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Two Faces of Regulatory T Cells: From Immune Defense to Tumoral Progression

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

T cells are the most important cellular element of human immunity defending against virus, bacteria, non-self-tissue and tumor cells. Regulatory T cells (Tregs) are the major responsible for self-tolerance maintenance, especially those expressing forkhead box protein 3 (FOXP3) transcription factor. Tregs suppressive function is established through several mechanisms that are essential to immune system homeostasis, but also related to tumoral microenvironment. Recent studies have provided deeper understanding of Tregs role in cancer as well as promising therapeutic targets for improving prognosis in cancer patients. This review approaches Tregs subtypes, functions and its implication in tumor progression.

Keywords: T regulatory cells; FOXP3; Cancer.

ABBREVIATIONS

DN : Double Negative
PC : Progenitor cells
WT : Wild type
ICI : Immune Checkpoint Inhibitor
FOXP3 : Forkhead box P3
ETP : Early Thymic Progenitor
PC : Progenitor Cells
TCR : T cell receptor

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NK cells : Natural Killer cell
TME : Tumoral Microenvironment
MHC : Major Histocompatibility Complex
PD-1 : Programmed cell death-1
Teff : Effector T cells
TGF-β : Transforming Growth Factor Beta
mAb : monoclonal antibodies

1. INTRODUCTION

T cells are the most important cellular element of human immunity and play a fundamental role in defending against virus, bacteria, non-self tissue and tumor cells. From the bone marrow, T cells migrate to the thymus, undergo several differentiations, are selected and become mature T cells [1].

Tregs, specially expressing FOXP3, are the major responsible for self-tolerance maintenance and various subsets, characterized by different cytokines, receptors and function, are elucidated. Treg-mediated suppression mechanismsinclude generation of inhibitory cytokines, such as IL-10 and TGF-β, death of effector cells by cytokine deprivation, and inhibition of dendritic cell (DC) functions [2,3].

Literature data demonstrated that high infiltration of Tregs in the tumoral microenvironment prevents effective anti-tumor immunity and leads to tumoral progression; therefore it is considered a sign of poor prognosis in several types of cancer [3]. In this scenario, monoclonal antibodies and low leptin plasma levels are promising therapeutic strategies.

This review will focus on Treg subsets and functions, particularly highlighting their participation in tumors environment.

2. T CELLS DEVELOPMENT

Hematopoietic stem cells in the bone marrow are responsible for providing the progenitor cells (PC) of the future T cells. Classically, multipotent PC differentiate into two strains: the common myeloid and lymphoid progenitors [4,5]; this leads to T cells, B cells and natural killers (NK) cells.

The thymus is constituted by two identical lobes, each one divided into a central medulla and a peripheral cortex, where the maturation and differentiation of PC into T cells occurs [6]. Thymus layers are divided into: cortex, corticomedullary junction, medulla, and subcapsular zone [7]. Cortical epithelial thymic cells are the major constituent of the subcapsular zone, but are also present in the cortex, with fibroblasts and macrophages. In turn, corticomedullary junction comprises endothelial cells that facilitate the flow of thymocytes through the circulatory current.

Following the differentiation process, cells that reach the cortical-medullary zone are named early thymic progenitor (ETP). Since they do not express CD4 or CD8 markers, they are known as double negative (DN) cells. This stage includes four phases as explained below [6].

Cells in DN1 phase remain in the cortical-medullary zone for approximately 10 days and are characterized by a large expression of CD117 marker and the presence of Notch1 receptor. Recent studies show that Notch1 signaling inhibits other ETP potentials from becoming the myeloid lineage or B cells.

As DN1 cells enter the cortical zone, they undergo stimulation and differentiate into DN2 [8,9]. Here, the genetic rearrangement process is initiated at the T cell receptor (TCR) γ, δ, and β gene loci [9]. The expression of CD117 reduces progressively as the subgroup DN2a is transformed into DN2b [10]. Both still have the potential to become NK cells, but only DN2a can originate a DC.The transition DN2b-DN3 is a critical point for the definitive T lineage through specification into αβ or γδ T cells. These DN3 cells continuously react their DNA at the β, γ, and δ loci to increasingly express TCRs [10].

Finally, the cells migrate to the medullary zone and become DN4 cells. Nineteen days after the arrival of the progenitor cell in the thymus, as future T cells circulate through the cortex again, the pre-TCR signals and the cells express both CD4 and CD8 markers, establishing the double positive stage [6].

