

**REVIEW**

# Targeting regulatory T cells for improving cancer therapy: Challenges and prospects

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**Abstract**

**Objective:** Regulatory T cells (Tregs) play a central role in immune responses to infectious agents and tumors. Paradoxically, Tregs protect self-cells from the immune response as a part of peripheral tolerance and prevents autoimmune disorders, whereas during the process of carcinogenesis, they are exploited by tumor cells for protection against antitumor immune responses. Therefore, Tregs are often considered as a major obstacle in anticancer therapy. The objective of this review is to provide a current understanding on Tregs as a potential cellular target for achieving therapeutic gain and discuss various approaches that are implicated at preclinical and clinical scenario.

**Recent findings:** Several approaches like immunotherapy and adjuvant chemotherapy, which reduce Tregs population, have been found to be useful in improving local tumor control. Our recent observations with the glycolytic inhibitor, 2-deoxy-D-glucose, established as an adjuvant in radiotherapy and chemotherapy of tumors also show that potential of 2-deoxy-D-glucose to improve local tumor control is linked with its ability to reduce the Tregs pool.

**Conclusions:** Several published studies and emerging evidences indicate that suppression of Treg numbers, infiltration into the tumors, and function can improve the cancer therapy by enhancing the antitumor immunity.

**KEYWORDS**

2-deoxy-D-glucose, antitumor immunity, cancer therapy, immune modulation, regulatory T cells

## 1 | INTRODUCTION

Cancer is the second biggest cause of morbidity and mortality after cardiovascular diseases in the world.<sup>1</sup> It is well established that cancer primarily arises because of uncontrolled and rampant growth of self-cells leading to what is loosely defined as “malignancy” besides the other hallmarks of cancer as described by Hanahan and Weinberg.<sup>2</sup> At the initial stages of tumor progression, tumor cells are recognized by the cells of the innate immune system, while at later stages, tumor cells use several strategies to evade immune responses.<sup>3,4</sup> The adaptive immune response is initiated and matured as a result of the

expression of tumor-associated antigens recognized by the immune system of the host.<sup>5,6</sup> Nevertheless, tumors can escape immune surveillance. The process of evasion (immune editing) results from various mechanisms indicating that the immune responses to tumor cells create selective pressures that decide their survival and progression including spread.<sup>7,8</sup> Among the several mechanisms known, suppression of cytotoxic T cell response to tumors by regulatory T cells (Tregs) plays an important role. Evidences from mouse models and cancer patients show that the population of Tregs increases in parallel with the tumor growth, while depletion of Tregs in mice increases the antitumor immunity and reduces tumor growth.<sup>9,10</sup>

Treg cells (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>) are a specialized subset of CD4<sup>+</sup> T cells and are different from other immune cells because of high expression of CD25 (interleukin [IL]-2 receptor) and transcription

Authorship of Dr Abdullah is posthumously included, who contributed in the initial conception of the review and unfortunately met with an untimely death.

factor FoxP3<sup>11</sup> (forkhead box P3). The role of Tregs has been extensively investigated in autoimmunity, allergy, and microbial infections.<sup>12-14</sup> Tregs are mainly classified into 2 types on the basis of their origin: n-Tregs (naturally occurring Tregs) and i-Tregs (inducible Tregs). n-Tregs are mainly generated in thymus and suppress immune effector cells in a contact-dependent manner, while i-Tregs are found to be generated in the periphery and suppress immune responses by several ways, which include production of inhibitory cytokines, such as IL-10, IL-35, and transforming growth factor (TGF)- $\beta$ , induction of cytotoxicity by the production of granzymes, disruption of effector cell metabolism, and dendritic cell-mediated suppression.<sup>15-17</sup> Several new subsets of Tregs have been discovered and extensively studied.<sup>18</sup>

