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REVIEW

Blocking tumor escape in hematologic malignancies: The anti-PD-1 strategy

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ABSTRACT

Immunotherapy remains an important tool for treatment of hematologic malignancies. The Programmed Death-1 (PD-1) immune checkpoint pathway has emerged as a mechanism of tumor evasion from the anti-tumor immune response. The recent development of anti-PD-1 monoclonal antibodies has offered a targeted approach to cancer therapy. Several agents are in various stages of development and have shown clinical responses across a broad spectrum of both solid and hematologic malignancies. The use of anti-PD-1 therapy in hematologic malignancies is limited but has demonstrated clinical responses in relapsed/refractory disease following multiple lines of therapy. PD-1 blockade may reduce relapse rates for patients who fail to obtain a complete remission prior to autologous hematopoietic cell transplant. The role of the PD-1 pathway for tumor escape is reviewed. We explore the use of anti-PD-1 therapy in hematologic malignancies. The proposed mechanism of PD-1 blockade as a modulator of the innate and acquired immune response is considered. Finally, the challenges of anti-PD-1 therapy and the future direction of investigation in this area are reviewed.

1. Introduction

The immune system plays an important role in the development of cancer [1,2]. The ability of the immune response to target malignant cells is best illustrated by treatments like hematopoietic cell transplantation and donor lymphocyte infusion where a graft versus leukemia/lymphoma effect has been well demonstrated [3,4]. Why immune targeting may fail can be explained by the concept of "tumor escape", which results from direct inhibition of cytotoxic T-lymphocytes, thereby allowing malignant cells to evade the immune response [5–7]. The Programmed Death-1 (PD-1) pathway has emerged as an important mechanism for tumor escape. Exploration into the tumor microenvironment has uncovered key mechanisms that regulate the unchecked nature of tumor cell growth. Treatment strategies that block the PD-1 pathway are currently under development and recent clinical trials have shown clinical responses in a variety of malignancies including both solid and hematologic cancers. In this review, we will discuss the role of newly developed agents for PD-1 blockade in hematologic malignancies.

2. PD-1 pathway

Programmed Death-1 (PD-1) is a member of the B7 receptor family, which plays an important role in the regulation of the immune response. The PD-1 receptor is a 288 amino acid type I transmembrane protein that is part of the immunoglobulin superfamily [8,9]. The PD-1 receptor, in conjunction with receptor ligands PD-LI and PD-L2, functions to regulate the immune response primarily by down regulating signals of the T-cell receptor (Fig. 1). The interaction of PD-1 and the receptor ligands induces processes resulting in apoptosis of activated T lymphocytes [10–13]. PD-1 is expressed on progenitor T-cells, activated T and B lymphocytes, natural killer cells, and myeloid cells. While PD-1 has broad expression across multiple immune cell types, the primary function of PD-1 is on effector/memory T lymphocytes resulting in regulation of T-cell activation and apoptotic pathways [8,14]. The mechanism of PD-1 regulation is related to its close proximity to the T-cell receptor (TCR) in activated T-cells. An increase in SHP-2, a cytoplasmic SH2 domain containing protein tyrosine phosphatase, is recruited to the cytoplasmic tail and interferes with the TCR signaling complex, thus blocking activation of the PI3K pathway and downstream activation of Akt. Blockade of PI3K results in a decrease in survival proteins, including Bcl-xL, a transmembrane mitochondrial molecule key to the intrinsic apoptotic pathway [8]. The end result of the PD-1 pathway is to function as a regulator of immune tolerance [15].