The next steps are the positive and negative selection. The first tests the strength and specificity of the connection between αβ TCR and MHC (major histocompatibility complex) of cells present in the thymic cortex such as DC, cortical epithelial thymic cells and fibroblasts. If there is insufficient avidity of the receptor by the MHC, there is apoptosis of the cell. The survivors start to express TCRs restricted to the individual's own MHC, and commit to the CD4 or CD8 lineage, depending on the prevalence of affinity for MHC class II or I respectively [1]. The

second selection occurs in the thymus medullary zone and eliminates, by apoptosis, cells whose TCR has a high affinity for its own antigen in order to avoid future autoimmune reactions.

3. FOXP3 TRANSCRIPTION FACTOR

Tregs share a striking ability to promote a reasonable operation of immune system disposing of a wide repertoire of particularities such as the high expression of CD25, CTLA-4 (cytotoxic T-lymphocyte associated protein 4), αβ TCR and FOXP3. Chatila et al. [11] related FOXP3 mutations to a severe immunodeficiency, polyendocrinopathy and enteropathy X-linked syndrome (IPEX), a fatal immune disorder. Right after, FOXP3 was defined as fundamental for immune homeostasis [12] and modulation of CD4+ T cells due to its ability to repress other transcription factors and cytokines related to T cells activation [13]. Indeed, recent literature supports it as a 'master transcription factor' and a key to confer Tregs identity.

First, it is indispensable to understand how to guarantee an ideal FOXP3 expression. Attias et al. [14] demonstrated that FOXP3 expression rises once activated its promoter. In Tregs,

Table 1. Suppressive mechanisms of regulatory T cells

Types of suppressive mechanisms	Specific mechanisms studied		References
Contact-dependent	Downregulation of costimulatory molecules on APCs	CTLA-4 causes extrinsic depletion of APC ligands CD80/86	Qureshi et al., 2011 [67] Onishi et al. 2008 [68]
	Starvation of T cells by induced catabolism of essential amino acid tryptophan	CTLA-4 stimulate IDO expression in human and murine DC subsets to induce catabolism	Yan et al., 2010 [69]
	Suppression of DC maturation	LAG-3 on Treg cells interacts with MHC-II of immature DC	Liang et al., 2008 [70] Rueda et al., 2016 [71] Akkaya et al., 2019 [72] Takodoro et al.,2006 [73] Mavin et al., 2017 [74]
Metabolic perturbation of target cells	Cytolysis of target cells	Treg cells express granzymes A and B to induce cytolysis	Gondek et al., 2005 [75]. Grossman et al., 2004 [76].
Immunomodulatory cytokines	IL-10 modulates specialized functions in mucosal interfaces	IL-10 limits immunological hyper reactivity at colon, skin and lungs	Rubtsov et al., 2008 [77] Chaudhry et al., 2011 [78].
		IL-10 regulates Th17 immune response IL10 contributes to Foxp3 functions by modulating the expression of Foxo 1 and STAT3	Hsu et al., 2015 [79].
	TFG-β regulates allergic and autoimmune processes in mucosal interfaces	TGF-β reduces TH17 cell responses in gastrointestinal tract	Konkel et al., 2017 [80].

**Treg- regulatory T cells; APC- antigen presenting cells; CTLA-4- cytotoxic T-lymphocyte antigen 4; IDO indoleamine 2,3-dioxygenase; DC- dendritic cells; LAG-3- Lymphocyte-associated gene 3; MHC-II- major histocompatibility complex class II; Foxp3- forkhead box P3; STAT3- signal transducer and activator of transcription 3; TGF-β- transforming growth factor beta*

the high expression of CD25 confers higher sensitivity to IL-2 signaling than T conventional (Tconv) cells. Through this, enough IL-2 is available to activate the signal transducer and activator of transcription (STAT)-5, which binds to various FOXP3 promoter sites. Likewise, transforming growth factor beta (TGF-β) promotes FOXP3 expression when conversing naïve Tconv to induced Treg cells as detailed ahead (subsection 4). Thus, the presence of cytokines signaling is necessary to maintain enough levels of FOXP3.

