infectious agents. Two major types of helper T (Th) cells may be induced by APCs: Th1 (characterized by $IFN\gamma$ secretion) for intracellular pathogens and Th2 [characterized by release of interleukin (IL) 4 and B-cell activation] for extracellular pathogens. T cells can only recognize antigens in the context of the MHC. In addition to Th cells, CTLs (NK cells, $CD8^+$) play a key role in clearing infections.

Immunology of Vaccines against Tumor-Associated Antigen

Of the approaches designed to harness an individual's immune system against cancer, vaccine's use are the best known; they have shown greater success in cancer prevention than treatment. The preferential success of preventive vaccination is attributable in large part to a minimal or nonexistent tumor burden. In addition, candidates for preventive vaccination still have fully competent immune systems capable of developing robust antitumor responses leading to eradication of abnormal cells and/or preventing disease onset and recurrence. The endogenous immune response may prevent cancer via three basic approaches by (i) using vaccines to prevent infection with cancer-associated agents; (ii) using vaccines to target tumor-associated antigens (TAA) or tumor-specific antigens; and (iii) using nonspecific immunomodulators that recruit components

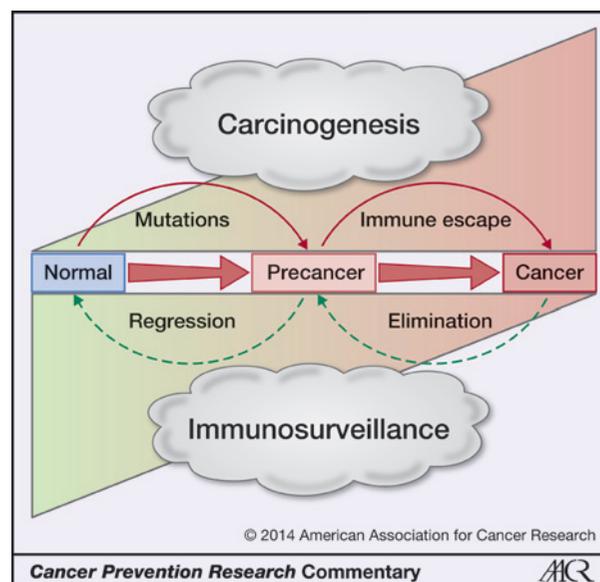


Figure 1. During progression from normal to precancer and cancer mutations may provide immune response to continuously survey and eliminate these mutated cells. However, during this evolutionary process especially in late stages of cancer mutations that make them capable of escaping this immunosurveillance often through immunosuppressive mechanisms are at the core of immune response against cancers.

of the innate immune system to exert their anticancer effect.

Advantages of Cancer Immunoprevention

In summary, the advantages of immunologic approaches for cancer include:

1. Minimal toxicity
2. Immediate as well as long-term (probably lifelong) memory
3. Ease of delivery and cost effectiveness
4. Potential to completely eliminate infectious agent-associated disease
5. Ease of combination with other effective cancer-preventive approaches (Fig. 2)

Minimal Toxicity

A key requirement of any drug given in the prevention setting—to high risk rather than actual patients with cancer—is a favorable toxicity profile. Historically, adverse effects of vaccination have been mild and localized, such

as pain, edema, and erythema at the injection site, fever, and rash. Vaccine-related serious side effects are rare but may include life-threatening allergic reaction, autoimmune reactions, or seizure (18).

