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REVIEW

Harnessing the immune response to target tumors [version 1; referees: 2 approved]

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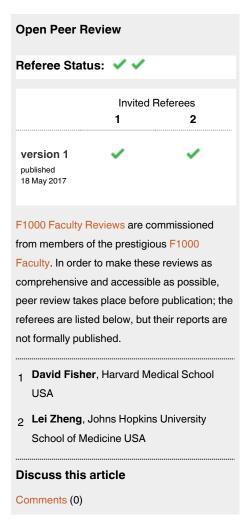
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Abstract

Development of "immune-based targeted therapy" in oncology has limited experience with signal pathway modulation. However, as we have become better versed in understanding immune function related to anticancer response, "hints" of specific targets associated with sensitivity and resistance have been identified with targeted immune therapy. This brief review summarizes the relationship of several targeted immune therapeutics and activity associated clinical responsiveness.

Open Peer Review

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	Invited Referees	
	1	**2**
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1   **David Fisher**, Harvard Medical School USA

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Competing interests: JN is a shareholder in Gradalis, Inc.

Introduction

Although the immune system distinguishes self versus non-self antigens with the intent to eliminate cells expressing non-self antigens, cancer cells have developed mechanisms to escape or suppress the "non-self attack", thereby enabling tumor proliferation and progression. Increasing numbers of innovative immunotherapies are being developed that address immune modulation of non-self targets to reverse cancer defenses.

Checkpoint inhibitors

Several targets have been associated with evidence of clinical benefit, resulting in a broad spectrum of investigational and approved immunotherapies. These include cellular therapies (adoptive T-cell and dendritic cell therapy, cytokine-induced killer cells, tumor vaccines, and autologous tumor cell therapy) and checkpoint inhibitors (PD-1/L-1 and CTLA-4 inhibitors). Several checkpoint inhibitors have shown superior clinical benefit over standard of care[1–3]; however, a high percentage of patients do not show durable response rates in monotherapies or combination therapies with checkpoint blockade. Factors like tumor-infiltrating lymphocyte (TIL) infiltration and PD-L1 expression levels are associated with response[4]. In addition, tumor mutation burden (TMB) appears to be a prognostic marker for immune response[5]. During cancer cell proliferation, somatic mutations increase the expression of a variety of tumor-associated antigens and neoantigens. Studies show that high TMB correlates with the amount of immunogenic neoantigens ($P < 0.0001$), presented by major histocompatibility complex (MHC) molecules to immune effector cells, inducing higher durable immune responses (overall response rate of 63% versus 0%; $P = 0.03$) and progression-free survival prolongation (14.5 versus 3.7 months; $P = 0.01$) than in tumor types with lower mutation burden[6]. Regardless of histology type, tumors with a mean mutational load of more than 10 somatic mutations per megabase of coding DNA appear more likely to be immunogenic to effector T cells eliciting antitumor immunity[7,8]. Other cancer types, such as colorectal cancer, and interestingly subgroups with a high number of somatic mutations and potential mutation-associated neoepitopes appear to correlate with higher responses to checkpoint inhibitors in mismatch repair-deficient tumors[9]. Recent studies show that the overall response rate to PD-1/L-1 therapies in high TMB tumor types has been durable for years with delayed relapse or disease progression[10]. On the other hand, signal pathways, such as those associated with interferon receptor expression related to loss of JAK 1 or JAK 2 function, result in unresponsiveness to interferon gamma, a common antiproliferative cytokine associated with oncolytic activity. This effect has been well demonstrated in a subset of PD-1/L1-refractory patients. Zaretsky et al.[10] identified inactivating mutations in JAK 1 and 2 that silence the CD8 T cell-induced interferon gamma signaling cascade, an adaptive antitumor response. Another mechanism such as beta 2-microglobulin inactivation results in loss of MHC1 expression. Moreover, mutations of death receptors—like Fas or tumor necrosis factor-related apoptosis-inducing ligand—are associated with insensitivities against granzymes or perforin or both, which also play major roles in immune escape and resistance.

