UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

The Role of Regulatory T cells (Tregs) in Tumorigenesis: A Comprehensive Literature Review

Kian Torabiardakani, BHSc Student [1]*

[1] Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada L8S 4L8

*Corresponding Author: torabiak@mcmaster.ca

Abstract

Introduction: Regulatory T cells (Tregs) are a subpopulation of $CD4^+$ T lymphocytes that contribute to immune homeostasis by suppressing excessive immune activation. However, these immunosuppressive properties can lead to the suppression of anti-tumor immune responses. Depletion or blocking of Tregs through therapeutics has emerged as a possible method for enhancing anti-tumor immunity. However, the lack of selective targeting of Tregs in the tumor microenvironment is a significant limitation to the effectiveness of Treg therapies. Therefore, this investigation aims to review current literature on how Tregs suppress the antitumor immune response and how they can be targeted to promote anti-tumor immunity.

Methods: This review examines recent literature on Tregs in the tumor microenvironment, focusing on both cell-contact dependent and independent mechanisms. Clinical trial studies were also included to assess therapeutic targeting of Tregs. The PubMed database was systematically searched for English articles from 2010 to present, supplemented by manual searches without date restrictions. Boolean expressions ensured comprehensive study retrieval.

Results: The involvement of Tregs in the development of multiple cancer types is evident, and targeting these cells could potentially enhance the efficacy of antitumor immunity. In addition, we compiled a list of the novel approaches currently being used for Treg targeting in the context of cancer.

Discussion: This review has identified the most promising targets for Treg-based therapies, opening avenues for accelerating the development of innovative cancer treatments.

Conclusion: Our literature review offers insights into the complex interplay between the immune system and cancer. The understanding of this interaction is not just an endpoint but could potentially act as a steppingstone towards new scientific discoveries.

Keywords: Treg cells; tumorigenesis; immune suppression; cancer immunity; Treg-based therapies; regulatory T cells in cancer; immune evasion; tumor microenvironment; Treg and cancer interaction; immune checkpoints

Introduction

Regulatory T cells (Tregs) are a subset of $CD4^+$ T lymphocytes crucial in maintaining immunological homeostasis [1]. Tregs serve to maintain immunological self-tolerance, which they achieve, by suppressing the activation and proliferation of effector T cells. This prevents the onset of autoimmunity, ensuring self-antigens do not elicit an immune response. While Tregs are present throughout the body, they are most abundant in immunologically active regions, such as the lymph nodes and spleen, where they modulate immune reactions [2].

The suppression mechanisms of Tregs are multifaceted, conducted through both cell-contact dependent and independent mechanisms. The dependent mechanisms require direct physical interaction between Tregs and their target cells, such as Tregs interacting with effector T cells, using pathways such as cytoxic T-lymphocyte associated protein 4 (CTLA-4). While cell-contact independent mechanisms do not require direct interactions with target cells but instead rely on the secretion of immunosuppressive cytokines, such as TGF-B and IL-10, to prevent excessive immune responses that can be detrimental to the body [3, 4].

Immune surveillance, a continuous process by which the immune system identifies and eliminates malignant cells, is essential in cancer prevention [5]. Yet, tumors can exploit the essential immunosuppressive properties of Tregs, leading to the formation of an immunosuppressive tumor microenvironment (TME), where Tregs support tumor cells in evading immune surveillance and allow their unchallenged growth, by suppressing the effector functions of anti-tumoral immune cells [6-8].

An overabundance of Tregs, particularly within the TME, often aligns with advanced tumor stages and poorer patient prognosis. This is particularly evident in cancers such as gastric, intestinal, and breast cancer where an

increased presence of Tregs often correlates with poorer prognosis [9-11]. Conversely, a systematic deficiency of Tregs is equally concerning. Without Tregs keeping the immune system in check, body's own tissues become vulnerable to the autoreactive T cells of the body, potentially leading to a range of autoimmune diseases such as rheumatoid arthritis, and multiple sclerosis [12].

Given the global significance of cancer and the complex role of Tregs, it is crucial to understand how Tregs both maintain immune balance and potentially aid tumor growth [13]. Herein, we explore the mechanisms of Treg-mediated suppression in cancer and discuss the challenges and opportunities in targeting Tregs therapeutically.

