MiniReview

**Personalized Immune-Interception of Cancer and the Battle of Two Adaptive Systems - When is the Time Right?**

Madhav V. Dhodapkar

**Author's Affiliation:** Departments of Medicine (Hematology) and Immunobiology, Yale University School of Medicine; Program in Hematologic Neoplasia, Yale Cancer Center, New Haven, CT

**Corresponding Author:** Madhav V. Dhodapkar, M.D., Arthur H. and Isabel Bunker Professor of Medicine and Immunobiology, Yale University School of Medicine, 333 Cedar Street, Box 208028, New Haven, CT 06510. E-mail: madhav.dhodapkar@yale.edu
Abstract

A growing body of evidence points to a co-evolutionary model of cancer wherein the cross-talk between tumor cells (or their subclones) and the host determine the malignant potential of individual tumors. Most of this natural history is clinically invisible and includes preneoplastic states. The capacity of the immune system to recognize these incipient lesions provides the basis for targeting them immunologically in order to arrest the development of preneoplasia towards clinical cancer. Kimura and colleagues provide evidence of immunogenicity of a potential cancer vaccine in patients with a history of advanced colon adenomas. These studies provide proof of principle or feasibility of such an approach in the clinic. Here we discuss emerging opportunities and challenges in harnessing the immune system to “intercept” the precursor or preneoplastic lesions. Both cancer cells as well as the immune system represent independent and complex systems with plasticity and adaptive potential. It is therefore likely that specific aspects of the cross talk between tumor cells and host may differ between individual tumors and determine the evolution of both tumors and the host response. We try to make the case to consider individualized approaches based on the genetic make-up of tumor cells and properties of the host response. Such strategies may be needed to optimally position the immune system to prevent cancers.
In any game of chess, the initial set of moves (termed the chess openings) play a critical role in determining the course and eventually the outcome of the game. In contrast, during the "end game", the strategic options may be limited and eventual outcome strongly biased already towards one side or another. To date, cancer immunologists have focused mostly on the end game, patients with advanced cancer.

While recent successes in the clinic (such as with T cell checkpoint blockade) (1-3) offer optimism even in this setting, we suggest that the field of immuno-oncology would be well served in moving at least part of its attention from the end game to the openings. Active interventions in this setting might have a greater and longer lasting impact than application of similar strategies to target advanced cancers. In 2011, Nobel Laureate Elizabeth Blackburn proposed a term cancer interception to describe active intervention to halt the progression of cancers in precursor states (4). Here we modify the term as immune-interception, to specifically discuss immune based approaches with this objective (5).

**Cancer as a battle of two adaptive systems**

The importance of the cross-talk between tumor cells and the microenvironment is now well appreciated (6). However, the analogy to the chess match, as noted above, is particularly suited for the interactions of tumors with the immune system, as both of these are highly adaptive systems. The immune system has evolved over a much longer time, and it could be argued, therefore, that a young immune system should have greater adaptive fitness than the nascent or young tumors. With age, however, the available repertoire of T cell receptors diminishes over time, which might contribute to lower adaptive fitness of the aging immune system (7). Tumors may also differ in their genetic complexity and adaptive potential. For example, many of the pediatric tumors appear to be genetically less complex with fewer mutations per cancer cell (8). In contrast, several tumors in adults are often genetically more complex and carry extensive sub-clonal evolution (9). This may in turn facilitate greater capacity for adaptive fitness and eventual immune escape. In addition, over time, growing tumors engage several strategies that may help facilitate escape from active pressure of
immune response. These include not only fundamental changes in the tumor cells themselves (such as mutations or alterations in MHC or antigen processing molecules) but also the suppression of tumor immunity via several mechanisms including regulatory T cells, myeloid derived suppressor cells (MDSCs), and immune-suppressive cytokines. Furthermore, expression of inhibitory receptors (such as programmed death ligand-1; PDL1) in the tumor-bed may lead to inhibition of T cell function and evolution of a dysfunctional or exhausted T cell response. Together, these studies suggest that while the balance might favor the immune system early in the course of evolution of tumors, over time as the tumors evolve (and as the immune system ages and tumors develop suppressive mechanisms), the balance tilts towards tumors (10, 11).

**Immune recognition of early tumors**

The consequences of early immune recognition have been extensively studied in murine models (12). These studies have indicated a role for both innate and adaptive immunity in mediating immune surveillance in both spontaneous and carcinogen-induced models. Further, tumors that are not rejected by the immune system can stay in an equilibrium with the immune system and undergo immune selection or editing, eventually contributing to escape of tumors from the immune pressure (13). Recent studies have also demonstrated the capacity of the immune system to delay the development of autochthonous tumors in mouse models (14). The concept of immune recognition of early tumors and immune surveillance has also been demonstrated in human tumors. For example, pioneering studies by Galon et al. have demonstrated that the nature of tumor infiltrating immune cells is a major determinant of prognosis in colorectal cancers (15). In this setting, the prognostic impact of immune signatures dominates over that from traditional staging systems. The impact of early immune recognition is particularly evident in patients with monoclonal gammopathy of undetermined significance (MGUS), which serve as precursor lesions for the development of myeloma. These lesions carry most of the genetic and cytogenetic abnormalities found in myeloma tumor cells, yet they may remain indolent for prolonged periods of time, and the majority never become clinically malignant (16).
MGUS patients was found to be enriched for preneoplasia-specific T cells, and the presence of spontaneous T cell immunity to SOX2, an antigen expressed on myeloma progenitor cells, was found to be a strong predictor of reduced risk of progression to clinical myeloma (17, 18). Thus, not only is the immune system capable of recognizing tumor cells in preneoplastic (and pathologically invisible) lesions, but the properties of this response, both in terms of the nature of the immune response and the target antigens, may impact the risk of malignant transformation. This capacity of the immune system to recognize pathologically invisible lesions has major implications for strategies in preventive immune-oncology.