Considering this, FOXP3 may highlight Tregs' mechanisms of suppression and its associated pathways, which are elucidated in Table 1. The main mechanisms involve contact-dependent methods; metabolic perturbation of target cells; and use of immunomodulatory cytokines [15], all of them required for clarifying key points in peripheral tolerance maintenance and how disorders can result in numerous diseases. By acknowledging each one in further detail, greater are the possibilities of discovering new effective treatments and therapies for such conditions.

4. SUBSETS OF REGULATORY T CELLS

Tregs can be differentiated into two ontogenic categories. The first subset involves thymus derived Treg cells, also known as natural Tregs (nTreg). These $CD4^+CD25^+$Tregs originate from immature precursors from thymus and are specifically responsible for tolerance to self-antigens due to their considerable TCR avidity to them. Its various immunosuppression abilities include inhibitory cytokines production [16], cell-to-cell contact [17], T cell induced apoptosis [18] and blocking of T cell activation [19].

The other branch encompasses induced Tregs (iTreg) [20] which emerge from naive $CD4^+CD25^-$ Tconv in peripheral lymphoid tissues and assume non-self-antigen tolerance including commensal and environmental antigens. iTregs differentiation mainly occurs in mucosal interfaces where specialized antigen-presenting cells (APCs) produces inducing cytokines [21]; for instance TGF-β and IL-2 production by dendritic cells in gastrointestinal tract in the presence of retinoic acid and, likewise, by alveolar macrophages in the lungs [22]. These same factors associated with TCR activation of naive T cells can originate iTregs in vitro [23].

Therefore, nTregs and iTregs play distinct roles since they present different responses and, consequently, distinguished effectiveness towards each condition of metabolic stress or autoimmune disease. These complementary approaches contribute to a non-overlapping teamwork, to lesser susceptibility to organism general destabilization and to a more complete immunological defense for maintaining adequate peripheral tolerance.

Both nTregs and iTregs present similar levels of FOXP3 in normal conditions. However, inflammatory scenarios may cause destabilization and even loss of FOXP3 expression in Treg cells [24]. Besides, it is important to emphasize the existence of $FOXP3^-$ Tregs as assistants to those $FOXP3^+$ in the architectural process of balancing the immune system through suppressive functions. Here Tr1 and Th3 Treg cells are highlighted.

Th3 cell differs from classical Tregs because of the absence of FOXP3 and CD25; and from other T helper cells - Th1,Th2 - for its ability to secret TGF-β and so provide this growth factor to be used by $FOXP3^+$Tregs in peripheral tolerance [25]. Also, Th3 expresses a latency-associated peptide to bind to TGF-β and form inactive complexes. Thus, this $CD4^+CD25^-FOXP3^-LAP^+$ cell plays a supporting role for Tregs in softening autoimmune and inflammatory conditions.

Tr1 cells do not express FOXP3 or CD25 either, yet they present a unique attribute including not only TGF-β but also IFN-γ, IL-5 and IL-10 production [26]. This last cytokine might be essential for Tr1 differentiation, although its specific transcription factor is yet unknown. In fact, studies showed that CD4+ T cells are induced to suppressive IL-10-producing Tr1 cells by nasal antigen [27] andby TGF-β allied to IL-27 produced by dendritic cells modified by Tregs [28]. CD49b, LAG3 and CD226 are some of the surface markers listed recently for Tr1 cells [29].

Beyond the classical immune portrait of Tregs, it is relevant to underline its functional plasticity in expressing diverse non-immune functions in response to tissue environment adaptation [30]. Unfortunately, these competences can result in pathogenic scenarios, where Tregs reprogramming ends to perpetuate pathological chronic conditions such as inflammatory, allergic and autoimmune diseases [15].

In the inflammatory condition of obesity, Tregs resident in visceral adipose tissue, also known as 'Fat Tregs', are involved in controlling metabolic parameters [31].