Tregs on the one hand save self-cells from recognition by immune system and protect body from autoimmunity, and on the other hand, they compromise the antitumor immunity.<sup>13,14</sup> It is well established that in mouse and human malignancies, body's own cells become deregulated and avoid death from chemotherapeutic agents by up-regulating the pool of Tregs and escaping immune response.<sup>19-21</sup> Therefore, strategies that target Treg cells have been found to be successful in achieving local tumor control. Targeting Tregs-specific molecules using monoclonal antibodies and several chemotherapeutic drugs have been found to deplete Tregs, besides their established antitumor effects.<sup>22-27</sup> Our recent studies have shown that the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) that target metabolic reprogramming of tumors also reduce the levels of i-Tregs.<sup>28,29</sup> All these studies suggest that suppression of Tregs level and/or function can restore antitumor immunity, which can be exploited for the treatment of tumors.

Other interesting approaches such as directing naïve T cells and Tregs into Th17 and other subpopulation of cell fates have been the topic of several recent reviews. This review summarizes the current status of Tregs-based targeted therapies as well as conventional chemotherapeutic agents that reduce Tregs thereby leading to improved therapeutic gain.

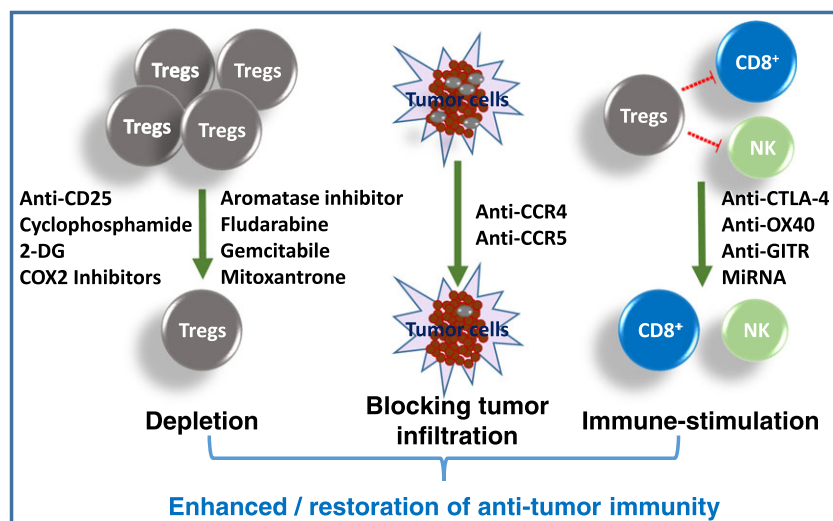
## 2 | T<sub>REGS</sub> IN SURVIVAL AND PROGNOSIS

Increased presence of Tregs is generally associated with reduced survival and poor prognosis in many types of cancer<sup>30,31</sup> such as renal

cell carcinoma<sup>32</sup> primarily due to their capacity to inhibit antitumor immunity. However, in colorectal carcinoma<sup>33-37</sup> and B-cell lymphoma<sup>38</sup> patients, high Treg cell infiltration is associated with a favorable prognosis. In case of B-cell lymphomas or other hematological cancers, this could be due to an additional role of Tregs in regulating malignant immune cell by recognizing tumor antigens on MHCII on the tumor cell leading to tumor cell killing.<sup>39</sup> Similarly, in large intestine, the presence of microbiological flora results in increased Th17-mediated inflammatory antimicrobial response that can promote cancer growth. Attenuation of this tumor-enhancing response by Tregs may provide an explanation for favorable prognosis in colorectal carcinoma patients with high Treg cell numbers in the tumor.<sup>34</sup> Therefore, it appears that Tregs play diverse roles in different types of cancers and may be useful in some settings, which need a thorough understanding of their relationship with other cells, effects of their anatomic distribution, and other factors.