Bu et al.[11] discussed PD-1 resistances and highlighted a pattern of upregulated genes first observed in patients with PD-1-resistant melanoma[12], termed innate PD-1 resistance effect. The analysis of somatic mutanomes and transcriptomes of pretreatment melanoma biopsies included the comparison of differentiated gene expression in PD-1 responders versus non-responders. Higher expressed genes in checkpoint non-responding tumors included mesenchymal transition genes (*AXL*, *ROR2*, *WNT5A*, *LOXL2*, *TWIST2*, *TAGLN*, and *FAP*), immunosuppressive genes (*IL10*, *VEGFA*, and *VEGFC*), and monocyte and macrophage chemotactic genes (*CCL2*, *CCL7*, *CCL8*, and *CCL13*)[12], while immune responsive tumors also contained transforming growth factor beta (TGFβ) signaling defects.

To address and overcome resistant mechanisms, ongoing studies are extensively investigating combination approaches (that is, with checkpoint inhibitors). For example, experiments of targeted inhibition of mitogen-activated protein kinase show synergy with PD-1/L1 pathway inhibition and increases in CD8 T-cell number within the tumor environment in association with increased tumor response[13].

Adoptive T-cell therapies

Adoptive dendritic cell or T-cell therapies show clinically meaningful value in hematologic malignancies, and a small number of case reports support efficacy in solid tumors with demonstration of durable clinical responses[14–16]. For example, 20 to 25% of patients with metastatic melanoma showed durable responses to expanded TIL therapies[14,17]. This is most likely related to neoantigen signal identification. A remarkable case of response of adoptive T-cell therapy to a common neoantigen target was recently demonstrated to *KRAS* G12D mutation[16] and other, lesser-known mutations[14,15]. However, currently, the majority of cancer vaccines and adoptive T-cell approaches fall short of significant efficacy targeting pre-selected MHC-dependent (genetically modified T cells) or independent—chimeric antigen receptor-T (CAR-T)—antigens showing limited activity in solid tumors, possibly related to the lack of knowledge of relevant neoantigens (Table 1). While CD19-targeting CAR-T cell therapies have demonstrated curative events in B-cell malignancies[18,19], efficacy in solid tumors appears to be limited by heterogeneity, lack of relevant tumor-specific or -associated antigens and low immunogenicity[20], in balance with other immunosuppressive pathways not addressed within the tumor microenvironment.

Adoptive T-cell therapy "exhaustion" may also be influenced by upregulation of pathways such as PD-L1 expression on tumor cells. Strategies to convert the negative signal of PD-L1 to co-stimulatory receptors by PD1:28 chimer alteration showed encouraging results in activation of CD8 effector T cells[21]. Tran et al. identified CD8 T-cell responses against mutant *KRAS* G12D and *HLA-C**08:02 in a patient with colorectal cancer, receiving a single-dose infusion of 1.48×10^{11} TILs (approximately 75% CD8 T cells) with durable regression of lung metastases with disease progression 9 months after treatment[16].

Tumor signaling/microenvironment modulation

Overcoming tumor-induced immunosuppression can also involve tumor signal modulation and microenvironment influence. Altered expressions of survival genes (Bcl-xL), increasing the

Table 1. Cellular immunotherapies.

