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Review

Anti-cancer vaccine therapy for hematologic malignancies: An evolving era

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ABSTRACT

The potential promise of therapeutic vaccination as effective therapy for hematologic malignancies is supported by the observation that allogeneic hematopoietic cell transplantation is curative for a subset of patients due to the graft-versus-tumor effect mediated by alloreactive lymphocytes. Tumor vaccines are being explored as a therapeutic strategy to re-educate host immunity to recognize and target malignant cells through the activation and expansion of effector cell populations. Via several mechanisms, tumor cells induce T cell dysfunction and senescence, amplifying and maintaining tumor cell immunosuppressive effects, resulting in failure of clinical trials of tumor vaccines and adoptive T cell therapies. The fundamental premise of successful vaccine design involves the introduction of tumor-associated antigens in the context of effective antigen presentation so that tolerance can be reversed and a productive response can be generated. With the increasing understanding of the role of both the tumor and tumor microenvironment in fostering immune tolerance, vaccine therapy is being explored in the context of immunomodulatory therapies. The most effective strategy may be to use combination therapies such as anti-cancer vaccines with checkpoint blockade to target critical aspects of this environment in an effort to prevent the re-establishment of tumor tolerance while limiting toxicity associated with auto-immunity.

1. Introduction

While hematologic malignancies demonstrate sensitivity to cytotoxic therapy, curative outcomes often are elusive due to presence of clonal heterogeneity and the emergence of disease resistance. The unique potency of cellular immunotherapy for targeting hematologic malignancies is highlighted by the observation that allogeneic hematopoietic cell transplantation (HCT) is curative for a subset of patients mediated by the eradication of malignant cells by alloreactive lymphocytes [1,2]. However, the lack of specificity of the alloreactive response results in the significant morbidity and mortality due to targeting of normal tissues by graft-versus-host disease (GvHD). In addition, efficacy remains limited as the risk of relapse after transplant may be high, particularly in patients whose disease exhibits poor prognostic factors.

Over many years, investigators have sought out therapeutic strategies to stimulate the patient's own immune system to selectively recognize and reject the tumor cell population while sparing normal tissues [3]. A major area of investigation is the development of anti-cancer vaccines to reverse tumor-associated tolerance, educate host immunity to recognize malignant cells as foreign pathogens, and stimulate effector cell populations to selectively eradicate cancer cells while maintaining normal immune regulation towards normal structures identified as self. An effective vaccine strategy requires the efficient presentation of antigens that capture tumor clonal diversity and the generation of a memory response to provide surveillance and long-term protection against disease recurrence. In the present review, we will summarize the critical aspects of immune dysregulation in hematologic malignancies and the anti-cancer vaccine strategies being developed to restore host immunity and generate an effective anti-tumor response.

2. Tumor cell evasion of host immune system

2.1. Tolerance

Immune function in the normal host requires the maintenance of a careful homeostasis between activation of effector cells to defend against foreign pathogens and the protection from over-activation associated with systemic damage and collateral injury to normal tissues. A critical regulator of this balance is the thymic deletion of high affinity T cells targeting self-antigens (central tolerance) and the tolerization of persisting autoreactive clonal populations by normal tissues that present antigen in the absence of positive costimulatory signals (peripheral tolerance) [4–6]. In contrast, pathogens present non-self targets in the

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context of danger signals that activate the adaptive immunity and subsequently result in the activation of reactive, high affinity T cell populations.

Hematologic malignant cells exploit many aspects of immune regulation found in the normal host to create an immunosuppressive milieu that fosters immune escape. Tumor-associated antigens are presented in the absence of positive costimulatory signals necessary for the induction of primary immune responses. Tumor cells demonstrate increased expression of negative costimulatory molecules such as PD-L1 and CTLA-4 that bind to the corresponding receptors on T cell populations and induce an exhausted phenotype characterized by inactivation and loss of cytolytic capacity [7–9]. Tumor cells also may induce senescence in T cells via alternative pathways. One such described mechanism occurs via the transfer of tumor-derived cAMP to T cells [10]. Tumor cells directly induce T cell senescence in a manner similar to that observed in age-associated dysregulation of the immune system during the normal aging process. In addition, antigen presenting cells such as dendritic cells (DCs) present in the tumor bed typically are rendered functionally incompetent due to blockade of maturation and polarization towards a tolerizing phenotype through the increased presence of factors such as indolamine (IDO). Moreover, exposure of DCs to inhibitory cytokines such as IL-10 further induces tolerance by virtue of halting DC maturation [11]. In contrast, IL-12 produced by functionally mature DCs fosters a state of immune activation [12].

Under homeostatic conditions, engulfment and clearance of apoptotic cells by phagocytes (efferocytosis) is characteristically associated with lack of immune activation and tolerance towards self-targets. Similarly, clearance of apoptotic malignant cells and associated debris facilitate the maintenance of tumor-associated tolerance. In contrast, alteration of this process may result in the extracellular release of cellular components from phagocytes, allowing for these antigens to be effectively presented by antigen presenting cells in the context of positive costimulation [13]. This strategy is currently being explored as a means to expose otherwise hidden tumor antigens to the immune system to reverse peripheral tolerance and promote anti-tumor immunity [14,15].

