



International Journal of Research in Hospital and Clinical Pharmacy



A review on immune checkpoint blockage therapy

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ABSTRACT



Activating the immune system to eliminate cancer cells and produce clinically relevant response has been a long standing goal of cancer research. Most promising therapeutic approaches of activating antitumor immunity include immune checkpoint inhibitors. Our immune system protect us from disease, killing bacteria and virus. One main type of immune cell called T-cells. T-cells have protein that turn it off. These are called checkpoint. Immune checkpoint are accessory molecules that either promote or inhibit T-cell activation. Checkpoint inhibitor are a type of immunotherapy. They block protein that stops the immune system from attacking the cancer cells. Checkpoint inhibitor are a type of monoclonal antibody or targeted treatment. Immune system cells, such as T-cells and Antigen presenting cells (APCs), defend and protect the body. Immune system play an important role in controlling and eradicating cancer. Cytotoxic T lymphocytes associated protein 4(CTLA-4) and Programmed cell death protein (PD-1) are checkpoint protein which is the negative regulation of T-cell immune function. Inhibition of the target, results in increased activation of immune system.

Keywords: Checkpoint inhibitor; Immune therapy; T-cell; Monoclonal antibody.

ISSN: 2582-0672

Review Article

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Article Info

Received on: 24-11-2019

Revised on: 03-02-2019

Accepted on: 13-02-2019

DOI: <https://doi.org/10.33974/ijrhcp.v2i1.159>



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for too long they should really be attacking the cancer cells. So the cancer cells are pushing to stop the immune system and T-cell can no longer recognize and kill cancer cells. Drugs that block checkpoint protein are called checkpoint inhibitors. They stop the protein on the cancer cells from pushing the stop button. This turns the immune system back on and T-cells are able to find and attack the cancer cells. Nivolumab are checkpoint inhibitors. Ipilimumab is a monoclonal antibody that attach to CTLA-4 and stop it from working. This can boost the body's immune response against cancer cells. Unlike radio and chemotherapy which aim to directly interfere with tumor cell growth and survival, Immunotherapy target the tumour indirectly by boosting the antitumor immune response that spontaneously arise in many patients[1].

Fundamental mechanism of immune checkpoint blockade therapy

Immune checkpoint blockade removes inhibitory signals of T-cell activation, which enables tumour-reactive T cells to overcome regulatory mechanism and form an effective antitumor response. Immune checkpoint blockade therapies are now FDA approved for the treatment of a broad range of tumor type with approval likely for additional indications in

INTRODUCTION

Our immune system protect us from disease, killing bacteria and virus. One main type of immune cell called T-cells. T-cells have protein that turn it off. These are called checkpoint. Some checkpoint protein help T-cells to become active, for example when an infection is present. But the T-cells are active

the future. Since the 2011 FDA approval of ipilimumab (anti-CTLA4) for the treatment of metastatic melanoma, 5 additional checkpoint blockade therapies, all targeting the PD-1/PD-L1 axis, have been approved for the treatment of a broad range of tumor types. Additionally, ipilimumab plus nivolumab (anti-PD-1) combination therapy has been approved for the treatment of advanced melanoma. The mechanism of checkpoint blockade is to be understood^[2].

Five types of mechanism involved are;

1. Mechanisms of CTLA4-mediated negative costimulation.
2. Mechanism of PD-1-mediated attenuation of T-cell activity.
3. Mechanism of negative costimulation versus mechanisms of checkpoint blockade.
4. Mechanism of action of CTLA4 blockade-induced tumor rejection.
5. Mechanism of action of PD-1 blockade-induced tumor rejection.

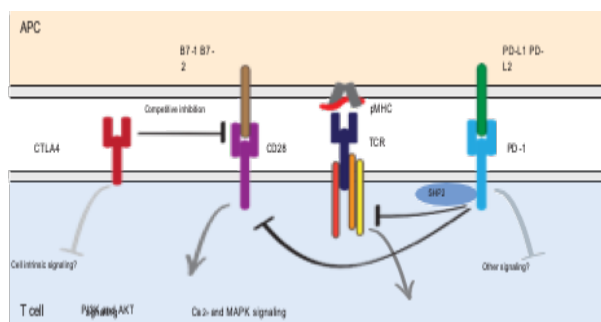


Figure 1: Molecular mechanisms of CTLA4 and PD-1 attenuation of T-cell activation.

