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Review Article

The Biomarkers of Cd4+ T Regulatory Cells Associated with Tumour Immune Escape

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Abstract

Objective: In this review, we endeavor to do a literature search mainly focusing on keywords CD4+FOXP3+, CD4+CD127-, CD4+CD39+, CD4+LAP+ cancer immunotherapy, cancer immunotherapy strategies and articles published between 2015 to 2019 to add onto the minimal definition of human Treg, by an international workshop organized by collaborative immunoguiding program.

Methodology: In this review, we highlight the antitumor suppressive biomarkers of CD4+ Treg cells, how they suppress the immune response.

Summary: The biomarkers play a role in designing of cancer immunotherapy to overcome resistance and enhance anti-tumor immune response among late-stage cancer patients who have exhausted the standard of care. There is evidence suggesting that a combination of treatment strategies has enhanced immune responses for some patients who have developed or are resistant to monoclonal immunotherapy treatments.

Introduction

There have been advances made in precision oncology in designing effective immunotherapies against cancer. However, it does not appear to benefit all cancer patients, as some have either developed resistance or do not respond at all to FDA approved immunotherapies. And we are yet to understand the mechanism underlying this resistance and why some patients appear to benefit while others do not. Therefore, it is paramount for us to understand the inhibitory mechanism and synergies between various CD4+ Treg cells associated with tumor immune escape. As such we chose the five subsets as there are several studies done on the post the minimal definition of Tregs. The biomarkers expressed of CD4+ Treg cells do make these regulatory cells more potent in suppressing effector immune responses against cancer cells. It is these biomarkers that have been used to monitor the efficacy of immunotherapy treatments and measure the treatment progress of cancer patients. Therefore, there is a need to design cancer immunotherapies against these antigens to enhance the body's effector immune response against cancer. Some studies suggest that inhibiting the expression of these biomarkers would improve anti-tumor immune response studies such as CD4+FOXP3+ Treg cells suppress the anti-tumor immune response, and it is an indication of poor patient prognosis [1-7].

Mechanism of tumor immune escape via CD4+CD25+FOXP3+ Treg cells

The first subset of CD4+ Treg cells to be described was the CD4+CD25+FOXP3+ cells discovered in several cancer types where it prevents autoimmune diseases, as activated suppressive markers where it hampered the T_{eff}. The Foxp3 is highly expressed in CD4+ T cells, and inhibit the proliferative activity of naïve CD4+ T cells [7], as it is an intracellular transcription factor and the master of all Treg cells as such its important to describe it here. However, reports indicate that the FOXP3 gene mutation may contribute to carcinogenesis [8], or gene promoter demethylation [7], the Foxp3 is an intracellular undruggable protein to date [9].

As such, there is evidence suggesting that CD4+CD25+FOXP3+ cell accumulation correlates with age among the elderly with Lung cancer, where the reduced T-cell mediated anti-

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tumor immunity contributes to immune evasion at the early stage, finally leading to high morbidity and mortality among the elderly with lung cancer [2]. Urinary bladder cancer [3] gastric cancer [4-6] non-small cell lung cancer [7-11] colorectal cancer [12-15] breast cancer [16] oral squamous cells carcinoma [17,18] cervical cancer in mice5 pediatric B-cell acute lymphocytic leukemia [19] prostate cancer [20] and head and neck squamous cell carcinoma [21]. It is also found in tumor-infiltrating lymphocytes, and abundant in the late stages of gastric cancer [22]. The study demonstrates that thyroid cancer cells express a high level of functional FOXP3+, that the inhibition of the FOXP3+ suppresses the proliferation, migration but promotes apoptosis suggesting that targeting FOXP3+ in thyroid cancer cells may offer a novel therapeutic option for thyroid cancer [23].