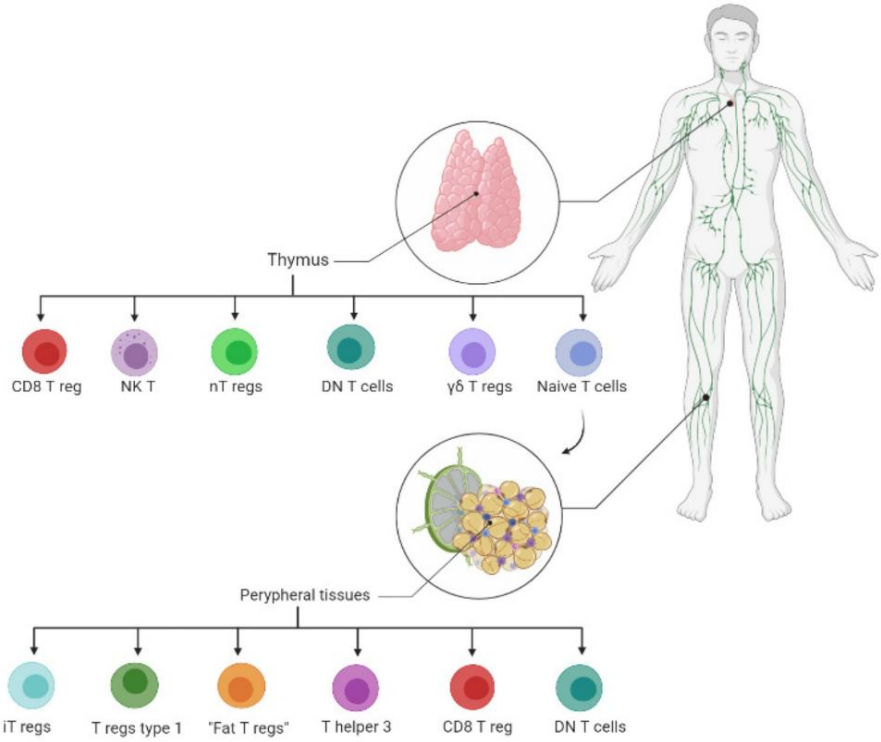

Fig. 1. Tregs Subtypes differentiation from the thymus

The regulatory T cells can be divided into two ontogenetic categories: natural regulatory T cells and induced regulatory T cells. The first subset of cells is produced in the Thymus, and emerge from immature precursors. The other is produced in peripheral tissues and emerges from naive T cells following specific antigenic stimulation.

CD8 T reg: CD8+ regulatory T cells; NK T: Natural killer T cells; nTregs: natural Tregs; DN T cells: Double negative T cells; γδ T regs: γδ regulatory T cells; iTregs: induced Tregs

These cells are distinct from lymphoid organ Treg cells. They have specific mechanisms to regulate immune response and metabolic states in normal or pathologic conditions [32]. It was demonstrated that Treg cells from visceral adipose tissue are reduced in different experimental models of obesity, such as ob/ob leptin-deficient mice and high fat diet-induced obese mice. However, high percentage and absolute number of circulating Treg cells were observed in leptin-deficient ob/obmice [33]. In this experimentalmodel, adoptive transfer of Treg cells from WT mice showed in vivo expansion of Treg cells [34]. In another study, it was highlighted the effect of leptin on Treg cells proliferation. It was suggested that in lean fat tissue that is related to little leptin, high proliferation of Treg cells was observed. In contrast, few Treg cells was observed in obese fat [35]. Likewise, fasting-induced hypoleptinemia in lupus-prone mice caused the expansion of functional Tregs that was reversed by leptin treatment [36]. These findings reflect the inhibitory properties of leptin in Treg cells and their consequent pro-inflammatory and autoimmune effects. Thus, hypoleptinemia is a beneficial intervention for those chronic conditions.

5. TREGS ROLE IN TUMOR PROGRESS-ION

From pioneer to recent studies, literature reveals Tregs involvement in tumor immunity [37,38]. Yet in the 90's, it was reported that depletion of $CD4^{+}CD25^{+}$Tregs in tumor-bearing mice by treatment with anti-CD25 antibody is associated with tumor rejection. Similar results were found with Treg deficient mice that were given splenocytes treated with anti-CD25 [37]. Afterwards, it became well established that high levels of Tregs in tumoral microenvironment (TME) from different types of cancer in humans corresponds to poor prognosis [39]. More

recently, parallel results are observed with decreased ratios of $CD8^+$ T cells to Tregs in breast, ovarian and gastrointestinal tumors [38,39]. In contrast, higher infiltration of Tregs is correlated with better prognosis in some cancers, such as colorrectal, head and neck and bladder cancer [40]. Naturally, Tregs infiltration may be beneficial in some contexts as for its ability to regulate inflammatory, allergic, and autoimmune conditions, [41] including to suppress inflammatory response to gut microbes in colorectal cancer [42]. In general, however, higher infiltration of Tregs remains associated with poor prognosis in cancer and new therapies focus on depleting or inhibiting Tregs suppressive mechanisms [42].