Methods

This review is underpinned by a thorough examination of the recent literature, specifically focusing on the role of Tregs in the TME. Emphasis is given to both cell-contact dependent and independent mechanisms of Treg action in the TME. Furthermore, the review incorporates emerging evidence from clinical trial studies to highlight both the potential and challenges of therapeutically targeting Tregs. An extensive search of the PubMed database was conducted to collate peer-reviewed articles published in English from 2010 to the present. In addition to the systematic search, a manual search was conducted throughout the project, with no date restriction. Boolean expressions "AND" and "OR" were utilized to ensure a comprehensive yield of relevant studies (Appendix A).

Results

Cell-contact Independent Mechanism of Inhibition

Cytokines/Chemokines

Tregs, with their unique immunosuppressive qualities, have an indispensable function in immune homeostasis, primarily through the production of anti-inflammatory cytokines such as IL-10, TGF-beta, and IL-35 [14]. These cytokines contribute to the general immunosuppressive milieu favoring tumorigenesis in various ways. IL-10 is a potent anti-inflammatory cytokine produced by Tregs, which directly inhibits the production of pro-inflammatory cytokines and chemokines by macrophages and dendritic cells [15]. By doing so, it hinders the activation and expansion of effector T cells, including cytotoxic T lymphocytes (CTLs), which are key players in anti-tumor immunity. In the context of cancer, this IL-10 mediated immune suppression allows cancer cells to avoid immune recognition and destruction, thereby facilitating their growth and spread.

TGF-beta is another pivotal cytokine released by Tregs. In the TME, TGF-beta, released by Tregs, inhibits effector T-cell proliferation, cytotoxic activity, and cytokine production [16]. Moreover, it stimulates the conversion of naïve T cells into induced Tregs, further augmenting the Treg pool in the TME. This bolsters the immunosuppressive environment, facilitating tumor cell proliferation and metastasis.

IL-35 is a more recently discovered member of the interleukin 12 family, primarily produced by Tregs [17]. It has strong immunosuppressive properties, and its overexpression in cancer correlates with poor prognosis [18]. IL-35 can suppress the proliferation and function of effector T cells, inducing apoptosis, and can also promote the conversion of naïve T cells into Tregs [19]. In the context of the TME, IL-35, by tipping the balance towards immune suppression, allows tumor cells to escape immune surveillance.

Beyond cytokine production, Tregs also impact the TME via manipulation of chemokines. Tregs have been shown to influence chemokine profiles to attract immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and more Tregs, while repelling effector immune cells [20-22]. For instance, Tregs can upregulate the production of CCL22, a chemokine that binds to CCR4 [23]. This creates a positive feedback loop, leading to the recruitment and accumulation of Tregs, promoting a denser Treg population. The resultant increase in Treg density in the TME promotes cancer progression by suppressing effector T cell function and enhancing immune evasion by the tumor cells [24].

Furthermore, Tregs can also modulate the chemokine profile to repel effector immune cells. They achieve this by downregulating the production of certain chemokines such as CXCL9 and CXCL10, which are involved in the recruitment of effector T cells and natural killer cells [24, 25]. This manipulation of the chemokine profile hinders the infiltration of these effector immune cells into the TME, further allowing the tumor cells to escape immune surveillance.

Metabolic Competition

Tregs contribute to tumorigenesis not only through immunosuppressive action but also through metabolic competition. Unlike conventional T cells, Tregs demonstrate significant metabolic flexibility, which enables them to thrive in the lactic acid rich TME [26]. Tumor cells undergo aerobic glycolysis, known as the "Warburg effect," to rapidly produce energy and essential metabolic intermediates needed for their swift proliferation. Aerobic glycolysis of tumor cells results in the accumulation of lactic acid in the TME which creates an acidic environment, impairing the functionality of anti-tumor immune cells and favouring tumor immune evasion [27-29].

