

Immune Evasion by Persistent Viruses and Cancers: Blocking Evasion as a Rational Design to Treat Viral Infections and Cancers

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Vaccines are the most cost-effective and successful preventative measure against infectious diseases. Childhood vaccinations had a tremendous impact on public health. The mortality and morbidity associated with diseases such as polio, smallpox, measles, mumps, rubella, diphtheria, pertussis, tetanus, have reduced radically (> 90-100%) due to prophylactic vaccines provided during childhood. The success of these preventive vaccines lies in their ability to induce an effective B cell memory and ongoing production of antibodies that either directly neutralize pathogens, or operate with complement system or other immune cells to kill pathogens. CD8⁺ T cell responses are also a key component of protective immunity, particularly in case of virus infections. More recently, development of cancer vaccines is breaking new grounds.

Ability to evade host immune system is a major roadblock in achieving complete protection against persistent viral infections and malignant diseases. DNA viruses such as herpes viruses and poxviruses encode several genes that directly evade the host innate and adaptive immune responses [1-2]. Because of potent immune evasion mechanisms, and ability of virus to persist in immune competent hosts, a vast majority of the global population remain infected with at least one of the herpes virus. Herpes Simplex virus (HSV) type 1 and 2, Varicella Zoster Virus (VZV), Human Cytomegalovirus (HCMV), Epstein-Barr virus (EBV) and are few examples of herpes viruses [3]. Poxviruses cause acute infections, and may establish persistent infection based on the immunocompetence of the host and route of infection [4]. Vaccinia virus is a poxvirus family virus, which was used as a successful vaccine to eradicate the human pathogen variola virus (smallpox). Human papilloma virus (HPV) is a causative agent for cervical cancer, and establishes persistent infection. Recombinant protein subunits vaccine is currently used to combat cervical cancer successfully. RNA viruses like human immunodeficiency virus (HIV) and hepatitis C virus (HCV) undergo extensive antigenic variations due to selective pressure of the immune system, which lead to immune escapes [5,6]. In a computational model of HIV-1 infection dynamics in lymphoid tissue demonstrated that evasion of immune surveillance by persistent virus is sufficient to cause treatment failure in case of structured interruption of highly active antiretroviral therapy (HAART) [7].

Although the development of cancer vaccines is gaining new grounds, developing immunity against tumors remains a difficult task. Recognition of tumor-specific antigens and tumor-associated antigens by the host T cells has not been straightforward [8-10]. Examples of tumor-specific antigens are p53, BCR-ABL, and Ras, and tumor-associated antigens are differentiation antigens (tyrosinase, MART-1), overexpressed antigens (MDM2, HER-2), and cancer/testis antigens (MAGE and RAGE families). These antigens are expressed by germ cells, tumor cells, but not by normal somatic cells. Viral infection associated cancers such as B cell lymphomas (EBV) and cervical cancer (HPV) express viral antigens, and these antigens are considered tumor antigens as well. Tumors cells acquire unique immune evasion mechanisms to evade host immune attack and develop tumor escapes [11,12].

An advance understanding of immune evasion mechanisms by viruses and tumors, and strategy to block evasion of host immune responses may lead to new prophylactic and therapeutic vaccination strategies against persistent viruses and cancers. Immune evasion mechanisms used by both viruses and tumors are surprisingly similar and achieve a common goal, that is to escape immune response, and persist in host.

Many current vaccination strategies use synthetic peptides, DNA-encoding tumor antigens, recombinant proteins, antigen-loaded DCs, and adoptive transfer of *in vitro* generated T cells to focus on the enhancement of antigen-specific T cell responses. A high frequency of specific T cells is critical, but does not guarantee therapeutic efficacy, as virus or cancers may evade immunity provided by vaccine and become resistant to immune attack. Therefore, strategies that target blocking immune evasion may make virus or tumor susceptible to host immunity and reduce immune escape variants. One such example is the pre-clinical development of vaccine against HSV-2 disease. Preclinical studies in animal model show enhanced efficacy of vaccine when blocking immune evasion is included in vaccine design [13,14].

The immune evasion by viruses and tumors exploit similar host immune pathways. It is also interesting to note that the identification of viral evasion proteins may also lead to new therapeutic agents and/or as targets of immunotherapy. An interesting example is the use of viral TAP inhibitors to induce T cells recognizing an alternative peptide repertoire carried by tumor cells with antigen processing defects [15,16]. Additionally, exploiting capacity of attenuated HCMV virus to induce strong memory T cell immunity may be advantageous to develop protective immunity against viruses as well as cancer [17]. Recently in a monkey CMV model, it is demonstrated that CMV-based vectors induces vast effector-memory T cell responses and reduces the risk of progressive infection following repeated exposure to simian immunodeficiency virus (SIV) [18]. Disruption of immune evasion by combined therapeutic (vaccine) strategies to prevent virus propagation or tumor growth shows promising outcome in preclinical animal models. Combinatorial treatments will presumably also diminish the likelihood of emerging viral mutants and malignant cells that become resistant.

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