## 3 | SPECIFIC AND NONSPECIFIC APPROACHES FOR THE MODULATION OF T<sub>REGS</sub>

Tumors use numerous mechanisms to suppress host immunity including altered antigen-presenting cell function, fostering dysfunctional T cell co-signaling and generating an immune-subversive cytokine milieu.<sup>3</sup> Moreover, accumulating evidences suggest that the effects of anticancer treatments on the immune system significantly contribute to their overall efficacy, besides their direct effects on the tumor cells/tissues.<sup>40</sup> Therefore, agents that have the potential to restore host immunity have been investigated as immunotherapeutic as well as adjuvant to other therapeutic modalities. Among several approaches to modulate immune status, eliminating CD4<sup>+</sup>CD25<sup>+</sup> T cells has been found to enhance antitumor immunity by abrogating immunological unresponsiveness of syngeneic tumor in-vivo and in-vitro.<sup>41</sup> This can be achieved through specific depletion of Tregs by blocking the specific surface receptors like CTLA-4, CD25, or various chemokine receptors (eg, CCR5, which induces migration of Tregs to tumor sites)<sup>22-25</sup> (Figure 1). Administration of agonist anti-GITR or anti-OX40 antibodies is also capable of evoking antitumor immunity



**FIGURE 1** Specific and nonspecific strategies to attenuate the numbers or function of regulatory T cells (Tregs). The depletion of Tregs, blocking of their recruitment to the tumor tissues or inhibition of their immunosuppressive function leads to restoration of antitumor immunity

and resulting in the eradication of established tumor<sup>25,26</sup> (Figure 1). Interestingly, several chemotherapeutic agents like aromatase inhibitor, cyclophosphamide, fludarabine, gemcitabine, and mitoxantrone have also been found to deplete Tregs, besides their established antitumor effects<sup>27</sup> (Figure 1). Our recent studies have shown that systemically administered 2-DG significantly enhances the antitumor effects of radiation and anticancer drugs<sup>42-44</sup> that appears to be related to the immunomodulation induced by the combination.<sup>28</sup> Interestingly, the complete response (tumor-free survival; cure) observed only in nearly 50% of the animals following the combined treatment with tumor irradiation and 2-DG was found to be strongly linked to the immune stimulation characterized by selective lymphodepletion, shift from Th2 to Th1 and attenuation of the immune-suppressive network.<sup>28</sup> Interestingly, the immune stimulation appeared to be related to the depletion of i-Tregs brought about by the combined treatment<sup>28,29</sup> in spleen, peripheral blood, lymph node, and in the tumor.<sup>44</sup> However, natural Tregs (Tregs in nontumor-bearing mice) were not influenced, suggesting a differential effect on n-Tregs and i-Tregs by the combination. Although inhibition of glycolysis (including by 2-DG) is known to reduce the FoxP3 level, essential for the functioning of Tregs,<sup>45</sup> the differential effects on n-Tregs and i-Tregs are not understood. These differential effects, however, could be related to differences in the metabolic profile as metabolic reprogramming of lymphocytes in general has been suggested to be context and environment dependent.<sup>46</sup> Thus, 2-DG not only sensitizes tumor cells by modifying glycolysis-dependent and glycolysis-independent damage response pathways<sup>47</sup> but also stimulates antitumor immunity mainly by reducing the Tregs (Figure 1). Therefore, 2-DG appears to be a good candidate as an adjuvant for immunotherapy besides its established role as an adjuvant for chemotherapy and radiotherapy.<sup>48,49</sup>

In addition, several studies have shown that disruption of chemokine signaling leads to reduced migration of Tregs to the tumors<sup>50,51</sup> (Figure 1). Reducing CCL5 production by tumors or CCR5 inhibition by TAK-779 resulted in reduction in tumor growth in human and murine pancreatic tumor models.<sup>50</sup> Targeting of CCL17/22-CCR4 axis, which is important in several types of cancers including lymphoma, lung, ovarian, gastric, breast, and prostate,<sup>52</sup> by CCR4-targeted antibodies has shown effective Treg depletion and antitumor response<sup>53-58</sup> (Figure 1).

Collectively, these studies suggest that suppressing the Treg function can restore antitumor immunity, which can be used as an approach for therapy.