This shift in metabolic landscape significantly impacts the function of T cells in the TME. Tregs, however, with their distinct metabolic profile, are well-equipped to survive these harsh conditions due to their ability to utilize lactic acid and continue to suppress the anti-tumor activity of effector T cells, thereby promoting tumorigenesis [30-32].

Here, the metabolic flexibility of Tregs becomes crucial. The study by Watson et al. has found that lactic acid acts as a

metabolic fuel for Tregs [33]. They observed that Tregs express high levels of the lactate transporter monocarboxylate transporter 1 (MCT1), allowing them to efficiently uptake lactic acid from the TME. This uptake of lactic acid by Tregs was found to be essential for their survival and function within the tumor. It was also revealed that lactic acid metabolism in Tregs promotes the production of ATP and supports the expression of key molecules involved in Treg suppressive function, such as forkhead box protein 3 (Foxp3) and CTLA-4. Interestingly, inhibition of lactate uptake or blocking lactate metabolism impaired Treg function and reduced their ability to suppress immune responses. This was demonstrated in mouse models, where blocking lactate uptake by Tregs enhanced anti-tumour immune responses and inhibited tumour growth [34].

Moreover, Tregs have been shown to rely on amino acid metabolism [35]. Amino acids such as glutamine and tryptophan are essential for T cell function and survival [36]. Tregs, by upregulating the expression of amino acid transporters such as L-type amino acid transporter 1, can deplete the TME of these essential nutrients, further impairing the metabolic fitness and anti-tumor function of effector T cells. Additionally, amino acid metabolism, particularly through the kynurenine pathway of tryptophan catabolism, can generate immunosuppressive metabolites that augment Treg suppressive function [37].

In addition, Tregs, express the interleukin-2 receptor α chain (CD25) at high levels, which enables them to sequester IL-2 within the TME [38]. IL-2 is a critical cytokine for T cell growth and survival, and its availability is crucial for the maintenance of conventional T cell populations. Tregs, by expressing high levels of CD25, can effectively compete for IL-2 binding and limit its availability for conventional T cells. This competition for IL-2 by Tregs diminishes the survival and proliferation signals that IL-2 provides to conventional T cells, thereby suppressing their activity within the TME. Together, these metabolic adaptations permit Tregs to outcompete other immune cells within the TME, contributing to the immunosuppressive environment and tumorigenesis.

Altogether, Tregs employ various metabolic strategies to enhance their survival and immunosuppressive function and impede effector T cell function. This metabolic competition, therefore, constitutes a significant mechanism through which Tregs contribute to tumorigenesis. Understanding these metabolic interplays in the TME offers opportunities for novel therapeutic interventions targeting the metabolic dependencies of Tregs.

Cell-Contact Dependent Mechanism of Inhibition – Immune Checkpoint Molecules

Tregs express several immune checkpoint molecules such as CTLA-4 and programmed death protein-1 (PD-1) [39]. These proteins interact with their ligands on effector cells, leading to inhibitory signals that suppress their activity. In the context of cancer, these interactions result in T-cell exhaustion and the eventual evasion of immune response by the tumor cells.

CTLA-4 and PD-1 are critical for maintaining self-tolerance and preventing autoimmunity by suppressing overactive immune responses [40]. Tregs highly express these immune checkpoint molecules, allowing them to impart a cell-contact dependent inhibition on effector T cells.

CTLA-4 competes with the co-stimulatory molecule CD28 on effector T cells for binding to CD80 and CD86 on antigen-presenting cells. CTLA-4 has a higher affinity for these ligands than CD28, allowing it to outcompete CD28 on conventional T cells and inhibit the co-stimulatory signal necessary for T cell activation. In doing so, Tregs using CTLA-4 can suppress the activation, proliferation, and effector functions of T cells, thereby promoting immune evasion by tumor cells [41-44].

Interaction of PD-1 with its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2), provides an inhibitory signal that reduces T cell activation and proliferation. In the context of cancer, tumor cells often overexpress PD-L1, and the interaction of PD-1 on Tregs with PD-L1 on tumor cells results in enhanced Treg function and survival. Moreover, it contributes to the exhaustion of effector T cells, a state of dysfunction characterized by poor effector function, sustained expression of inhibitory receptors, and a transcriptional state distinct from that of functional effector or memory T cells [45].