The CD4+CD25+FOXP3+ serves as a master prognostic biomarker and a crucial determinant of immunosuppressive microenvironment via recruiting Treg cells by directly trans-activating CCL5. Therefore, FOXP3+ could be used to select patients with better responses to CCL5/CCR5 blockade immunotherapy [24]. In additional they are markers associated with the master FOXP3+ transcription factor, which make it more suppressive such as interleukin-IL-12 [5,25], interleukins IL-10 [26], IL-2 & 35 [24], interferons such as IFN-γ [5,16], transforming growth factor TGF-β [19,25,26], tumor necrosis factor receptor type-11 [14], CCR5, CCR7, and their ligands CCL5, CCL19, and CCL21 [24]. Besides, there are additional anti-tumor suppressor markers associated with FOXP3 including PD-L1 [8,18], PD-L1/CTLA-4, PD-1/CD39 [13], CTLA-4, LAG-3 [8], excessive activation of IL-2/ pSTAT5, and TGF-β/Smad signaling and insufficient pSTAT3 in case of acute lymphocytic leukemia [19], suppression of NKG20- mediated NK cell cytotoxicity and contact-dependent manner [26].

No known immunotherapy directly blocks the CD4+CD25+FOXP3+ Treg cells in humans. There is a suggestion that methionine enkephalin an endogenous neuropeptide inhibited the expression of FOXP3 during the process of TGF-βinduction, which is accompanied by diminishing phosphorylation and nuclear translocation of Smad2/3 in S180 tumor-bearing mice [27]. Another example indicated that the INF-X-2b inhibits cancer cell immune evasion by decreasing levels of CD4+FOXP3+ suppressing TGF-β and IL-10 in the tumor microenvironment [28] Genetic targeting of Usp7 impairs FOXP3 + Treg suppressive functions by stabilizing the expression and promoting the multimerization of histone/ protein acetyltransferaseTip60 and FOXP3+ [29]. But these mechanisms do not directly affect biomarkers of Treg cells. There are efforts out there trying to discover or innovate new therapies that may overcome the FOXP3 inhibitors.

In this article, we focus on the markers of Treg cells, since FOXP3 is a transcription factor and difficult to target. We explore other ways to deplete the anti-tumor suppressive effects of FOXP3 by using other markers co-expressed on Treg cells. Therefore, studies on the anti-CTLA-4 mAbs on mice models, indicated that it selectively depleted intratumoral FOXP3+ regulatory T cells via an Fc-dependent mechanism [18,30,31] And a humanized anti-CCR4 monoclonal antibody, which functions in an antibody-dependent cellular cytotoxicity activity depleting CD4+CD25+FOXP3+ increasing survivor rates [32] Further, studies suggest that Mogamulizumab an anti-CCR4 monoclonal antibody with a defucosylated Fc region (Potelligent® Technology), enhances antibody-dependent cellular cytotoxicity by increasing its binding affinity to the Fcx03B3; receptor expressed on effector cells [33,34] Effective on patients with CCR4-positive adult T-cell leukemia and peripheral T-cell lymphoma [35] Whereas Dao and colleagues, generated a T cell receptor mimic antibody, "FOXP3-#32," recognizing a FOXP3-derived epitope in the context of HLA-A*02:01. Selectively recognizes CD4+CD25+CD127low and FOXP3+ Tregs and depletes these cells via antibody-mediated cellular cytotoxicity in xenografts of PBMCs from a healthy donor and ascites fluid from cancer patient [36]. We suggest that immunotherapy targeting CD4+CD25+FOXP3+ should focus on other co-expressed markers on the CD4+ Treg cells because these markers enhance the anti-tumor suppressive mechanism of CD4+CD25+FOXP3+ T regulatory cells. As indicated on the table below Table 1.

Inhibition mechanism of CD4+ CD127-Treg to enhance tumor immune escape

The CD4+CD25hiCD127low/- Treg cells have been detected in follicular lymphoma,39 childhood acute lymphoblastic leukemia [39] peripheral blood of gastric cancer [40,41] nasopharyngeal carcinomas [45] in peripheral blood of non-small cell lung cancer [20,46] colorectal cancer [47,63] hepatocellular carcinoma [42] breast cancer [43] lung adenocarcinoma cells [44]

The CD127 suppresses anti-tumor responses PD-1+ and Tim3+ elevated in gastric cancer in gastric cancer [40]. Treg cells from late stages of Colitis-Associated Colon Cancer CAC displayed an activated phenotype by expressing PD1, CD127 and Tim-3, suggesting an increased suppressive capacity [64] The cytokines such as IL-35 upregulated in colorectal cancer [47] IL-10, and TGF-β secretion in hepatocellular carcinoma [29]. And increased in both plasma concentrations of IL-2, IL-4, IL-6, IL-10, and proportions of latency-associated peptide LAP/ TGF-β [44].

