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Cancer Vaccines: The Next Generation Immunotherapy

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Opinion

The notion that the immune system is critical for lifelong control of malignant transformation has been around for decades, and is under scored by anecdotal observations of spontaneously regressing tumors as well as evidence that cancer incidence increases with age alongside a waning immune system. Over the past half century research has provided solid mechanistic evidence in support for the critical role of the immune system in preventing cancer and has ushered in the current era of cancer immunotherapy. The employment of the immune system to treat or prevent cancer is commonly referred to as immunotherapy and is comprised of two overarching categories, passive and active [1]. Passive immunotherapy largely involves the administration of specific antibodies, cytokines or T cells. Indeed, passive administration of specific-T cells or of monoclonal antibodies against the T cell inhibitory receptor CTLA-4 and more recently against the death receptor PD-1/PD-L-1, which is collectively referred to as immune checkpoint blockade, has recently gained international acclaim [2], though not without immune related adverse effects [3]. Active immunotherapy can be most easily defined by vaccination. While passive immunotherapies often engage the immune system independent of the knowledge of defined tumor antigens (an exception being some forms of adoptive cell therapy [4], vaccines elicit antigen-specific immune responses by targeting tumor associated antigens [5]. This is not to say that the immune responses elicited by checkpoint blockade are anything but specific. It is becoming clear that tumor associated antigen-specific T cells are elicited following administration of antibodies to immune checkpoints underscoring the widely accepted belief that specificity is critical for immune therapy of cancer. It should be emphasized here that passive forms of immunotherapy have rightly taken center stage at this time, and have proven as effective as current standard forms of treatment if not more effective, particularly for malignant melanoma. However passive approaches are by no means a cure. In this light, two overarching questions must be addressed. Why have vaccines against cancers lagged behind the advancement of passive therapies in clinical trials? And, will vaccines that target defined tumor-associated antigens emerge as the next generation immunotherapy?

To address these questions it is necessary to first identify the best choice for tumor antigens to target and second to define some surmountable obstacles impacting the success of vaccines. Given the indigenous power with which the immune system is regulated against self-recognition and response, early candidates for vaccine antigen targets were logically those farthest from self-proteins and normal self-expression. Viral antigens, mutated antigens, and tissue-restricted antigens were demonstrably the most immunogenic and most foreign relative to the host. For those not so common cancers with viral etiologies, cervical carcinoma being the exception in regard to incidence and mortality, vaccines are proving to be powerful. However, for the most common and most lethal solid malignancies, lung cancer, breast cancer, colon cancer and prostate cancer for example, there appears to be no virus association and few to no mutated proteins that are critical for the cancer to survive. This may have been perceived as a dilemma a decade ago and indeed impaired the progress of cancer vaccine development, only recently has targeting self-proteins with vaccines against cancers been realized. Proteins that are self, non-mutated with wide tissue expression, but overexpressed or up regulated in malignant cells compared to the normal counter parts include telomerase, survive in and most recently Tumor Protein D52 (TPD52) [6]. Importantly, TPD52 is involved in initiating and maintaining the malignant state [7] and thus critical for the cancer cells to survive [8]. Tumor associated antigens such as these are being classified as over expressed oncogenic tumor-self antigens and may represent the spearhead of the next generation of vaccines against cancer [9]. Preclinical studies have demonstrated that vaccine induced immunity against TPD52 is effective against prostate cancer and sarcomas in murine models, without inducing autoimmunity against healthy tissues and cells [10-13]. A powerful and important characteristic of these antigens is their universal or near universal over expression in a large number of cancers making the clinical administration of vaccines against them wide spread in application [6,9].

It is arguable that the early years of cancer vaccine development, though driven by sound rationale, were largely an effort to ascribe to a cancer an antigen that would be immunogenic, i.e. looking for viruses in multiple cancers. In hindsight this was likely an early obstacle to vaccine development given the time and effort spent without success for most solid malignancies. In contrast, recent efforts have focused on asking cancer cells to reveal their content of candidate antigens whether self in nature or not. This approach required investigation in spite of the dogma that tolerance would not allow a vaccine to elicit an immune response against a self-protein even if over expressed, a second obstacle that had to be overcome. The development of high throughput genomic and proteomic technologies clearly facilitated the new recent era of tumor antigen discovery through differential gene expression analyses. A third obstacle was the concerted effort and time spent developing more potent vaccine vehicles to make targeting of poor antigens more immunogenic (again poor antigen is no longer ascribed to self- proteins that are overexpressed and indispensable to the tumor). Again this effort was undergirded by sound logic and has delivered some very powerful formulations that will be useful in the near future. However, this overall effort was another setback to vaccine development due largely to the use of poor antigens in the innovative and potent vehicles, this supports the notions that in the end it's the antigen(s) that are the most important component of the vaccine and the cancer cells decide what those antigens are. Notably,