In fact, in TME, cancer cells adapt mechanisms to escape immune surveillance through promotion of immunosuppressive conditions related to Tregs, tumor associated macrophages and immunosuppressive molecules and cytokines [42]. Beyond that, various chemokines produced by tumor or host cells are involved in Tregs recruitments to TME by chemo-attraction and combination of chemokine-chemokine receptors. Such combinations differ from each cancer but the most important are: CCL17/22-CCR4, CCL5-CCR5, CCL28-CCR10 and CXCL9/10/11-CXCR3 [43]. For instance, CCR4 is bound by CCL22 in breast and ovarian cancer [44] while in colorrectal, oral squamous cancer and Hodgkin lymphoma, it is bound by undefined chemokines [44].

Still, Tregs present in TME, unlike Treg cells in non-lymphoid tissues, lymphoid tissues or blood, have a highly activated status with major expression ofsuppressive cell surface molecules such as CD25, PD-1,CTLA-4 and TIGIT [45]. TME has also many tumor-associated antigens from dying tumor cells, which are rather recognized by Tregs instead of effector T (Teff) cells by high-affinity TCR, causing clonal expansion of Tregs in TME by neoantigens. Also, dendritic, cancer and stromal cells produce abundant growth factors and molecules facilitating expansion of Tregs through conversion of Tconvcells iniTregs: TGF-β, IL-10, indoleamine 2,3-dioxygenase (IDO), cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2) [45].

Under these conditions, Treg cells suppress activation, proliferation and function of immune effector cells and settle an immunosuppressive milieu. First, there is expression of co-inhibitory molecules such as PD-1, LAG-3, TIM-3, TIGIT and CTLA-4, the latter being a key negative regulator of T cell activation, expressed by Tregs [46,47]. Furthermore, as Tregs produces IL-10, IL-35 and TGF-β inhibitory cytokines, there is great consumption of IL-2, due to Tregs high affinity to IL-2 receptor, resulting in lesser IL-2 available for proliferation and activation of Teffs.

In summary, Tregs play inhibitory effects by three main mechanisms in TME: generation of inhibitory cytokines and proteins; death of effector cells by cytokine deprivation; and inhibition of dendritic cell (DC) functions [2,3]. Tregs produce immunomodulatory cytokines such as IL-10, TGF-β and IL-35, inhibiting the immune function against cancer [46]. They also secrete granzymes and perforin, leading to apoptosis of NK and CD8+ T cells and reducing tumor clearance. Still, Tregs produces extracellular enzymes CD39 and CD73, increasing adenosine in the TME, which is a known inhibitory molecule that binds to A2A receptors on the surface of Teffs [48]. The death of effector cells is due to Tregs competition and consumption of large amounts of IL-2, leading to IL-2 withdrawal in TME, like so, inhibiting Teffs growth. Additionally, the accumulation of Tregs in the TME impairs the functionality of the DCs, since CTLA-4 expressed by Tregs binds with costimulatory molecules CD80 and CD86 on DCs and downregulates its signaling by transendocytosis [47]. Likewise, LAG3 expressing Tregs suppress MHC II expression on DCs. The last two methods can further impair T cell incapacity by IDO Finally, Tregs suppressive mechanisms are perpetuated in TME through: chemotaxis of Tregs to tumor infiltrates in lymph nodes (specially for CCR4 and CCR8 receptors); the conversion of Teffs into Tregs by stimulating TCR and TGFb; clonal expansion of Tregs by neoantigens; and through its interaction to myeloid derived suppressor cells (MDSCs), which forms positive feedback loops that enhances each other population expansion: MDSCs promotes induction of Tregs by producing IL-10, TGF-β, CD73 and IDO, and Tregs promotes induction of MDSCs by producing IL-35 and TGF-β (Fig. 3).