CD4+CD25hiCD127low/- elevated IFN-γ and IL-21 secretion, and it acted a cell-to-cell contact-dependent manner and depended on IL-6 secretion [65]. And activated by three main pathways STAT5, PI3K/Akt/mTOR and MEK/Erk [49]. There is evidence suggesting that CD4+CD25hiCD127low/- host cells are major targets of anti-CD127 that modulate therapeutic CD8+ T cell responses and the outcome of anti-CD127 -assisted [66]. By contrast, excessive CD4+CD25hiCD127low/- mediated signaling can drive lymphoid leukemia development, disease acceleration and resistance to chemotherapy [49] combination therapy relies on the interdependence between IL-7 and IFN-γ signaling it increases CD4+CD25hiCD127low/- the expression on tumor-infiltrating T cells in an IFN-γ/IFN-γR signaling-dependent manner, which could be an effective modality to improve immunotherapeutic efficacy [48].

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Table 1: Summary of the Subsets of CD4+ Tcells.

Type of CD4+ Treg cell	Present on organ/tissue	Mechanism of tumour immune escape	Immunotherapy used in treatment
CD4+FOXP3+	Breast [21] Cervical cancer in mice [10] Colorectal [17-20] Gastric [9,18] Head and neck squamous cell carcinoma [26] Lung [8] Non-small lung cancer [12-16] Oral squamous cells carcinoma [22, 23] Pediatric B-cell acute lymphocytic leukemia [24] Prostate [25] Urinary bladder [5]	IL-2, IL-10, IL-12, IL- 35 [10,28] IFN-γ [10,21] TGF-β [24,27,28] tumour necrosis factor receptor type-11[19] CCR5,CCR7 and their ligands CCL5, CCL19 and CCL21 [32] PD-L1 [13,23] PD-L1/CTLA-4 [18] PD-1/CD39 [18] CTLA-4 [13] LAG-3 [13] IL-2/pSTAT5 [24] TGF-β/Smad signaling [24] Insufficient pSTAT3 [24] Suppression of NKG20- mediated NK cell cytotoxicity [28] Contact dependent manner [28]	Anti-CTLA-423 32 Anti-CCR4 35
CD4+CD127lo	Follicular lymphoma [38] Childhood acute lympoblastic leukemia [39] Gastric [40,41] Hepatocellular carcinoma [42] Breast [43] Lung adenocarcinoma cells [44] Nasopharyngeal carcinoma [45] Non small cell lung [25,46] colorectal	PD-L1 [40] Tim-3 [40] IL-35, IL-10, IL-2, IL-4, IL-6 [47] TGF-β, LAP/TGF-*β* [44] IFN-γ/IFN-γR [48] STAT5, P13k/Akt/mTOR, MEK/Erk [44,49]	Anti-PD-1*42 Anti-Tim-3***42
CD4+CD39+	Breast [50,51] Colon [52] Colorectal [53] Gastric [5] Chronic lymphocytic leukemia [54] Adult T-cell leukemia lymphoma [54] Hepatocellular carcinoma [55] Myeloma [56] Ovarian [34]	Adenosine-mediated pathway [57] IL-17A [56] GM-CSF [56] PD-L1 [58] CD73 [58]	Anti-PD-L1* [52] Anti-CTLA-4* [52] Anti-CD39+*** [59]
CD4+LAP+	B-cell lymphoma Colorectal Gastric carcinoma Hepatocellular carcinoma Liver metastasis,	IL-10 [60] TGF-*β* [60] LAP/ TGF-*β* [60] CTLA-4 [61] CCR4, CCR5 [61]	Ant-LAP*** [60,62]

Approved* under clinical trails** basic research***

How treatment is carried out by blockade of PD-1+ and Tim-3+ inhibition as a synergistic effect on IFN-γ secretion [41] blockades of Notch signaling inhibits suppression function of CD127dim/- in gastric cancer [40].

