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Cancer Immunoprevention

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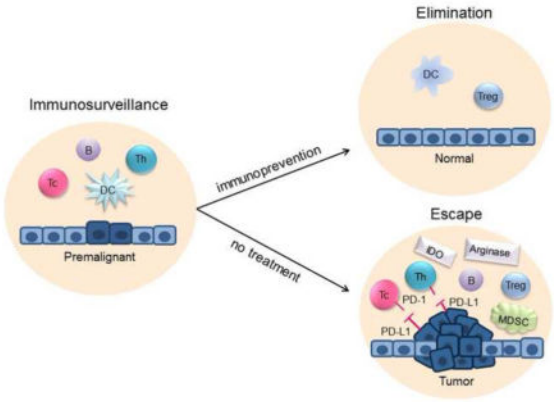
Abstract

Cancer immunotherapy is now a reality. The results are phenomenal but the cost is outrageous. Even if the cost eventually comes down and immunotherapy becomes more broadly available, using the knowledge derived from immunotherapy to apply to immunoprevention would be a good strategy. The most likely approach to cancer immunoprevention is cancer vaccines. To date, cancer vaccines have been tested mostly in the setting of advanced disease. Numerous immunosuppressive mechanisms have been identified in the tumor microenvironment as well as systemically that compromise the ability of cancer patients to respond to the vaccines. Multiple approaches are being tested to improve therapeutic cancer vaccine efficacy, including combinations with other immunotherapies. An alternative approach is to administer the vaccines to individuals without cancer but at high risk for cancer. Data in support of this approach and immunoprevention in general is accumulating and clinical testing has started.

Graphical Abstract



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Introduction

It had been hypothesized for decades that correctly functioning immune system played an important role in cancer surveillance and prevention. It is only relatively recently, however, that conclusive experimental evidence could be obtained in new and superior animal models. Direct evidence for immunosurveillance of human cancers has been much harder to prove experimentally. Most of the knowledge of the immune system-cancer interactions came from patients with cancer raising doubts that immune control of cancer was possible. Identification of human tumor antigens using anti-tumor antibodies and T cells generated by cancer patients allowed studies that ultimately showed the importance of tumor specific immunity in preventing or delaying cancer recurrence. Furthermore, the presence of immune infiltrates in primary tumors, which was shown to be a marker of better outcome [1–4], was an indication that the tumor is under immunosurveillance. The latest and the most convincing evidence, however, has come from the phenomenal clinical successes of the type of cancer immunotherapy that is predicated on activating the immune system of cancer patients, such as the check-point inhibitors, leading to complete tumor elimination in many patients with advanced disease [5,6]. Immunosurveillance of and protection from cancer is a prime function of the immune system, equal to its defense function against pathogens. In this review, we will discuss how this new basic knowledge of cancer-immune system interactions and the history of cancer immunotherapy, especially the newest clinical successes, support efforts to develop cancer immunoprevention.

Feasibility of Cancer Immunoprevention

The role of immune surveillance is to eliminate nascent tumors. Tumors that escape elimination and become clinical disease do so under selective pressure termed “immunoediting” [7]. This process is carried out by tumor antigen specific T cells [8,9] and outgrowth of antigen escape variants is facilitated by immunosuppressive mechanisms in the tumor microenvironment, including regulatory T cells (Treg), myeloid derived suppressor cells (MDSC), expression of indoleamine 2,3 dioxygenase (IDO) causing loss of MHC Class I expression and T cell anergy, and expression of inhibitory receptors, PD-1, LAG-3, and TIM-3, promoting T cell exhaustion [10–13]. A reasonable hypothesis supported by these results is that strengthening immunosurveillance prior to cancer occurrence would favor complete cancer elimination thus avoiding cancer editing and escape. One long-established and highly successful method of strengthening immunosurveillance ahead of disease has been through specific vaccination. Cancer vaccines have a long history in cancer therapy where they have had a limited success. They have not been tested in a significant way for cancer prevention, even though results from animal models fully support that approach.