The role of PD-1 and its receptor ligands has been described in the regulation of immune defense mechanisms against microbes related to both acute and chronic infections. The PD-1 pathway is instrumental in controlling the balance of effective antimicrobial immune defenses against immune-mediated damage to host tissues. Chronic viral infections including HIV, hepatitis B, and hepatitis C have been studied with established alterations in the PD-1 pathway [16–19]. Chronic

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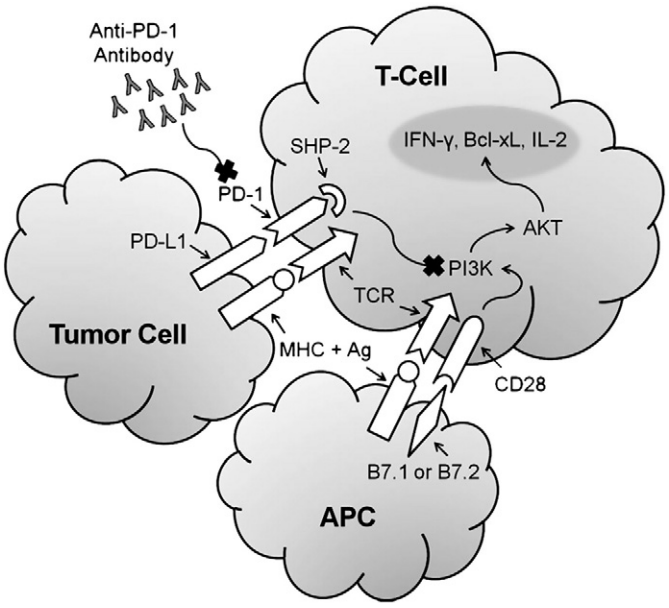

Fig. 1. The antigen presenting cell (APC) presents antigen (Ag) with the major histocompatibility complex (MHC) to the T-cell receptor (TCR). Binding of CD28 on T-cells with B7.1 or B7.2 on the APC results in activation of the AKT pathway through PI3K resulting in up-regulation T-cell survival proteins including IFN-γ, Bcl-xL, and IL-2. Increased T-cell proliferation creates the anti-tumor response. Conversely, PD-L1 expressed on tumor cells binds to PD-1 on T-cells recruiting a phosphatase, SHP-2, which blocks the PI3K pathway and leads to down-regulation of T-cell survival proteins. T-cell clearance leads to anergy or "immune exhaustion". The anti-PD-1 antibodies block the PD-1 pathway preventing suppression of the anti-tumor response.

infections with *Helicobacter pylori* have also been shown to utilize the PD-1 pathway in promoting T-cell suppression through regulation of effector/memory T-cells [20]. Additionally, parasitic worms utilize the PD-1 pathway to induce macrophages to produce immune suppression [21]. In inflammatory states like chronic infections, sustained expression of PD-1 and the receptor ligands results in T-cell exhaustion and immune escape. The resulting changes protect the host from an excessive immune response. There is ongoing investigation into PD-1 blockade for the treatment of chronic infectious diseases.

Similarly, tumors have adopted this mechanism in order to escape the anti-tumor activity of tumor-infiltrating lymphocytes that are present in the microenvironment [22]. The pathway has been demonstrated in a broad spectrum of solid malignancies including breast, colon, esophageal, lung, pancreatic, renal cell, and skin cancers. Furthermore, hematologic malignancies including lymphomas and leukemia have adopted the PD-1 pathway to mitigate anti-tumor immune response. The aberrant expression of PD-L1 has been demonstrated on tumor-infiltrating lymphocytes of lymphomas [23]. The result is T-cell exhaustion, resulting in inhibition of the anti-tumor response. The mechanism likely affects both the innate and the adaptive immune response. Innate immunity is demonstrated by upregulation of PD-L1 expression via amplified gene expression. Chromosomal abnormalities of 9p24.1 in Hodgkin lymphoma have been correlated with increased PD-L1 expression [24]. Adaptive immunity is demonstrated by upregulation of PD-L1 expression in response to inflammatory cytokines related to tumor development [25]. Together, tumors are protected from the destructive processes of a targeted immune response. Using a mouse animal model, researchers were able to show that by increasing expression of PD-L1 one could induce resistance to previously established effective immunotherapies [26]. For tumors, the chronic antigen exposure creates persistently elevated levels of PD-1 expression resulting in exhaustion or anergy of antigen-specific T-cells.