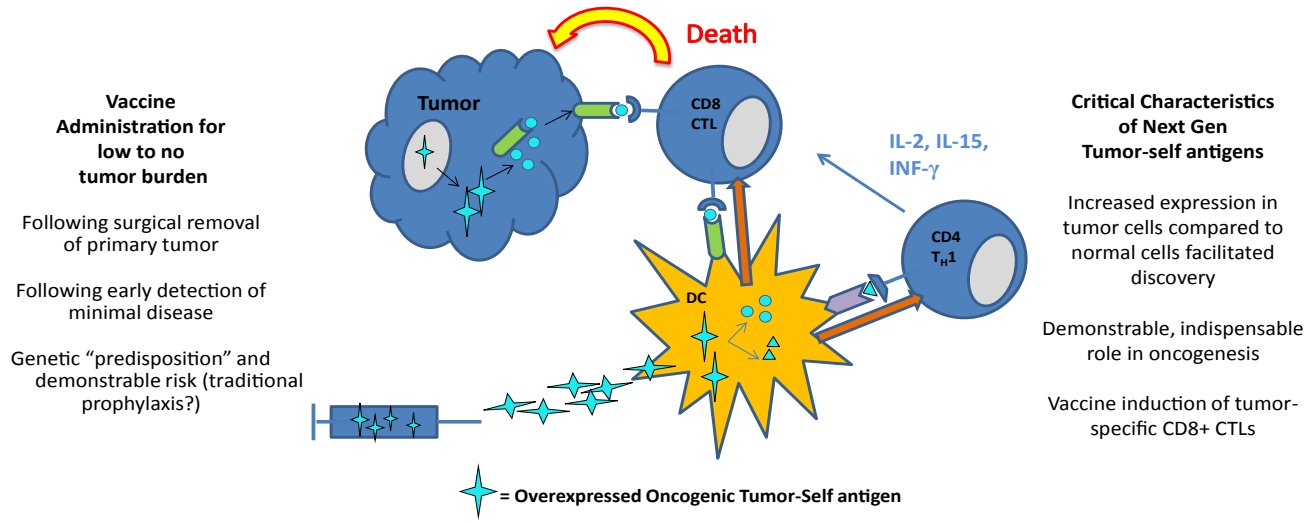

Figure 1: Cancer Vaccination Targeting: Over expressed Oncogenic Tumor-Self Antigens

The changes defining next generation cancer vaccines that will result in greater clinical success include the character of the antigenic target and the timing of administration. It is arguable that the early years of cancer vaccine development were largely an effort to ascribe to a cancer an antigen that might be immunogenic and foreign relative to the host. More recent efforts have focused on asking cancer cells to reveal their content of candidate antigens whether self in nature or not. Overexpressed oncogenic tumor-self antigens may represent the spearhead of the next generation of cancer vaccines. Rapid advances in early cancer detection technologies, refinement of genetic monitoring and diagnostics and the reality of personalized medicine, will usher in vaccine trials approved for low to no tumor burden cases with demonstrable risk of developing clinically relevant disease, a scenario that will yield astounding progress. Traditional prophylactic vaccination for most cancers may not be attainable and may not be necessary.

vaccines comprised of protein with chemical and/or molecular adjuvants, antigen pulsed dendritic cells, or plasmid DNA delivered by common established routes proved to be effective when the right antigen was included [9]. Finally, and likely the most difficult obstacle to overcome is clinical timing of vaccine administration. Most if not all clinical trials involving cancer vaccines are approved for the late stage therapeutic setting, this is understandable relative to patient safety. However, even vaccine trials against completely foreign pathogenic microbes would be just as disappointing as many cancer vaccine trials have been to date if they were administered therapeutically in the presence of full on infectious disease. Small pox may still be a serious health issue. Perhaps with rapid advances in early cancer detection technologies, refinement of genetic monitoring and diagnostics, and the reality of personalized medicine, vaccine trials will be approved for low to no tumor burden cases with demonstrable risk. With continued study and development of the newest overexpressed oncogenic tumor-self antigens as vaccine targets administered perhaps in combination with passive cell transfer therapies or immune checkpoint blockade, it will be realized that vaccination is the next generation immunotherapy for solid malignancies (Figure 1).

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