#### 4 | REGULATION OF ANTITUMOR IMMUNITY BY T<sub>REGS</sub> AND IMPLICATIONS ON THE OUTCOME OF THERAPIES

Studies in mouse models suggest that Tregs are major regulators of antitumor immunity.<sup>59-61</sup> They not only inhibit natural killer cell-mediated cytotoxicity but also suppress the proliferation of and IFN- $\gamma$  production by CD4<sup>+</sup> and CD8<sup>+</sup> T cells thus impairing the antitumor immune response.<sup>59,60</sup> However, in the clinical scenario, increased level of Tregs has also been shown to be associated with reduced

survival and poor prognosis in patients of different types of cancers.<sup>30,62-65</sup> As discussed in this review, one of the obstacles for specific depletion of FoxP3<sup>+</sup> Tregs is that both FoxP3<sup>+</sup> Tregs and effector T cells exhibit an activated phenotype, especially in expression patterns of cell surface molecules. Both are high in expression of CD25, an activation marker; CTLA-4, an immune checkpoint; and OX40 and GITR, immune co-stimulatory molecules.<sup>25,66-69</sup> Therefore, there may be a limitation in differentially targeting each molecule alone for Treg depletion. With current knowledge, however, the search is under way to find a highly specific cell surface marker for FoxP3<sup>+</sup> Tregs. Another way of augmenting tumor immunity is to design combination therapy targeting both Tregs and non-Treg cells and alter numerical or functional balance between the 2 populations, ie, to deplete Tregs or attenuate Treg suppressive function and to simultaneously expand effector T cells or augment their effector activity.<sup>65</sup> Therefore, it appears that a delicate balance between Treg and effector T cells is important, as a very low number of Tregs will result in autoimmunity, while a higher number can suppress the immune system and result in tumor chemoresistance leading to poor prognosis and reduced survival of patients.

#### 5 | CROSS TALK BETWEEN T<sub>REGS</sub> AND INFLAMMATION

Tregs are known to suppress the antitumor immune response during cancer progression. They not only suppress innate but also the adaptive immune responses activated during the cancer progression.<sup>70</sup> Although Tregs have always been a fascinating target for cancer therapy, manipulating them as a therapeutic approach has received relatively less attention.<sup>71</sup> Targeting Tregs without addressing the cause of their up-regulation might even lead to more inflammation and aggressive cancer progression. Indeed, we recently reported this in tumor-bearing mice following the administration of 2-DG alone.<sup>72</sup> Up-regulation of Tregs during heightened inflammation as in the case of cancer is a defense mechanism to protect the collateral damage, but suppression induced by the Tregs becomes nonspecific and also suppresses the antitumor immune response. Therefore, approaches that target the source of inflammation (source of induction of Tregs) besides decreasing (depleting) Tregs may be more efficient in enhancing the therapeutic gain, as observed following the combination treatment with 2-DG and radiation.<sup>28</sup> These studies also indicate that the extent of decrease in Tregs coupled with reduction in the inflammation are essential in achieving local tumor control as modifying any one of them did not elicit complete response.<sup>28,72</sup> Further, induction of Tregs associated with different malignancies has been shown to polarize macrophages toward M2 type,<sup>73,74</sup> suggesting that depletion of Tregs may lead to macrophagic polarization toward M1 and correlate with local tumor control, as has been reported by us recently.<sup>72</sup>

#### 6 | NEW APPROACHES FOR TARGETING T<sub>REGS</sub>

Although many approaches are currently available for the depletion of Tregs, relentless search for novel targets or depletors of Tregs are