The upregulation of these checkpoint molecules in the TME is a strategy used by Tregs to maintain an immunosuppressive environment that supports tumor survival and growth. Consequently, these molecules serve as potential targets for cancer immunotherapy, with the goal of releasing the 'brakes' on the immune system to boost anti-tumor responses. This has led to the development of immune checkpoint inhibitors, such as anti-CTLA-4, anti-PD-1 and anti-PDL1 therapies, which have shown considerable success in treating various types of cancer. Understanding the nuanced role of these molecules in Treg-mediated immune suppression is therefore of great importance for the development of effective cancer immunotherapies.

Challenges of Targeting Tregs

Treg depletion has shown promise in preclinical models, but the translation to clinical settings is fraught with challenges [46]. A significant obstacle lies in distinguishing Tregs from beneficial immune cells to avoid off-target effects, as many surface markers are shared between them [47]. In addition, systemic depletion of Tregs can result in autoimmune conditions due to their role in maintaining immune homeostasis [48]. Recent clinical trials have observed some adverse effects, including exacerbated autoimmunity and inflammation, underlining the need for careful balancing [49].

While Tregs are an attractive target for immunotherapy due to their role in suppressing anti-tumor immunity, strategies aimed at depleting or inhibiting Tregs present significant challenges. The primary challenge in targeting Tregs therapeutically lies in their similarity to other beneficial immune cells. Tregs share many surface markers with effector T cells and other immune cell subsets. For instance, in a study conducted by Wegrzyn *et al.* the researchers presented a report of the surface markers expressed on Tregs and conventional T cells. Out of the 371 surface markers, Tregs and conventional T cells expressed 118 markers in common, with only five antigens expressed exclusively by Tregs and 38 exclusively expressed by conventional T cells. Moreover, CD25 and CTLA-4, two commonly used targets for Treg depletion, are also expressed on activated effector T cells [50]. This overlap in marker expression complicates the selective targeting of Tregs without impacting other immune cells necessary for a robust anti-tumor response.

Furthermore, Tregs play an essential role in maintaining immune homeostasis and preventing autoimmunity [51-57]. Based on a recent comprehensive review looking into the immune-related adverse events (IRAEs) of the cancer immunotherapies anti-PD1 and anti-CTLA4, close to 90% of patients with anti-CTLA4 and close to 70% of patients on anti-PD1/PD-L1 therapy suffered with IRAEs [58-60]. Majority of the IRAEs occur in 3-6 months from the start of anti-CTLA4, anti-PD1/PDL1 therapy [58, 61, 62]. The spectrum of IRAEs caused by the mentioned cancer immunotherapies range from vitiligo, dry mouth, diarrhoea, colitis, thyroid dysfunction, lung disorders, renal disorders and many more [59, 61, 63-72].

These challenges underscore the need for a careful balancing act in Treg-targeting strategies. Therapies must effectively mitigate Treg-mediated immune suppression to enhance anti-tumor responses, while avoiding the induction of harmful autoimmune responses. This delicate balance is a primary focus of ongoing research in the field of cancer immunotherapy.

Approaches to Targeting Tregs

In light of the challenges associated with Treg-targeting strategies, researchers are exploring multiple approaches to harness anti-tumor immunity while minimizing off-target effects and autoimmunity safely and effectively.

Depletion of Tregs

Chemotherapy: Certain chemotherapy drugs like cyclophosphamide and paclitaxel can deplete Treg cells by promoting dendritic cell maturation and targeting proliferating cells more common in the Treg population than non-Treg cells [73-77]. These drugs are administered in low metronomic doses to selectively deplete Tregs. The downside of this approach is a low therapeutic index due to toxicity to effector T cells.

CD25 antibody and denileukin diftitox: Treg role in tumor immunity was initially studied via depletion of CD25+ T cells. Anti-CD25 antibodies can suppress tumor growth, but since CD25 is also expressed by activated effector T cells, this complicates the targeting strategy [78]. Daclizumab, an anti-CD25 monoclonal antibody, has been used to deplete Treg with varied results [79, 80]. Denileukin diftitox was developed to target T cells with high CD25 expression, showing some efficacy in renal cell carcinoma and melanoma patients [81]. However, its effectiveness is limited in the presence of CD25lowFoxp3+T cells [80].