Mechanism of ctnla4-mediated negative costimulation

CTLA4 expression and function is basically linked with T-cell activation. CTLA4 is immediately upregulated following T-cell receptor (TCR) commitment (signal 1), with its expression peaking 2 to 3 days after activation. CTLA4 dampens TCR signaling through competition with the costimulatory molecule CD28 for the B7 ligands B7-1 (CD80) and B7-2 (CD86), for which CTLA4 has higher avidity and affinity (Figure :1). Because of both B7-1 and B7-2 provide positive costimulatory signals through CD28, competitive inhibition of both molecules by CTLA4 is necessary to useful. It satisfy T-cells activation. In addition to up-regulation of CTLA4 expression upon T-cell activation, CTLA4 contained in intracellular vesicles is rapidly trafficked to the immunologic synapse^[3]. The degree of recruitment to the immunologic synapse correlates directly with TCR signal strength. Through this mechanism, CTLA4 attenuates positive costimulation by CD28 and thus limits CD28 downstream signaling, which is primarily mediated PI3K and AKT^[4]. This fallout in robust regulation of TCR signal amplitude and thus, T-cell activity. Because CTLA4 negative

costimulation is intrinsically linked to expression of B7 ligands and CD28-mediated positive costimulation, CTLA4 primarily functions to regulate T-cell activity at site of T-cell priming (eg; secondary lymphoid organs). In addition to this core function, CTLA4 also attenuates T-cell activation in peripheral tissues given that B7 ligands are constitutively expressed to varying degrees by antigen-presenting cells (APC) but can also expressed by activated T cells^[5]. Because of its vital role in regulating T-cell activation, negative costimulation by CTLA4 is critical for tolerance. The majority of cell-extrinsic suppressive function of CTLA4 is mediated through Regulatory T cells (Tregs). The genetic loss of CTLA4 in Tregs in middle age. A significant implication of this finding is that Treg depletion may counter expansion of Treg cells induced by CTLA4 blockade and thus lead to enhanced efficacy of anti-CTLA4 therapy^[6].

Table 1: List of FDA approved immune checkpoint blockade therapy

Tumor type	Therapeutic agent
Melanoma	Ipilimumab
Melanoma	Nivolumab
Melanoma	Pembrolizumab
Non-small cell lung cancer	Nivolumab
Non-small cell lung cancer	Pembrolizumab
Melanoma (BRAF wild-type)	Ipilimumab & nivolumab
Melanoma (adjuvant)	Ipilimumab
Renal cell carcinoma	Nivolumab
Hodgkin lymphoma	Nivolumab
Urothelial carcinoma	Atezolizumab
Head and neck squamous cell carcinoma	Nivolumab
Head and neck squamous cell carcinoma	Pembrolizumab
Melanoma (any BRAF status)	Ipilimumab & nivolumab
Non-small cell lung cancer	Atezolizumab
Hodgkin lymphoma	Pembrolizumab
Merkel cell carcinoma	Avelumab
Urothelial carcinoma	Avelumab
Urothelial carcinoma	Durvalumab
Urothelial carcinoma	Nivolumab

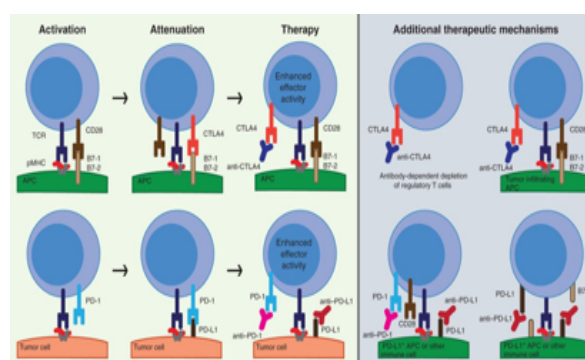


Figure 2: Schematic of the molecular mechanisms of action of CTLA4 and PD blockade