increasing the hope for an effective cancer immunotherapy. In line with this, RANKL expression on Tregs has been shown to activate RANK (NF- $\kappa$ B) receptor on cancer cells<sup>75</sup>. RANKL activity is greatly increased in the cancers that metastasize to bones such as breast and prostate cancers.<sup>76,77</sup> Furthermore, RANKL-RANK signaling appears to have a role in the functioning of the immune system as RANKL is expressed by T helper cells as well as Tregs and are also involved in dendritic cell maturation.<sup>75,78</sup> Therefore, inhibitors of RANK signaling, like anti-RANKL antibody denosumab, holds promising potential in preventing Tregs-assisted metastases of established cancers.<sup>75</sup> Another novel strategy for Tregs immunotherapy is targeting FoxP3, a master transcription factor of Tregs, through RNA interference (Figure 1). This window of hope opened up when it was shown that administration of miR-31, a negative regulator of FoxP3, through a lentiviral vector abrogated Treg function.<sup>79</sup> The issue to be addressed while targeting FoxP3 is that it is also expressed in T effector population<sup>80</sup> as well as in some cancer cells,<sup>81</sup> so the outcome can also be therapeutically detrimental. Furthermore, up-regulated COX-2 expression is a characteristic feature of tumor environment<sup>82</sup> and several COX-2 inhibitors have been shown to deplete Tregs (Figure 1).<sup>83</sup>

Tumor-derived exosomes have been found to influence the levels and functioning of Tregs in the effusions from malignant cells, with the cell surface TGF- $\beta$ 1 mediating the FoxP3 expression.<sup>84</sup> Therefore, containing malignant effusion-derived exosomes expressing TGF- $\beta$ 1 appears to be an attractive immunotherapeutic strategy for overcoming Treg-induced immune suppression.<sup>84</sup> Furthermore, recent evidences point toward the contribution of vascular endothelial growth factor receptor 2 in the induction of Tregs,<sup>85</sup> suggesting thereby that vascular endothelial growth factor receptor 2 may be a useful target in overcoming immune suppression caused by tumors and improve therapy. The safety of combining peptide vaccination using VEGFR1/2 with or without chemotherapy has been established in phase I clinical trials in patients with pancreatic cancer and renal cell carcinoma,<sup>86,87</sup> while the clinical efficacy is yet to be established.

## 7 | CONCLUSIONS

Emerging evidences are convincing enough to support the notion that attenuating the impact of Tregs (by depletion, blocking their infiltration into tumors and reducing differentiation and signaling) has the potential to enhance tumor immunity<sup>88-91</sup> thereby improving the efficacy of cancers therapy and, in particular, the immunotherapy<sup>92</sup> (Figure 1). Unfortunately, it has the risk of enhancing normal tissue toxicity and induction of autoimmunity due to the sharing of the same receptor by other effector T cells leading to autoimmune disorders and diseases because of uncontrolled pathological immune responses.<sup>93-102</sup> Therefore, a careful consideration is required on the extent of depletion and the context (ie, location, homing, and cytokine milieu) and an approach that selectively depletes tumor-associated i-Tregs, while maintaining the naturally occurring n-Tregs. Several interesting approaches including the conversion of inducible Tregs into other antitumor T cell subpopulations have been found to be useful, besides certain chemotherapeutic agents, which

reduce Tregs in addition to their primary target (tumor).<sup>25,27</sup> Our recent observations with the glycolytic inhibitor, 2-DG<sup>42,44,48,49,103-106</sup> suggest that metabolic modifiers like this glucose analog can also effectively deplete Tregs and may be related to their antitumor efficacy. Since 2-DG/metabolic modifiers have little or no undesirable effects on the normal cells, they can be used more successfully to boost antitumor immune response and enhance the efficacy of radiotherapy, chemotherapy, and immunotherapy.

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## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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## AUTHORS' CONTRIBUTION

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, B.S.D., A.F., S.G.; *Methodology*, B.S.D., S.G.; *Investigation*, B.S.D., S.G.; *Formal Analysis*, B.S.D., S.G.; *Resources*, B.S.D., A. F., S.G.; *Writing - Original Draft*, B.S.D., S.G.; *Writing - Review & Editing*, B.S.D., S.G.; *Visualization*, B.S.D., A.F., S.G.; *Supervision*, B.S.D., S.G.; *Funding Acquisition*, B.S.D.

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