In addition to new discoveries about immunosurveillance and increasing evidence of effective immune control of tumors, developments in other areas of medical research and technology are increasing the feasibility of developing cancer vaccines for prevention. Cancer immunoprevention practiced currently is through three FDA approved vaccines for virally induced cancers. Two are for prevention of infection with the human papillomavirus (HPV) that is the underlying cause of over 70% of cervical cancers [14], and the third is for

prevention of hepatitis B virus (HBV) infection that can cause liver cancer [15]. The majority of human cancers are not caused by viruses or their viral origin is not known, which highlights the need to develop vaccines for prevention of non-viral cancers. The only FDA approved vaccine based on a tumor antigen and not on a viral antigen is Sipuleucel [16], which is not for prevention but rather for therapy of advanced prostate cancer. Lack of tumor antigen specific preventative vaccines is in part due to the wrong assumption that all non-viral and/or non-mutated tumor antigens are either too close to self antigens and would not elicit strong protective immunity, or if they do, this would result in autoimmunity. With very few exceptions (primarily melanoma antigens), immune responses against tumor antigens have been shown to be protective without causing autoimmunity. Many candidate antigens for prophylactic vaccines can be found among the known differentiation antigens, overexpressed and differentially processed antigens and cancer testis antigens, among others. Plenty of information is already available on their differential expression on tumors versus normal cells and many have already been tested in clinical trials as antigens in therapeutic vaccines[17].

Advancements in clinical imaging and screening modalities have enabled early detection of many cancers or premalignant lesions in high-risk populations but there are still no acceptable methods, other than surgery when possible, to prevent those lesions from progressing to invasive cancer [18]. Preventative vaccines in combination with early detection might be able to accomplish this goal. For example, women that carry mutated BRCA genes have a 56–84% increased risk for development of breast cancer and 27–54% for ovarian cancer [19]. Currently the recommended prevention strategy is prophylactic mastectomy and bilateral salpingo-oophorectomy. A number of tumor antigens have been identified in breast cancer that could be included in a preventative vaccine that together with regular surveillance could reduce cancer risk without this life-altering surgery[20]. Current efforts in the field of cancer immunoprevention are focused primarily on identifying tumor antigens that are expressed on early cancers or premalignant lesions. These could be incorporated into vaccines to be tested first in patients with these lesions and later at an even earlier stage, in high-risk populations [21].

Candidate Antigens for Preventative Vaccines

In 2009, US National Cancer Institute (NCI) organized a workshop to review accumulated knowledge on tumor-specific expression, immunogenicity, and therapeutic potential of a large number of tumor antigens identified to date, which could be used to prioritize some of them for translation into the clinic [22]. The goal was to identify targets for immunotherapy rather than immunoprevention, but many of the top 75 prioritized antigens could also be candidates for preventative vaccines. For example, recent work has shown that CT antigens on that list, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-C1.CT7, NYESO-1, MAGE-C2/CT10, and GAGE are found in breast cancers resulting from BRCA1 and/or 2 mutations. The samples tested included both early-stage invasive ductal carcinomas as well as ductal carcinoma in situ (DCIS). MAGE-A was expressed in 13/26 and NY-ESO-1 was expressed in 10/26 tumors. 13/26 tumors expressed 2 or more CT antigens, 10/26 expressed 3 or more CT antigens, and three tumors expressed all examined CT antigens. Morphologically normal breast tissue or tissue adjacent to either in situ or invasive carcinomas did not express any of

the examined CT antigens [23]. CT antigens have been used in therapeutic vaccines in a variety of tumors and have demonstrated tumor-specific immunogenicity without evidence of autoimmunity. This suggests that raising immunity to one or more of these antigens with a vaccine prior to any evidence of tumor would strengthen immunosurveillance and reduce risk, eventually replacing prophylactic mastectomies. CT antigens have also been found in squamous dysplasia leading to head and neck cancer, and squamous cell carcinoma in situ in esophageal biopsies [24,25], two other cancers that could be targeted for prevention in the premalignant stage.

Pancreatic cancer (PC) is resistant to standard therapy and the 5-year survival rate is still the lowest among all cancer types. A large-scale, high throughput tissue microarray analysis found overexpressed tumor antigens MUC1 and mesothelin (MSLN) to be highly significant predictors of early cancer-specific mortality in PC and superior to pathological features in predicting survival [26]. Mesothelin has also been found on pancreatic mucinous cysts, premalignant precursor of PC [27]. Similarly, MUC1 has been found on premalignant precursor PanIn lesions where it positively correlated with their malignant potential [28]. MUC1 is also expressed on breast ductal carcinomas in situ where it can be an independent predictor of local recurrence [29]. These types of results suggest that strengthening anti-MUC1 and anti-mesothelin immunosurveillance could be a good approach to prevention of these malignancies.