As discussed in subsection 4, high leptin plasma levels that can be found in conditions of obesity, seem to decrease Treg numbers and so have been considered for prevention and treatment of certain tumor types. Therefore, leptin could

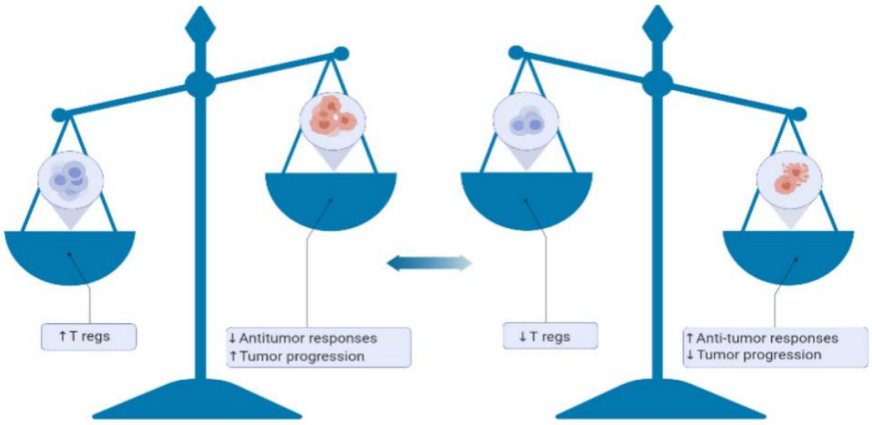

Fig. 2. Balance between regulatory T cells numbers and anti-tumor responses/tumor progression

The number of regulatory T cells are associated with tumor progression or suppression. Tregs: regulatory T cells

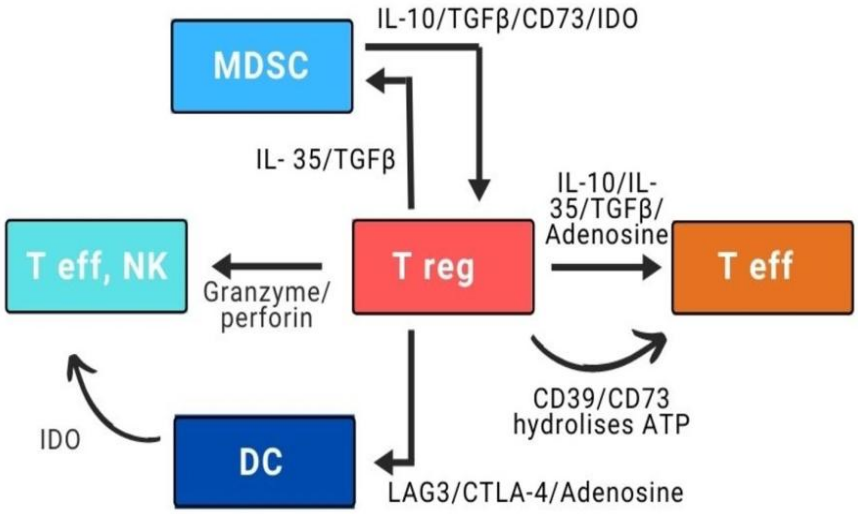

Fig 3. Regulatory T cells immunosuppressive roles in tumoral microenvironment

There are three main mechanism: (1) generation of inhibitory cytokines and proteins, including (1a) secretion of IL-10, IL-35 and TGF-β, (1b) granzymes and perforin and (1c) extracellular enzymes CD39 and CD73; (2) death of effector cells by IL-2 cytokine deprivation; (3) inhibition of DC functions through (3a) downregulation by CTLA-4 and (3b) LAG 3. Besides, it is shown the perpetuation of such mechanisms in tumoral microenvironment due to chemotaxis of Tregs, the conversion of Teffs into Tregs, clonal expansion of Tregs by neoantigens, and Tregs stimulating interaction to MDSC.Treg: regulatory T cells. IL: interleukin. DC: dendritic cells. TGF-β: transforming growth factor beta. CTLA-4: cytotoxic T-lymphocyte associated protein 4. LAG 3: Lymphocyte-associated gene 3 Teff: effector T cells. MDSC: myeloid derived suppressor cells.IDO- indoleamine 2,3-dioxygenase

contribute to lesser infiltration of Tregs in the tumor environment and to a better prognosis for cancer patients. In addition, leptin can also be involved in in the response of immunotherapy in obese patients [49,50]. Obese patients with metastatic melanoma showed a better response to immune checkpoint inhibitors anti-PD1/PD-L1 [51]. It was demonstrated, however, that low levels of leptin contributes against tumor development in some contexts. Fasting with low levels of leptin is a possible strategy for both B and T cell acute lymphoblastic leukemia as it

inhibits leukemic initiation and progression, but in this condition, Treg cells are not involved in the anti-tumoral mechanisms [52].