Mechanism of pd-1 mediated attenuation of t-cell activity

The key biological functions of PD-1 are to maintain peripheral tolerance and to maintain T-cell response within a desired physiologic range. Because the PD-1/PD-L1 regulatory system is induced by immune responses, this forms a negative feedback loop to attenuate local T-cell response and reduce tissue damage^[7]. PD-L1 regulates T-cell activation through interaction with PD-L1 and PD-L2 (Figure:2). PD-1 is expressed upon activation of T and B lymphocytes. PD-1 acts primarily to reduce T-cell activation in the periphery. Upon meeting with PD-L1 and PD-L2, PD-1 is through to primarily convey a negative costimulatory signal through the tyrosine phosphatase SHP2 to attenuate T-cell activation. The molecular mechanism reflects a dichotomy in modes of regulation utilized by CTLA4 and PD-1 engagement^[8,9]. These data indicate that in contrast to CTLA4 mediated regulation, PD-1 directly regulates TCR signaling to attenuate T-cell activity. Recently indicates that CD28 is a primary target for PD-1 induced attenuation of T-cell signaling. PD-1 is essential for homeostatic maintenance of peripheral tolerance as evidenced by the autoimmune pathologies that arise upon genetic deletion of *pdc1* (encoding PD-1). As an example, genetic loss of *pdc1* leads to development of lupus like autoimmune pathology in aged mice and autoimmune dilated cardiomyopathy in mice^[10].

Mechanism of negative costimulation versus mechanisms of checkpoint blockade

Based on study of how the molecule themselves act to attenuate T-cell activity, it is thought that anti-CTLA4 and anti-PD-1 primarily act at different stages of the cancer-immunity cycle. Obstruction of PD-1 is sufficient to improve the activity of exhausted T cells in the context of chronic viral infection, leading to viral clearance. Recent findings demonstrate that CD28 costimulation is necessary for response to PD-1 blockade in the setting of both viral infection and tumor rejection^[11,12]. These findings indicate that additional positive costimulation is required for therapeutic efficacy despite prior activation. Mechanism of action of PD-1 and CTLA4 blockade and of the normal biological functions of these molecules are highly complex and clearly not fully understood^[13].

Mechanism of action of ctla4 blockade-induced tumor rejection

CTLA4 blockade is thought to encourage tumor rejection through a number of distinct mechanisms. The primary mechanism seems to be through direct blockade of CTLA4 competition of B7-1 and B7-2 costimulatory ligands, which allows for unrestrained CD-28 mediated positive costimulation^[14]. CTLA4 complex disclose that the ipilimumab binding epitope overlaps with the B7 interaction domain, indicating that steric inhibition of B7 interaction underlies the

primary mechanism of action of ipilimumab. It is also possible that APCs within the tumor microenvironment may also cross present tumor antigens to activate cognate tumor-associated antigens^[15]. Promising evidence suggest that anti-CTLA4 does not impose a generalized effect on all T cells. CTLA4 blockade leads to specific expansion of tumor neoantigen-specific CD8 T cells within the tumor microenvironment, but secondary lymphoid organs^[16]. In addition to these mechanism of CTLA4 blockade-induced tumor rejection, reduction of Treg population has also been identified as a mechanism of action of anti-CTLA4 therapy in murine tumor models. Although other prior studies do suggest that Treg depletion contributes to the mechanism of action of anti-CTLA4, a large body of work powerfully implicates regulation of B7 ligand interaction as a critical mechanism^[17].

Mechanism of action of pd-1 blockade-induced tumor rejection

PD-1 blockade is capable to induce tumor rejection through energy of CD8 T cells, leading to both increased functional activity and frequency. Blockade of the PD-1 signaling axis avoid PD-1 mediated attenuation of proximal TCR signaling, allowing for restoration of activity of exhausted CD8 effectors^[18,19]. Current evidence from a neoadjuvant trial of nivolumab in the context of non-small cell lung cancer support the motion that anti-PD-1 therapy develop neoantigen-specific T cell response. It is probable that only specific T-cell populations functionally mediate response to checkpoint blockade therapy^[20]. These data suggest that PD-1 blockade may not be enough to functionally restore T cells once they reach a threshold level of exhaustion. It remains unclear what specific aspects of CD4 help are functionally necessary for clinical response to checkpoint blockade^[21].

Mechanisms of resistance to immune checkpoint inhibitor

Monoclonal antibodies targeting co-inhibitory immune checkpoints (eg; PD-1 and CTLA 4) have demonstrated clinical activity in several malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma and bladder cancer. Immune checkpoint inhibitor therapy has been particularly successful in melanoma, for which approved treatments now include anti-PD-1 (nivolumab and pembrolizumab), anti-CTLA4 (ipilimumab), and combination anti-PD-1/CTLA-4 regimens (nivolumab-ipilimumab). Long-term survival data for patients with melanoma treated with ipilimumab (anti-CTLA4) indicates 20% of patients show evidence of continued durable disease control or response 5-10 years after starting therapy. The response rate for melanoma patient treated with pembrolizumab (anti-PD-1) was 33% at 3 years with

70-80% of patient initially responding maintaining clinical response (Figure; 3). Combination immunotherapy or dual immune checkpoint blockade (anti-PD-1 and anti-CTLA-4) has recently shown spectacular response rates in patients with metastatic melanoma^[3].