In addition to known tumor antigens, efforts are underway to identify new antigens specifically expressed on premalignant lesions or cancer stem cells. Disis and colleagues compared human colon adenomas and colorectal cancer (CRC) microarray datasets and identified 160 genes that were expressed more than two-fold higher in adenomas and CRC relative to normal colon. They identified 23 genes whose proteins were already reported to be overexpressed in colon adenoma and CRC. To determine whether these proteins could be targets of immunosurveillance, they examined sera from early stage CRC patients and controls and found significantly elevated IgG against several of the molecules [30]. The same group has tested in mouse models the ability of vaccines based on non-mutated tumor antigens to prevent cancer. They showed that a multi-antigen vaccine that included Neu, IGFBP2 and IGF-IR could prevent breast cancer development in two different transgenic mouse models even in mice that already had premalignant lesions [31]. This report also showed that a multi-antigen vaccine was more effective than a single antigen vaccine, and that the vaccine could be combined with some chemopreventative agents resulting in increased efficacy of both. In another recent report, vaccination against the Epidermal Growth Factor Receptor (EGFR) using a multipeptide vaccine in a preventive setting decreased EGFR-driven lung carcinogenesis by 76.4% in a mouse model of EGFR-driven lung cancer, by inducing robust immunity. Of a particular interest is a recent study that showed that immunizing against the common mutation in H-ras oncogene can prevent chemical carcinogen-induced tumors that are known to carry that mutation [32]. Thus identification of common oncogene mutations in premalignant lesions could provide mutated epitopes against which a very safe and likely very strong immune response could be generated with a vaccine. Vaccines based on mutated oncogens such as H-ras, K-ras and p53 have been tested in animal models and in clinical trials in advanced cancer with marginal

successes similar to vaccines based on non-mutated antigens [33–35]. Testing of vaccines based on these antigens in the prophylactic setting has not yet been tried in the clinic.

Another good source of antigens for preventative cancer vaccines are the many targets of spontaneous immunity against a developing tumor that are being reported with increasing frequency. A recent study identified cyclin B1 [36] as an important antibody target in prostate cancer but also in early PSA negative stage of disease [37]. A new study in asymptomatic monoclonal gammopathy (AMG) identified potential targets for prevention of multiple myeloma (MM). All cases of multiple myeloma (MM) are preceded by AMG that is classified as either monoclonal gammopathy of undetermined significance (MGUS) or asymptomatic multiple myeloma (AMM). Not all patients with AMG progress to myelomas suggesting an important mechanism of prevention. Previous studies in MGUS patients demonstrated immune control of MGUS precursors [38–40] leading to the identification of target antigens [41,42]. MGUS patients frequently mount an immune response against SOX2, a transcription factor critical for self-renewal in stem cells and expressed in both MGUS and MM but MM patients lose immunity to SOX2 [42]. The latest publication reports results from a prospective study to evaluate the effect of antigen-specific immunity and immune checkpoint inhibitors on the risk of progression to MM [43]. Anti-SOX2 T cells were detected in 71% of MGUS and 31% in AMM patients. Presence of anti-SOX2 T cells at diagnosis was associated with reduced risk of progression to MM and inversely correlated with the presence of PD-L1 on T cells. PD-L1 blockade led to an increase in antigen-dependent proliferation of SOX2-specific T cells in 4 out 6 AMM patients tested. This work highlights the potential of using a vaccine to boost SOX2-specific immunity with the goal to eliminate MGUS and prevent MM.

Table 1 summarizes some of the above observations and highlights numerous opportunities for testing several very well-known and extensively studied antigens in the setting of an increasing number of newly identified premalignant lesions that give rise to major human cancers.