Effects of adenosine mediated immunesuppression by CD4+CD39+Treg

The CD39+ detected in colorectal cancer [53] breast tumour [50,51] gastric cancer [52] Colon cancer [54] colorectal cancer [55] chronic lymphocytic leukemia [55] and hepatocellular carcinoma [56], Ovarian cancer [67] myeloma [68] adult T-cell leukemia/lymphoma [58]. Frequencies of CD39+, PD-1+, and CD39+/PD-1+cells were higher among both CD4+ and CD8+ T cells isolated from NSCLC tumor tissue [57].

The ectonucleotidases CD39 and CD73 hydrolyze extracellular adenosine triphosphate and adenosine diphosphate to generate adenosine, which binds to adenosine receptors and inhibits T-cell and natural killer–cell responses thereby suppressing the immune system [69]. The CD39+ the suppress anti-tumor immune response via the adenosine-mediated pathway but independent of TGF-β or IL-10 and secrete IL-17A and GM-CSF. CD4+CD25hiCD39+ Tregs inhibit the proliferative response and the secretion of IL-17 and IFN-γ of autologous CD4+ T effector cells [68]. Which chemoattract myeloid-derived suppressive cells [53], suppressive capacity of CD39+ Treg on proliferation, and IFN-γ secretion by conventional T cells colon cancer [54]. CD39+CD73+ cancer cells inhibited the proliferation of CD4 and CD8 T cells and the generation of cytotoxic effector CD8 T cells in a CD39- and adenosine-dependent manner [69]. Through cooperation between CD39+ Treg and CD73+ expressing Th1/Th17 subset in breast cancer [70] Adenosine derived from the degradation of ATP via ectonucleotidases CD39 and CD73 is a critical immunosuppressive metabolite in the hypoxic microenvironment of tumor tissue and Adenosine signaling via A2aR can inhibit the antitumor immune response of CD8+ T cells [70-73]. The generation of adenosine by CD73 also suppresses antitumor immune responses through the activation of A2A receptors on T cells and natural killer cells [74-76] They express the Th17-associated surface markers CCR6 and IL-23R and phosphorylate the transcription factor Stat3. Further, suppression of IL-17 by CD4+CD25hiCD39+ Tregs occurs via a Stat3-dependent mechanism as inhibition of Stat3 activation in the CD39+ Tregs reverses their ability to suppress IL-17 [77,78].

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The potential of CD73 as a double-edged sword in anti-leukemia immunity and argue strongly for the combinational treatment by adding immune checkpoint inhibitors to the CD73-targeting approaches [59,79] it has high expression of immunosuppressive surface molecules such as ICOS, PD-L1, and CTLA-4 [54]. The anti-CD39+ monoclonal antibody is a selective and potent CD39 enzymatic inhibitor capable of preventing adenosine-mediated immune suppression and increasing T-cell activation in the tumor microenvironment [80]. Anti-CD39 treatment alleviated the tumor-induced inhibition of CD4 and CD8 T-cell proliferation and increased CTL- and NK cell-mediated cytotoxicity [70]. Anti-CD39+ reduced Tregs, increased the CD8 / Treg ratio and reduced CD73 expression on immune suppressive cells, and in combination with radiation resulted in enhanced efficacy when compared to either agent [61].

CD4+LAP+ Treg-mediated suppression of anti-tumor immune response

The latency-associated peptide (LAP) is a recently discovered subset of CD4+ Treg cells. LAP+ Treg cells accumulate in the tumor microenvironment of colorectal cancer, were elevated in liver metastasis from colorectal cancer [81]. It is present as clusters in the tumor stroma of patients with hepatocellular carcinoma [82] in tumor-infiltrating B-cells [83] and gastric carcinoma [60]. And it is 50-fold more potent immunosuppressive ability than traditional CD4+CD25+ T cells [84],