The case for immune-interception by targeting precursor lesions

Several lines of evidence point to the need to consider precursor lesions as targets of vaccines (19, 20). In addition to immunology itself, another compelling argument has emerged from cancer genetics, wherein it appears that several of the precursor or “early” lesions are genetically quite “advanced.” For example, the great majority of genetic changes observed in tumor cells in breast cancer or myeloma can be observed in tumor cells from ductal carcinoma in situ (DCIS) or MGUS, respectively (16, 21, 22). If these genetic or epigenetic changes form the very basis of neoantigens, then they are already present in the premalignant stage wherein the tumor cells are potentially less formidable and less evolved. Preneoplastic lesions likely also express the driver mutations or trunk mutations expressed on both the parent clone and the subclones within the tumor. In addition, in most preclinical studies, vaccines are more effective and often tested in the setting of prevention of tumors as opposed to therapy of established tumors (23). Even when a particular vaccine is tested in preclinical models of “established tumors,” it is not entirely clear as to how well such tumors reflect the biology of an established tumor that has grown in vivo over a period of many years. The capacity of the immune system to prevent virally-induced tumors provides an excellent example of how the immune system may be targeted against tumors. Even in this setting, the administration of a vaccine based on human papilloma virus was shown to be quite effective in inducing regression of vulvar intraepithelial neoplasia (VIN; ref. 24).
Preclinical studies also suggest that vaccines based on tumor-associated antigens such as muc-1 and Her2 are quite immunogenic and effective in terms of prevention of tumors (25). The recent study by Kimura et al. provides an example of testing muc-1-targeted vaccine towards prevention as opposed to therapy of human cancer (5). In this study, the vaccine was found to be immunogenic, except in patients with elevated MDSCs. Evaluation of immunogenicity was however largely based on humoral responses and detailed data on T cell immunity would be of interest. Immune approaches to prevent cancer do not need to be restricted to adaptive immunity, as innate mechanisms such as natural killer or natural killer T (NKT) cells also play an important role in immune surveillance against tumors. In a recent study, we demonstrated that a combination approach targeting innate NKT cells led to durable clinical regression of tumors in patients with asymptomatic myeloma, a precursor to clinical myeloma (26). Such studies now offer the potential for extension to larger scale efforts to prevent clinical malignancy. The role of immunomodulatory drugs (such as lenalidomide) in preventing clinical myeloma is actively being tested in the clinic.

**The case for personalized interception**

Recent advances in cancer genetics and next generation sequencing are providing unprecedented opportunities for the development and testing of targeted therapeutics in cancer. We suggest that sequencing the genomes of precursor states will yield an equally rich database of genomic alterations and mutations. While the traditional approach in cancer prevention tries to find pathways that could be targeted by drugs, it is possible that such therapies would carry the risk of toxicities due to effects on normal tissues and may require longterm administration. For example, inhibitors of hedgehog signaling were effective in patients with basal cell nevus syndrome, but most lesions recurred after stopping therapy (27). While the plethora of genetic somatic mutations can be a challenge for pharmacologic approaches for prevention, it is equally a boon for immunologic approaches, as they allow the immune system to specifically target the tumor while sparing normal tissues (28). For example, reverse immunology could help identify the mutations that might lead to aberrant proteins and predict the
potential immune epitopes generated, which in turn could help develop personalized vaccines (29). It is also useful to remember that even at this “early stage,” there is already a naturally occurring host response against these lesions. In this setting, control mechanisms that limit such immune responses may also be operative. Therefore, the optimal strategy for several patients may not be simply to vaccinate in order to elicit or boost immunity against tumors but also to address the mechanisms that may limit the immunogenicity of the vaccines or naturally occurring immunity. Here again, understanding the properties of the host response in the specific patient may allow the correct choice of the combination approach. Alternatively, deeper understanding of the kind of immune suppressive mechanisms operative early on in an individual patient may also aid in patient selection and in limiting patients for vaccine studies to those that lack such responses. It is equally important to note that not all premalignant lesions may be equally likely to transform to clinical malignancy. Therefore, understanding the risk of transformation in a specific premalignant lesion may be essential for balancing the potential risks and benefits of a preventive intervention. Timing is a key element for a successful attack in a chess game: too early and your preparations are incomplete; too late and your opponent has rallied his defenses and even launched a counterattack. Perhaps the same lessons will apply to harnessing the immune system to prevent cancer.
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