Early Days of Clinical Testing of Vaccines for Cancer Prevention

The first preventative vaccine applied in the setting of premalignant disease was composed of long peptides derived from HPV16 oncoproteins E6 and E7 and incomplete Freund's adjuvant, administered to women with grade 3 vulvar intraepithelial neoplasia [44]. At 12 months of follow-up, 15 of 19 women had significant clinical responses with 9 of 19 completely clearing the lesions. The complete responses were maintained at 24 months of follow-up and correlated with induction and maintenance of HPV-specific CD4 and CD8 T cells. A similar vaccine composed of 13 overlapping 25–35 mer peptides spanning the entire sequence of HPV E6 and E7 with Montanide ISA-51 adjuvant was tested in another randomized trial in women with high-grade cervical dysplasia who were scheduled for the LEEP procedure. The aims of the trial were to test immunogenicity of the vaccine and ability to promote infiltration of T cells into the lesions. The vaccination resulted in the development of strong T cell responses but there was no HPV clearance and increase in infiltrating T cells was not confirmed [45]. The most recent placebo controlled phase II trial tested a similar HPV vaccine in women with low-grade premalignancy of the uterine cervix

showed high immunogenicity of the vaccine and induction of long term memory T cells [46]. A number of interesting observations were made concerning the importance of pre-existing immunity and induction of both Th1 and Th2 responses, which will help design a potentially effective vaccine for the next trial.

The first preventative vaccine for non-viral cancers was tested in the premalignant setting in otherwise healthy individuals but with a recent history of an advanced adenoma of the colon and therefore high risk for colon cancer [47]. Tumor antigen MUC1 has been found to be significantly overexpressed in colonic polyps with increased dysplasia and villous histology [48,49]. The vaccine consisted of the 100 mer peptide derived from the tandem repeat region in the extracellular domain of MUC1, admixed with an adjuvant, TLR3 agonist Poly-LCIC (Oncovir®). MUC1 peptide vaccines have been tested in many therapeutic trials over the years [50], where they have shown low immunogenicity and only marginal efficacy. In the prophylactic setting in animal models, a similar MUC1 vaccine could ameliorate inflammation associated with spontaneous inflammatory bowel disease (IBD) and completely prevent progression to colitis associated colon cancer (CACC) [51,52]. In patients, this vaccine elicited strong immunity in 43% of the patients and long-term memory as measured by high antibody responses to a booster injection at one year. Importantly, there has been no toxicity or evidence of autoimmunity associated with this immune response. The non-responders to the vaccine were found to have increased levels of circulating myeloid derived suppressor cells (MDSC), previously observed only in patients with advanced tumors. This result shows that full immunocompetence is important for a good response to a vaccine. Currently the same vaccine is being tested for efficacy (prevention of polyp recurrence) in a multi-center phase II randomized, placebo-controlled clinical trial (clinicaltrials.gov). Given this vaccine’s safety, future trials will be performed in earlier premalignant settings.

Vaccine Formulations and Adjuvants

While the focus of this review is primarily on feasibility and desirability of preventative cancer vaccines, as the field moves forward careful consideration will have to be given not only to issues raised by specific antigens but also to issues surrounding vaccine design and delivery (peptides and proteins either soluble or incorporated into various particles, naked DNA or inserted into a viral or bacterial vector, RNA, etc.), as well as immunostimulatory substances known as adjuvants. There has been a lot of progress in developing new delivery vehicles and adjuvants[53] but very few have been components of FDA approved vaccines that have been administered to large numbers of adults or children to provide a track record of acceptable toxicity. Those that have been used in vaccines against pathogens by and large induce type 2 immunity, which is not considered the most appropriate for anti-cancer vaccines. Taking stock as a community of what is known about the many already available delivery systems and adjuvants, not unlike the review the community undertook of cancer antigens [22], could help prioritize some of them for further development for use in cancer prevention.

Conclusion

Cancer vaccines can be cost-effective, off-the shelf reagents that can be made broadly available around the world. In this review we have highlighted work that supports development of cancer vaccines that can be administered before cancer occurs and the cancer induced immunosuppression gets established, in order to elicit strong immunity and prevent this often incurable disease. With the new knowledge in immunology and cancer biology and new technological advances in medical diagnostics that could help identify individuals who would benefit from such vaccines, the time has come to focus more attention on cancer immunoprevention.