The anti-LAP suppresses anti-tumor immune response through IL-10, TGF-γ [84]. IL-10 in liver metastasis [61,85] Anti-LAP antibody targets the LAP/TGF-β complex on Treg to enhance immune responses and reduces tumor growth by increasing the infiltration of tumors by cytotoxic CD8+ T cells [83]. Anti-LAP decreases LAP+ Tregs, tolerogenic dendritic cells and TGF-β secretion, and is associated with CD8+ T cell activation, with increased expression of CTLA-4 and IL-10 and decreased expression of IFN-γ, TNF-α, and granzymes.79 85 Thus, anti-LAP targets multiple immunoregulatory pathways and represents a potential approach for cancer immunotherapy [83]. LAP+CD4+ T cells showed lower Foxp3 expression but significantly higher levels of CTLA-4, CCR4, and CCR5 [81]. LAP+CD4+ T cells expressed significantly higher amounts of IL-10 and TGF-β but lower levels of IL-2, IL-4, IL-17, and interferon-γ, compared with LAP-CD4+ T cells [81].

Furthermore, within the HCC tissues, LAP CD4 T cells were a gift as clusters within the neoplasm stroma and closely related to CD4 T lymphocytes in contrast, within the peri-cancer liver tissues and HBV-infected viscus tissues around benign lesions LAP, CD4 T cells sparsely distributed [83]. LAP+CD4+ T cells have anti-tumor suppressive effects within the peripheral blood of neoplasm tissues, and it is a factor in the suppression of anti-tumor immunity in the neoplasm cells [83]. Anti-LAP antibodies inhibit the discharge, inhibit neoplasm growth in mouse models [84] and have promise as a novel cancer medicine the situation of the LAP-TGFβ1 advanced is of crucial biological, clinical importance, once the mature TGFβ1 protein, is free, it acts domestically, either in associate degree autocrine or close to paracrine fashion [85]. These results warrant additional analysis to work out the effectiveness of anti-LAP in inhibiting the discharge and its effects on immunological disorder within the neoplasm microenvironment [86]. They compared the suppressive activity of CD4+CD25+ regulatory T cells (conventional Treg) with T cells expressing T cell immunoglobulin-3+ (TIM–3+) and latency–associated peptide (LAP)+ T cells [87]. They found that LAP-expressing T cells were more suppressive than conventional Treg, but TIM-3-expressing T cells were not suppressive [88].

Summary

The biomarkers such as PD-L1, CTLA-4 are markers of CD4 Treg cells commonly found on most cancers are thus far been exploited in designing cancer immunotherapies. Some patients do not benefit from them, either because of resistance or outrightly not effective. In overcoming resistance and the low number of patients who benefit from cancer immunotherapies treatment, we suggest that the combination of antibodies. Several studies are ongoing either on animal models or on clinical trials that have tried the combination or single analysis of antibodies against CD4 Treg cell's surface markers. The other biomarkers such as CD39, CD127-, FOXP3, or LAP are more potent in suppressing the anti-tumor immune response, and the antibodies developed against these biomarkers as been effective in eliciting immune responses against several cancers. However, it is the anti-PD-L1 and CTLA-4 that have been approved for use. From this review, we can recommend the combination of these biomarkers will be more effective if they are combined to design polyclonal cancer immunotherapies taking into account individual cancer patient's tumor microenvironment and their status of the immune system. There is a future in precision oncology, whereby polyclonal immunotherapies will be the standard of treatment.

There is a need for a precision oncologist to adopt polyclonal immunotherapy to combat cancer, especially in patients who have exhausted the standard of care. We can personalize and administer a combination of antibodies depending on the number and type of antigen markers present on specific cancer cells to elicit anti-tumor immune responses. In genetically engineered cancer models using mass cytometry, they observed that the immune activation was evident and systemic. However, only peripheral immune cells sustained their proliferation upon tumor rejection. This systemic response was coordinated across tissues and required for tumor medication in several immunotherapy models. But an emerging population of peripheral CD4 T cells conferred protection against new tumors and was significantly expanded in patients responding to immunotherapy. We recommend further research on the dual, triple, and multiple combinations of immunotherapies, chemotherapy, radiation, and surgical to combat tumor immune escape.

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