Target	Tumor type(s)	Reference/Clinical trial(s)
Chimeric antigen receptor–T cell therapies/targets		
CD19	B-cell malignancies	18,19; NCT02975687; NCT02842138; NCT02813837
Mesothelin	Mesothelioma, lung cancer, breast cancer	36,37; NCT02930993; NCT02706782
L1-CAM	Metastatic neuroblastoma	38; NCT02311621
GD2	Neuroblastoma	25,39; NCT02107963; NCT02919046
Lewis Y	Myeloid malignancies	24,40; NCT01716364
EGFRvIII	Brain tumor	NCT01454596
HER2	Colon cancer, HER2-positive lung cancer, malignant glioma, Her2-positive sarcoma	26,41; NCT00889954; NCT00902044; NCT01109095
CD20	Follicular and mantel cell lymphoma	42,43; NCT00621452
CEA	Stomach cancer, metastatic adenocarcinoma, breast cancer	44; NCT00673829; NCT00673322
MUC-16/IL-12	Ovarian cancer	45; NCT02498912
WT1	Acute myeloid leukemia, NSCLC, breast, pancreatic, ovarian, colorectal cancer, mesothelioma	27,28; NCT02408016
CAIX	Renal cell carcinoma	46,47
FAP	Malignant pleural mesothelioma	48
PSMA	Prostate cancer	NCT00664196; NCT01140373
Kappa light chain (kIC)	B-cell lymphoma, chronic lymphocytic leukemia, multiple myeloma	NCT00881920
CD30	Hodgkin's lymphoma, non-Hodgkin's lymphomas	NCT01316146
HLA-A1/MAGE1	Melanoma	49,50
HLA-A2/NY-ESO-1	Sarcoma, melanoma	51
MUC1	Ovarian, breast, pancreas, colorectal, malignant glioma, NSCLC, hepatocellular	52; NCT02587689; NCT02617134; NCT02839954
VEGFR-2	Solid tumors	53,54; NCT01218867
Adoptive cell therapies		
Autologous tumor-infiltrating lymphocyte therapy and IL-2	Metastatic melanoma	14
Dendritic cell vaccine and cytokine-induced killer cell therapy	Hepatobiliary, pancreatic cancer	55
Adoptive T-cell transfer	Metastatic melanoma	15
Dendritic cell-derived exosomes (Dex)	NSCLC, melanoma, colorectal cancer	56–59
Adoptive CD8+ T cells	KRAS, G12D, colorectal	16
Autologous tumor cell therapy		
Vigil EATC	Ovarian cancer, Ewing's sarcoma, NSCLC, melanoma, triple-negative breast cancer, solid tumors	32–35

IL, interleukin; NSCLC, non-small cell lung cancer.

expression of dominant negative TGFβ receptors to overcome inhibitory effects[22], regulatory T suppression, indoleamine 2,3-dioxygenase downregulation, and other signaling microenvironment therapeutics, such as WNT/β-catenin signaling pathway[23], are being tested to address benefit opportunity.

CAR-T: selective antigen targets

Targeting driver mutations or their *de novo* neoepitopes are very attractive and appear to be very promising in effective anticancer therapies. There are several cancer-associated or -specific antigen-loaded CAR-T cell therapies, selected by different algorithms, in clinical trials to investigate further efficacy in solid tumors (Table 1). *In vivo* activity of gene-modified T cells was demonstrated in the delayed growth and prolonged survival of Lewis Y antigen CAR-T cell therapy in lymphoma with the report of two cases with stable disease[24]. Louis *et al.* reported other responses, including three complete responses in patients with neuroblastoma treated with specific CAR-T cells targeting GD2 ganglioside[25]. HER2-positive colon, lung cancer, and sarcomas are also under investigational therapy with HER2 CAR-T therapy, showing promising results with stable diseases for 12 weeks up to 14 months but no partial or complete responses in HER2-positive sarcomas[26]. Other targets—that is, carcinoembryonic antigen (CEA) in colon cancer and WT1 in mesothelioma and ovarian cancer[27,28]—are being studied as well. Among the most challenging aspects of adoptive cell therapies and CAR-T engineering are the identification and use of antigens for focused immune effector cell activation to cancer targets only. Despite the large number of investigated tumor antigens with limited encouraging results, high rates of undesirable off-tumor effects, such as cytokine-release syndrome (CRS) or other immune-related adverse events, are widely seen in CAR-T cell therapies. Thus, new approaches with implications for suicide genes like inducible caspase9 or herpes simplex thymidine kinase are under investigation to enhance the safety of T-cell therapies[29,30] along with novel regimens to directly address CRS (that is, interleukin-6 inhibitor)[31].

Interestingly, one investigational personalized cellular immunotherapy product with a mechanism directly associated with autologous DNA engineered tumor cells called Vigil[32–35] shows evidence of enhanced tumor-specific antigen targeting via effector T-cell activation in correlation with clinical benefit in solid tumors. Autologous tumor cells include the full patient- and tumor-specific antigen repertoire. This is a unique aspect of the Vigil therapy.

Conclusions

The future is bright for combination immunotherapy, particularly as exact targets are identified with the tumor microenvironment, thereby enabling access to tumor "non-self" neoantigens.

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The referees who approved this article are:

Version 1

1   **Lei Zheng**, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
    Competing Interests: No competing interests were disclosed.

1   **David Fisher**, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
    Competing Interests: No competing interests were disclosed.