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Cancer vaccines in hematologic malignancies: advances, challenges and therapeutic potential

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"A central area of investigation is the use of cancer vaccines to educate host immunity to selectively target malignant cells while minimizing damage to normal tissues."

The observation that activation of patient immunity may induce regression of cancer was first noted by William Colley in the 19th Century who described a case of sarcoma that spontaneously resolved after an erysipelas infection. The unique efficacy of cellular immunity in the setting of hematological malignancies has been supported by the finding that allogeneic transplantation is curative for a subset of patients with leukemia, lymphoma and multiple myeloma. The primary mechanism is known as the 'graft-versus-disease effect' in which alloreactive effector cells eliminate post-transplant residual disease [1–4]. However, the lack of specificity of this immune response results in the concurrent risk of graft-versus-host disease (GvHD) due to targeting of normal epithelial and hematopoietic cells. A central area of investigation is the use of cancer vaccines to educate host immunity to selectively target malignant cells while minimizing damage to normal tissues.

Tumor cells express unique antigens that are recognized by the T-cell repertoire of patients with malignancy. However, tumor cells present antigen in the absence of costimulatory signals and directly suppress the functional potency of professional antigen-presenting and effector cells, thus creating an immunologic milieu that promotes tumor tolerance and ineffective immune response [5]. A primary challenge in designing an effective vaccine involves approaches that augment tumor antigen presentation by placing this in the context of necessary costimulation [6]. In addition, it is crucial to identify key pathways that induce tolerance and reverse the associated immunosuppressive environment. Strategies to achieve this goal include increasing expression of factors that promote T-cell activation, polarization of antigen-presenting cells towards an activated phenotype, depletion of regulatory T cells, restoration of the complexity of the immune repertoire, expansion of both tumor-reactive helper and cytotoxic T cells, and promoting the development of tumor-specific central memory effector cells that result in more sustained immune responses. Notably, in pursuing strategies to reverse tumor tolerance, the development of autoimmune manifestations is a potential concern.

An increasing number of tumor-associated antigens expressed by hematological malignancies have been identified, including the idiotype protein specific to the malignant lymphoid clone; myeloma-associated markers such as MUC1 and NY-ESO, telomerase reverse transcriptase, RHAMM/CD168 and survivin in chronic lymphocytic leukemia (CLL); and WT1 and PR3 antigens expressed by myeloid leukemia cells [7–15]. Targeting of minor histocompatibility antigens has also been pursued to amplify graft-versus-disease effects following allogeneic transplantation [16]. A variety of strategies have been pursued to enhance the immunogenicity of peptide-based vaccines, including the alteration of amino acids to increase MHC binding affinity and the use of adjuvants to recruit and activate native

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antigen-presenting cells to the site of activation. Vaccination of patients targeting individual peptide antigens have resulted in immunologic and clinical responses. For example, use of the PR1 peptide derived from PR3 was associated with the expansion of circulating antigen-specific $CD8^+$ T cells in patients with myeloid leukemia who were undergoing vaccination alone or following stem cell transplantation [17]. Notably, immunologic response was statistically associated with clinical response and disease-free survival. Similarly, vaccination with the WT1 peptide in conjunction with immune adjuvant in patients with acute myelogenous leukemia, breast or lung cancer was associated with WT1-specific T-cell responses that correlated with a decrease in circulating or marrow-based blasts as well as tumor regression [18,19]. While the expansion of antigen-specific T-cell responses has been documented and associated with effects on disease, the clinical significance of these findings remain uncertain. Potential limitations of this strategy include the limited number of identified tumor antigens for hematological malignancies and their uncertain immunogenicity, the required HLA restriction for peptide-based vaccines, and the dependence on native antigen-presenting cells, which demonstrate functional deficiencies in the setting of malignancy – particularly those derived from the tumor bed.

One approach to enhance antigen presentation of tumor antigens, including those yet to be identified, has been through the alteration of tumor cells to amplify their capacity to elicit immunologic responses. Transduction of CLL cells with the triad of costimulatory molecules (TRICOM) vector containing CD80, CD54 and CD58 has been shown to amplify costimulation in an animal model [20]. Insertion of CD40L (CD154) into CLL cells using a replication-deficient adenoviral vector has been associated with upregulation of stimulatory receptors on T cells [21]. In a Phase I clinical trial, infusion of gene-modified T cells resulted in increased CD154 expression by bystander CLL cells, increased presence of circulating stimulatory cytokines, expansion of CLL-specific T cells and the transient depression in circulating tumor cells [22]. In a recent report, patients underwent vaccination with autologous acute myelogenous leukemia cells genetically modified to express GM-CSF following reduced intensity allogeneic transplantation [23]. Vaccination was not associated with increased GvHD and the majority of patients achieved complete remission.