Analysis of clinical trial data can identify three populations of patient

1. Peoples that respond initially and continue to respond (responder).
2. Peoples that fail to ever respond (innate resistance).
3. Peoples that initially respond but eventually develop disease progression (acquired resistance).

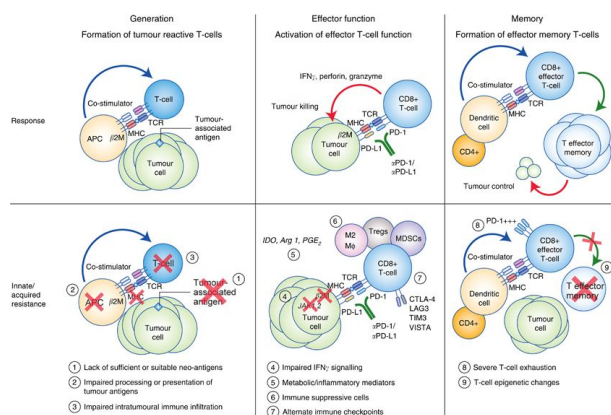


Figure 3: Schematic representation of mechanism of resistance to immune checkpoint inhibitor

Mechanism of innate and acquired resistance to ICI (Immune checkpoint inhibitor) therapy are not fully understood. In addition, few immune competent preclinical models exist in which tumor regression is induced by ICIs, limiting the ability to recapitulate the diversity of tumor-immune interactions in patients^[22]

3 simple categories

1. Inadequate generation of anti tumor T cells
2. Insufficient function of tumour-specific T cells
3. Impaired formation of T-cell memory

Inadequate generation of anti-tumour t-cell

Tumors can evolve to evade both innate and adaptive arms of the immune system there by rendering ICI therapy ineffective^[23,24]. Tumor intrinsic mechanisms of immune evasion include genetic and epigenetic alterations to influence neoantigen formation, presentation, and/or processing, as well as alterations in cellular signalling pathways that disrupt the action of cytotoxic T cells. Tumor extrinsic mechanisms involve non-cancerous stromal or immune cells, or other systemic influences (e.g., host microbiota) that can act in

concert with cancer cells to uphold growth and resistance to ICI^[25].

Insufficient function of tumor specific cell

Successful neoantigen presentation/cross-presentation and T-cell priming, the expanded repertoire of anti-tumour T cells faces an inhospitable TME that may preclude proper T-cell function, thereby limiting the efficacy of ICI therapy^[26]. These tumour intrinsic and tumour-extrinsic factors include mutations in key effector pathways, high levels of PD-L1 on tumour cells (and immune cells), high levels of alternate immune checkpoints or co-inhibitory receptors on T cells (e.g;PD-1, CTLA-4), high levels of immune suppressive cytokines or metabolites, and associated recruitment of immune suppressive cells (e.g;myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)^[27].

Impaired formation of t-cell memory

The most compelling clinical evidence for the success of ICI relates to the potential for long-term, durable clinical profit. Thus, although ICI may temporarily strengthen CTLs to enhance tumour control, if formation of T_{EM} cells is impaired then clinical response could fade leading to acquired resistance or recurrence of disease following discontinuation of therapy. Expansion of intratumoural T_{EM} in response to PD-1 blockade has been demonstrated, and is more pronounced in patients responding to therapy, suggesting a key role for T_{EM} cells in anti-PD-1 action and clinical response. The cellular and molecular mechanisms of T_{EM} expansion following PD-1 blockade are not fully understood^[28,29].

CONCLUSION

Immune checkpoint therapy, which target regulatory pathways in T cells to enhance antitumor immune responses, has lead to important clinical advances and provide a new weapons against cancer. This therapy has elicited clinical responses and, in a fraction of patient, long term remissions where patient exhibit no clinical signs of cancer for many years. The way forward for this class of novel agents lies in our ability to understand human immune responses in tumor microenvironment. This will provide valuable information regarding the dynamic nature of immune responses and regulate additional pathways that will need to be targeted through combination therapies to provide survival benefits for greater numbers of patients.

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