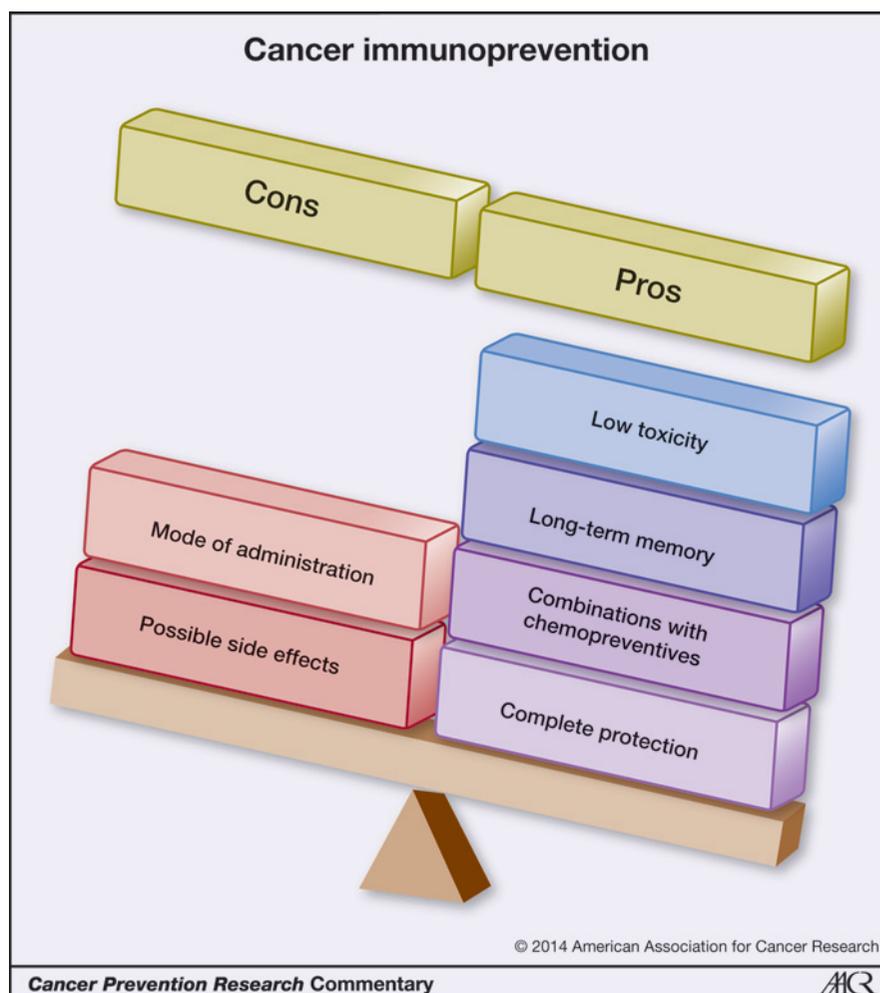
Long-term or Lifelong Protection

By effectively activating the adaptive immune response, cancer immunoprevention approaches may provide immunologic memory and convey long term, if not lifelong protection. This has been demonstrated in the infectious disease setting by the eradication of smallpox, as well as the huge success with polio, measles, mumps, rubella, and other serious infectious agents (19). In terms of vaccines against oncogenic infectious agents, positive data are accumulating for hepatitis B vaccine (HBV) and human papilloma virus (HPV) that suggest a long-term protection against HBV (20, 21) and HPV (22).

Ease of Delivery and Cost Effectiveness

A consecutive immunization strategy that consists of one prime and just a few boosts is used for most peptide and

Figure 2. Pros and cons of cancer immunoprevention strategies include, minimal or low toxicity, long-term memory of the immune response, and possibility of complete protection (especially vaccines against oncogenic infectious agents). However, since many cancer vaccines are against self antigens and stimulating immune response via modulation of immune checkpoints potential side effects and toxicities are still a concern until we better understand these. Further, combination of some of the most effective chemopreventives (e.g., aspirin or other NSAIDs) might provide further additive or synergistic effects.