3. Targeting the PD-1 pathway in hematologic malignancies

Expression of the PD-1 pathway markers has been demonstrated in multiple hematologic malignancies (Table 1). Plasma cell myeloma cells, but not normal plasma cells express PD-L1 [27]. PD-L1 is expressed on primary T-cell lymphomas including high expression particularly in anaplastic large T-cell lymphomas [28]. Nodular lymphocyte-predominant Hodgkin lymphomas have tumor-infiltrating T-cells that express PD-1 [29]. Interestingly, the PD-1 expressing cells form a rosette surrounding the tumor nodules within involved lymph nodes [28]. Both PD-1 and PD-L1 expression is found on T-cells of HTLV-1 mediated adult T-cell lymphoma and leukemia [30]. Marker expression related to the PD-1 pathway has been demonstrated in acute myeloid leukemia [31]. PD-L2 expression has been identified in primary mediastinal B-cell lymphoma, a specific subtype of diffuse large B-cell lymphoma [32]. Other B-cell non-Hodgkin lymphomas expressing PD-1 include small lymphocytic lymphoma, follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) [33–35]. For T-cell non-Hodgkin lymphomas, PD-1 is restricted to angioimmunoblastic T-cell lymphoma [35]. PD-1 is expressed by tumor-infiltrating lymphocytes of the tumor microenvironment in several hematologic malignancies including follicular lymphoma, diffuse large B-cell lymphoma, and classical Hodgkin lymphoma [33,34,36].

Expression of PD-1 and the receptor ligands has proven to be a difficult marker for predicting prognosis. PD ligand expression including both PD-L1 and PD-L2 on malignant cells has been negatively correlated with prognosis for solid tumors [37]. For hematologic malignancies, particularly lymphomas, PD-1 expression as a prognostic marker is variable across lymphoma subtypes. The expression of PD-1 on tumor-infiltrating lymphocytes is associated with improved disease specific survival, progression free survival, and importantly overall survival in follicular lymphoma [33,38]. In follicular lymphoma, the type of tumor-infiltrating PD-1 positive T-cell subset, exhausted T-cells versus T follicular helper cells, may have differing influences on patient outcomes accounting for the discrepancies in previous clinical observations [39]. Early clinical data may support the use of soluble PD-L1 protein expression in the peripheral blood as a predictive biomarker in diffuse large B-cell lymphoma [40].

The expression of PD-1 and the receptor ligand, PD-L1, has drawn interest as potential therapeutic targets. Preclinical models for PD-1 pathway blockade have shown promising results in tumor responses across a broad spectrum of malignancies [41]. The proposed mechanism of PD-1 blockade as a therapeutic intervention is likely through either of two processes. The first proposed process is direct anti-tumor effect related to binding to PD-1 or PD-L1 receptors expressed on tumor cells. The varied receptor expression and inconsistent clinical responses

Table 1
PD-1 pathway receptor expression in hematologic malignancies.

Disease	Receptor(s)	Location(s)	Reference(s)
AITL	PD-1	Tumor cells	[35]
ALCL	PD-L1	Tumor cells	[28]
AML	PD-1	Tumor cells	[31]
ATL, HTLV-1 mediated	PD-1, PD-L1	Tumor cells	[30]
CLL/SLL	PD-1	Tumor cells	[35]
DLCBL	PD-1	Tumor cells; TMI	[34,35]
FL	PD-1	Tumor cells; TMI	[33,35]
HL			
Classical	PD-1	TMI	[36]
NLPHL	PD-1	TMI	[29]
PCM	PD-L1	Tumor cells	[27]
PMBCL	PD-L2	Tumor cells	[32]

AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large T-cell lymphoma; AML: acute myeloid leukemia; ATL: adult T-cell leukemia/lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; HTLV-1: human T-lymphotropic virus-1; NLPHL: nodular lymphocyte predominant Hodgkin lymphoma; PCM: plasma cell myeloma; PMBCL: primary mediastinal B-cell lymphoma; SLL: small lymphocytic lymphoma; TMI: tumor microenvironment.