2.2. Tumor microenvironment in immune tolerance

The immunosuppressive milieu of the tumor microenvironment is further shaped by the presence of accessory cells that down-modulate effector cell function including T regulatory lymphocytes (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) [16–18]. Under homeostatic conditions, $FOXP3^+CD4^+$ Tregs are critical for preventing autoimmunity through the preservation of self-tolerance [19]. Increased presence of Tregs in the tumor microenvironment has been associated with poor prognosis in follicular lymphoma [17,20–22]. MDSCs are a heterogeneous population of cells characterized by immature myeloid markers that function to suppress T cell anti-cancer responses [16,23]. In multiple myeloma (MM) and acute myeloid leukemia (AML), MDSCs are characteristically increased in the tumor microenvironment [24–26]. Our group recently has demonstrated that AML cells recruit MDSCs via the export of extracellular vesicles carrying oncogenic proteins that induce proliferation of MDSCs and prevent their maturation into functionally competent APCs [27]. Tumor and accessory cells in the microenvironment release immunosuppressive substances which further contribute to immune evasion as is the case in AML (Fig. 1) [28,29].

3. Tumor vaccine design

3.1. Target antigens in vaccine design for hematologic malignancies

An effective vaccine design requires: 1) identifying targets that segregate tumor cells from normal tissues and are recognized by the T cell repertoire; 2) creating enhanced antigen presentation to mediate the expansion and activation of tumor-reactive lymphocytes; and 3) attempting to provide a durable response through the development of immunologic memory and inhibition of immunosuppressive factors in the tumor microenvironment [6,30,31]. The ideal properties of vaccine will be reviewed in detail including the unique properties of peptide-based vaccines as compared to whole cell and neoantigen vaccines (Table 1). Antigenic targets are processed via endosomal degradation and creation of peptide epitopes that are presented in the context of HLA restriction to corresponding T cell receptors [32]. Differential expression of tumor-associated antigens may result from normal tissue expression restricted to embryonic development (NY-ESO, WT-1, MAGE-A3, survivin) or the upregulation of transcription factors linked to malignant transformation (SOX2, XBP1) [33–36]. MUC1 is an oncogenic glycoprotein aberrantly expressed on solid tumor and hematopoietic malignancies that interacts with pro-tumor kinase pathways, induces reactive oxygen species, and has been shown to play a role in leukemic differentiation. MUC1 is highly expressed on leukemia and malignant plasma cells and is aberrantly under glycosylated in hematologic malignancies allowing for exposure of its immunogenic epitopes that are ordinarily hidden within MUC1's inner peptide component [37]. Wilms-tumor 1 (WT-1), first recognized in the context of retinoblastoma, is a targetable, ubiquitous leukemia-associated protein [38–40]. Of note, blood WT-1 mRNA transcript levels can serve as a diagnostic relapse test with greater sensitivity than a morphologic approach [41]. WT-1 is expressed at high levels on AML and myeloma cells, alike, with restricted expression on normal tissues–a critical feature favoring the targeting of WT-1 in hematologic malignancies [42,43]. A vital aspect of vaccine design involves the effective targeting of malignant stem cell populations that are a critical reservoir contributing to disease relapse. Tumor associated antigens such as WT-1 and MUC1 have also been identified on the leukemia stem cell (Table 2) [40,44].

Vaccines can be characterized based on their source of antigen and the platform used for antigen presentation. Individual antigen-based approaches include the use of peptide, protein, or RNA encoding shared tumor antigens in an effort to elicit tumor-specific responses that would selectively target malignant cells. These strategies are dependent on the effective expansion of functionally competent antigen specific tumor-reactive lymphocytes and are subject to immune escape via down-regulation of the target antigen. In addition, peptide-based vaccines require a specific HLA-restriction (most commonly HLA-A2.1) and induce CD8 cytotoxic T cell immune response in the absence of CD4 helper T cells often required to promote epitope spreading and persistence [45]. Alternatively, antigen extracted from whole tumor cells, tumor lysate, exosomes, and apoptotic bodies, potentially elicit a broader and balanced helper and cytotoxic T cell response targeting multiple antigens. However, both approaches are dependent on an effective platform of antigen presentation. Potential strategies include the use of immune adjuvants to attract and activate intrinsic antigen presenting cells. In contrast, functionally DCs may be generated ex vivo through the differentiation of precursor populations that exhibit greater capacity to reverse tumor mediated immune tolerance. DCs orchestrate both a cell-mediated (activation of TH1 CD4 T cells and cytotoxic CD8 T cells) and humoral (activation of B and NK cells) immune response thereby activating a broad panel of immune-mediating cells [31,46,47].

3.1.1. Idiotype vaccines

Idiotype vaccines historically have been pursued in lymphoma and myeloma patients. The idiotype protein is derived from the unique recombination of the V, D, J regions of the immunoglobulin genome that is unique to each B cell clone and as such the malignant lymphoid or plasma cell [48]. Generation of the idiotype protein may be accomplished via the creation of a hybridoma (patient cell fused to cell line) or through recombinant technologies [49]. Idiotype-based vaccination strategies may incorporate the use of idiotype-specific peptides, proteins or mRNA.

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