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Highlights

- Cancer is under immunosurveillance by innate and adaptive immunity throughout its development.
- Target antigens for immunosurveillance are mutated or abnormally expressed self-molecules.
- Preventative vaccines could eliminate premalignant lesions and their progression to cancer.

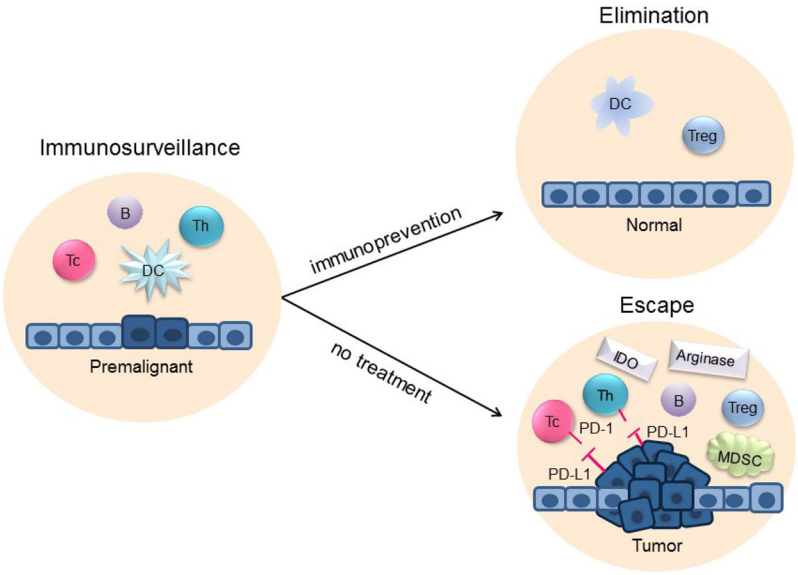

Figure 1. Importance of developing immunoprevention approaches for strengthening immunosurveillance and cancer control.<

br>As healthy cells under various carcinogenic influences start to undergo changes in their normal phenotype and function, adaptive immunity (cytotoxic T cells, helper T cells and B cells stimulated by dendritic cells) is alerted to come to the site, generate large numbers of antigen-specific cells and antibodies and eliminate abnormal (premalignant) cells. Inadequate immunosurveillance allows progression leading to a diagnosis of premalignant disease. Left untreated, these lesions eventually give rise to invasive cancer growing in a highly immunosuppressive microenvironment that foils all therapies including immunotherapy. If, however, immunosurveillance is strengthened through immunoprevention (e.g. vaccines), premalignant cells are eliminated restoring normal homeostasis between healthy tissues and now quiescent (tolerant) immune system.

Table 1

Proposed antigens for preventative cancer vaccines in the setting of premalignant disease

Candidate Antigens	**Premalignant lesions (cancer type)**
HPV16 E6 and E7	Cervical intraepithelial neoplasia (CIN) (cervical) Vulvar intraepithelial neoplasia (vulvar)
Cancer Testis (CT) antigens MAGE-A1-A4, NYESO-1, GAGE	Ductal carcinoma in situ (breast) Squamous dysplasia of the head and neck (SCCHN) Esophageal squamous carcinoma in situ (esophageal)
Her-2/neu	Ductal carcinoma in situ (breast) Colon adenomas (colorectal)
MUC1	Pancreatic intraepithelial neoplasia (PanIn) (pancreatic) Intraductal papillary mucinous neoplasms (IPMN) (pancreatic) Berrett's Esophagus (esophageal) Adenomatous polyps (colon) Monoclonal gammopathy of undetermined significance (MGUS) and Asymptomatic multiple myeloma (AMM) (multiple myeloma) Bronchial preneoplasia (lung)
Mesothelin	Pancreatic intraepithelial neoplasia (PanIn) (pancreatic) Intraductal papillary mucinous neoplasms (IPMN) (pancreatic)
Cyclin B1	Bronchial preneoplasia (lung) Squamous dysplasia of the head and neck (SCCHN) Ductal carcinoma in situ (breast) Preneoplastic PSA negative stage (prostate)
SOX-2	Monoclonal gammopathy of undetermined significance (MGUS) and Asymptomatic multiple myeloma (AMM) (multiple myeloma)
EGFR	Bronchial preneoplasia (lung)