Another strategy for vaccination involves the use of potent antigen-presenting cells known as dendritic cells (DCs) loaded *ex vivo* with tumor antigens. DCs represent a complex network of antigen-presenting cells that are key mediators of T-cell activation and tolerance [24]. Myeloid DCs are uniquely capable of inducing primary immunity. As DCs undergo maturation they evolve from cells located at sites of antigen capture that excel at processing to those who migrate to areas of T-cell interaction with upregulated expression of costimulatory molecules. DCs may be generated *ex vivo* from peripheral blood- or bone marrow-derived progenitors cultured with cytokines and agents such as TNF-α, CpG oligonucleotides, Toll-like receptor agonists, lipopolysaccharide and prostaglandin E2 that induce maturation [24]. Notably, the phenotypic characteristics of the DC population have a significant impact on T-cell polarization. Increased levels of plasmacytoid-derived DCs (DC2) have been associated with a decreased risk of GvHD and an increased risk of recurrence following allogeneic transplantation [25]. Approaches to enhance DC function have included the blocking of the indoleamine inhibitory pathway and the use of antigen-loading strategies that facilitate DC maturation.

A wide spectrum of approaches to load antigen onto DCs have been pursued including pulsing with individual tumor-associated peptides or proteins, transduction with viral-based vectors containing genes expressing antigens and costimulatory molecules, use of antigen-specific or whole-tumor-derived RNA, tumor lysate, apoptotic bodies, and cell fusion with whole autologous tumor cells [24,26–29]. Use of whole-cell-derived antigens has the potential advantage of stimulating a broader polyclonal antitumor response directed against multiple tumor antigens, including those not yet identified. One strategy unique to myeloid leukemia involves the use of cytokines to induce differentiation of leukemia-derived progenitors into DCs that express tumor antigens and DC-derived costimulatory factors. A potential concern with this approach is the loss of antigens associated with the more primitive phenotype of leukemic blast with maturation towards DC lineage. DC-based vaccines have been shown to be feasible and associated with immunologic responses but definitive evidence of clinical benefit remains uncertain.

We and others have explored a strategy in which patient-derived tumor cells are fused chemically with autologous DCs using polyethylene glycol [30]. In an animal model, we have demonstrated that vaccination with DC/multiple myeloma cell (MM) fusions is protective against an otherwise lethal challenge of tumor cells and may result in regression of established disease and long-term survival, particularly when coadministered with IL-12 [31]. In preclinical human studies, fusion of MM and DCs results in upregulation of DC expression of costimulatory molecules and stimulatory cytokines, elicits a potent CD4- and CD8-mediated antitumor response, and stimulates cytotoxic T-lymphocyte (CTL)-mediated lysis of autologous myeloma targets [32]. In a Phase I study, vaccination with DC/MM fusions resulted in potent cellular and humoral myeloma-specific responses and prolonged disease stabilization in a subset of patients with advanced disease [33].

Reversal of tumor-mediated tolerance is a crucial component in designing an effective tumor vaccine. One of the main protective mechanisms is the presence of inhibitory regulatory T cells that have been shown to be increased in the peripheral blood, lymph nodes and tumor bed of patients with malignancy, and are associated with worse outcomes [34,35]. Preclinical models have demonstrated that tumor vaccines may paradoxically increase expansion of regulatory T cells, blunting their immunologic potency [36]. Efforts to selectively deplete regulatory T cells in conjunction with immunotherapy have included chemotherapy and antibody-based approaches [37–43]. Notably, vaccination with DC/MM fusions following autologous transplantation resulted in augmentation of myeloma-specific immunity that appears to be facilitated by depletion of regulatory T cells [44].

A primary focus of vaccine therapy is the identification of additional inhibitory factors and the use of agents to inhibit tumor-mediated immune suppression. A key pathway found to mediate tolerance and T-cell anergy is via signaling through programmed death (PD) ligand 1 (PD-L1)/PD-1 [45,46]. Ligation of PD-1 on T cells results in an 'exhausted' phenotype, found in chronic infections and malignancy. By contrast, blockade of this pathway results in restoration of an effective immune response. Combination of PD-1 blockade and DC/tumor fusion vaccination has resulted in enhanced antitumor responses [44]. Another key inhibitory pathway is mediated by CTLA4, a negative regulator of the costimulatory complex. Blockade of CTLA4 has been associated with induction of antitumor responses associated with manifestations of autoimmunity and may amplify vaccine-induced immunologic responses [47]. The efficiency of vaccines may be further enhanced through the blockade of inhibitory cytokines such as IL-10 [48], TGF-β [49], IL-13 [50] and VEGF [51]. By contrast, use of immunostimulatory molecules such as agonistic antibodies for 4-IBB, OX40, Toll-like receptor ligands can enhance the immunogenicity of vaccines [52]. IL-15 promotes the expansion of central memory cells and may be used to generate more durable antitumor immunity [53,54].

In the field of cancer vaccines there is still much to be learned to improve the clinical efficacy of this novel strategy. While initial efforts focused on optimizing vaccine design, overcoming the immunosuppressive environment in patients with malignancy remains a major challenge. Recent advances in the understanding of the complex interactions between tumor cells and host immunity have provided approaches to enhance vaccine potency in this setting. In seeking strategies to further augment antigen presentation and reverse tumor-mediated immune tolerance, we are hopefully drawing closer to successful development of this promising approach to cancer immunotherapy.

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