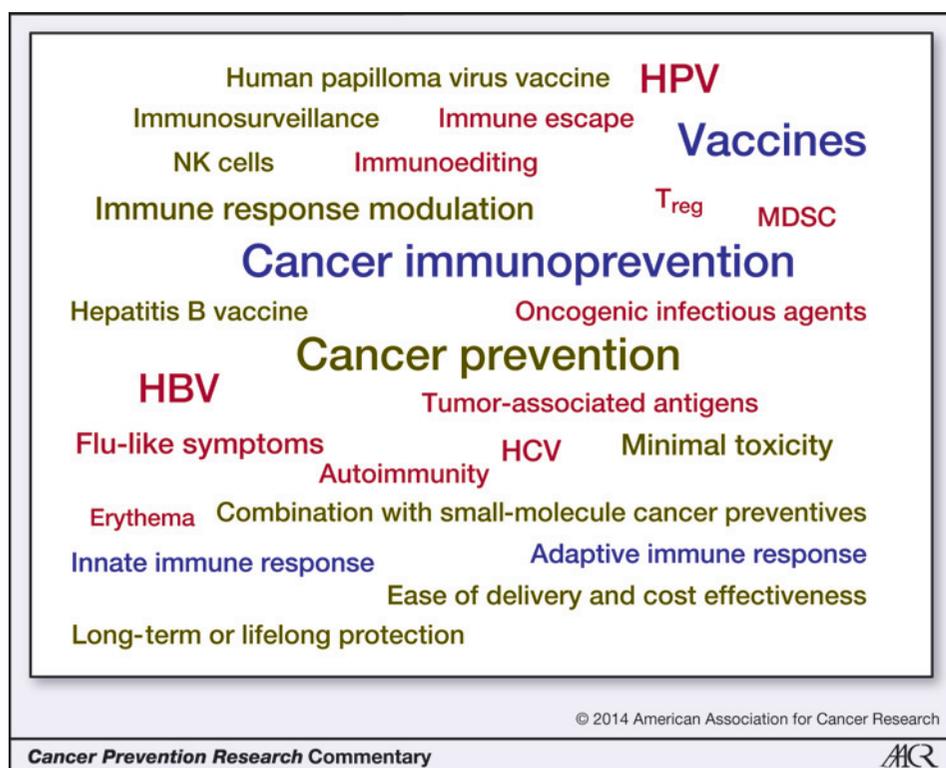


Figure 3. A text tag cloud as a visual representation of this commentary providing a quick guide to topics of discussion.

DNA-based vaccines to provide full immunity against many antigens (23–25). Compared with lifelong administration required for most proposed cancer prevention agents, a short series of vaccinations is much more feasible, especially in at-risk populations that are difficult to reach. For any cancer-preventive approach to be successful at the population and mass level, affordability and cost effectiveness are critical. Currently approved cancer-preventive vaccines against HBV and HPV are available at affordable levels for the general public. HPV vaccines, one of the newer arrivals, are in fact, substantially more expensive and seem to be contributing to difficulty in their wider dissemination globally.

Combination with Small-Molecule Cancer Preventives

There are a handful of cancer chemopreventive agents that have shown their efficacy through the rigor of phase III clinical trials. However, many promising agents either have high-toxicity profiles or are not feasible for administration on a regular basis. One approach to minimizing the side effects without losing effectiveness of the later agents while maintaining effectiveness is dose reduction and combination with vaccines for an additive or preferably synergistic effect.

The availability of safe, effective vaccines for immunoprevention of cancers associated with infectious agents has led to recommendations from professional societies for implementation at the population level that could

decrease cancer burden worldwide. However, slow implementation of the recommendations in several countries due to social, cultural, and economic issues remains a challenge. Future development of vaccine strategies should factor in the need for more accessible, cost-effective, and broad-spectrum vaccines for oncogenic infections (e.g., HPV, HCV, etc.) that can be deployed at an international level. Cancer immunoprevention strategies for TAAs are in the early stage of development. These vaccines have been successful in numerous genetic and carcinogen-induced mouse models, but the translation of preclinical findings to humans is challenged by the need for meaningful target antigens in the precancer/early neoplasia setting. However, promising approaches are in early development, and several vaccines are in clinical trials. This series is intended to encourage a dialogue about immune response modulation as a viable approach to cancer prevention (Fig. 3). To stimulate the conversation, a series of thoughtful articles by the leaders in the fields of immunology and cancer prevention will provide informed perspectives as well as new findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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