6. TREGS AS TARGETS OF CANCER IMMUNOTHERAPY

Since Treg cells narrow effective immune surveillance and responses, they are the main character in TME allowing cancer growth. For this reason, many techniques have been developed aiming to reduce Tregs activity, mostly in TME, in order to avoid autoimmune diseases, including: depletion of Tregs, disruption of Tregs to the TME, suppression of Treg function and inhibition of iTreg generation [3,53]. Importantly, immune checkpoint molecules - co-inhibitory ligands that downregulate activation of T cells - are often upregulated in intratumoral lymphocytes [54].

Wherefore, using immune checkpoint inhibitors (ICI), consisting of blocking antibodies for immune checkpoint molecules, is a promising therapeutic strategy, since ICI approaches have shown relevant success in many types of cancer, yet limited to 10-20% of the patients [54,55]. ICI targeting CTLA-4 was the first targeted immune checkpoint molecule, with two fully humanized anti-CTLA-4 monoclonal antibodies (mAb) of IgG1 and IgG2 developed: ipilimumab and tremelimumab, respectively. The former has been approved by FDA for the treatment of non-small cell lung cancer, melanoma, bladder cancer and renal carcinoma [56]. The last, has been studied in clinical trials for melanoma, colon cancer, and mesothelioma [57,58]. Thus, the increased antitumor effects by anti-CTLA-4 mAb are mostly due to the suppression and elimination of Treg in the TME [59]. Programmed cell death-1 (PD-1) protein and its ligand (PD-L1) have been front-line ICI targets for melanoma and lung cancer immunotherapies, avoiding the suppression of CD8+ T cells and allowing them to effectively pursue tumor cells [60,61].

Other possible targets for Tregs depletion and manipulation has been tested in current clinical trials with promising results: OX40 and GITR molecules [62,63]. Both are co-stimulatory receptors expressed by Tregs and are members of the TNF receptor superfamily, reducing Tregs suppressive function. OX40 promotes survival and effector function of Teffs, and, in animal models, an anti-OX40 agonistic antibody enhance anti-tumor responses in melanoma, glioma, sarcoma, colon, breast, renal and prostate cancer [62]. Likewise, activation of GITR signaling with its ligands or agonistic antibody inhibits $FOXP3^{+}$Tregs activity and turns Teffs sheltered to their mediated suppression [63]. Additionally, in mouse models, anti-GITR antibody prompted strong anti-tumor responses in fibrosarcoma, colorectal carcinoma and melanoma models while decreased Treg levels.

A recent study demonstrated effective tumor regression combining strategies to block TGF-β signalling in Th cells and inhibit vascular endothelial growth factor (VEGF) in TME. Indeed, previous studies have evidentiated the suppression of anti-tumour immunity by TGF-β1 produced by activated CD4+ T cells, rather than by Tregs or cancer cells [64-66]. Thus, Li et al. 2020 designed the CD4 TGF-β Trap (4-T-Trap), a TGF-β-neutralizing TGFBR2 extracellular domain linked to ibalizumab. The association to VEGF inhibitors amplifies its antitumor effect since it is necessary to neutralize the increase in proangiogenic factors resulting from the tumour tissue hypoxia induced by 4T-Trap in order to achieve an effective cancer defence response [64].

Wherefore, antibodies that are able to restrict suppressive functions of Tregs and other molecules in TME through inhibition of co-inhibitory or stimulation of co-stimulatory molecules, potentiate effector immunity elements, thus acting as promising therapeutic targets. Many are the immunotherapeutic possibilities for fighting cancer, making it a necessary and growing field of modern research.

7. CONCLUSION

Tregs are essential for an adequate immunological defense towards metabolic stress and autoimmune conditions and a key to peripheral tolerance maintenance. However, they are a signal of poor prognosis in the tumoral microenvironment as inhibiting effector T cells responses to tumor progression. Monoclonal antibodies that regulate the inhibitory activity of Tregs are promising therapeutic targets for cancer treatment. Therefore, more research is needed in order to boost the comprehension of such conditions and the discovery of new biomarkers, essentials to amplify immunotherapy spectrum and predict immune responses.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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