Inhibition of Tregs

Anti-OX40: OX40 also known as CD134, a member of the TNFR family is predominantly expressed on activated T cells. Anti-OX40 antibodies, particularly agonistic forms, bind to OX40 on Tregs. This binding can interfere with the suppressive function of Tregs, as a result, diminished suppression of effector T cells by Tregs, leading to increased immune responses that will be beneficial during cancer immunotherapy [82-84]. In 2022, the first-ever human study involving the investigational drug INCAGN01949, an anti-OX40 monoclonal antibody, was conducted in patients with advanced or metastatic solid tumors, yielding important insights into its safety and preliminary efficacy [85]. The study revealed that INCAGN01949 monotherapy demonstrated good safety in advanced solid tumor patients, but its effectiveness in terms of tumor response and T-cell-related effects was limited, emphasizing the necessity for further research with combination therapies.

Anti-Glucocorticoid-Induced TNFR-Related Protein (GITR): The GITR protein is a receptor that is highly expressed on Tregs. When GITR is activated, it has been found to reduce the suppressive functions of Tregs, leading to an overall increase in immune response [86-88]. The binding of anti-GITR antibody to the GITR receptor on Tregs and effector T cells leads to inhibition of the immunosuppressive properties of Tregs and enhancing the proliferation and activation of effector T cells. In 2021, the first-ever human study involving GWN323, an anti-GITR monoclonal antibody was conducted in patients with advanced/metastatic solid tumors [89]. The anti-GITR therapy was generally safe for the patients, but showed limited effectiveness alone, with modest improvement when combined with spartalizumab (another monoclonal antibody).

Beyond the previously stated mechanisms, many other Treg-targeting strategies have emerged. In particular, mechanisms like Toll-like receptors (TLR) ligands, adenosine inhibitors, and peptide inhibitors of Foxp3 have been identified to potentially inhibit Treg-mediated tolerance and improve cancer vaccine efficacy [90-97].

Another approach involves disrupting Treg homing by targeting chemokine receptor molecules, though this carries risks related to effector T cell trafficking [22, 23, 98-104]. Additionally, anti-angiogenic molecules, such as sunitinib, have shown potential in reducing Treg number [105-110].

Discussion

Tregs play a significant role in the complex interplay of tumorigenesis by establishing and maintaining an immunosuppressive TME, which allows tumor cells to evade immune destruction. In this literature review, we have explored various mechanisms through which Tregs contribute to cancer progression, including the secretion of immunosuppressive cytokines, manipulation of the chemokine milieu, metabolic competition, and the expression of immune checkpoint molecules and how they can be targeted therapeutically. However, targeting Tregs is tricky; they shared markers with essential immune cells and help maintain immune balance. Striking the right balance to combat tumors without harming immunity is delicate. Current strategies being researched include selectively inhibiting Treg functions in tumor environments, using immune checkpoint inhibitors, and converting Tregs into effector T cells. These approaches show promise but need careful handling to prevent side effects.

Conclusions

This review highlights areas for potential therapeutic intervention and points to the need for a better understanding of Treg biology. Investigations into Treg metabolic adaptability, their modulation of chemokines and cytokines, and potential plasticity are promising future directions. Further, refining Treg-targeting strategies by better differentiating Tregs from other immune cells could improve treatments and reduce off-target effects. In conclusion, the potential of Treg targeting in cancer immunotherapy is significant, promising to pave the way for innovative strategies that could revolutionize cancer treatment. Understanding Treg biology and function in more depth is critical to unlocking this potential and improving patient outcomes in the fight against cancer.

List of Abbreviations Used

Tregs: regulatory T cells
TME: tumor microenvironment
CTLs: cytotoxic T lymphocytes
MDSCs: myeloid-derived suppressor cells
MCT1: lactate transporter monocarboxylate transporter 1
Foxp3: forkhead box protein 3
CTLA-4: cytotoxic T-lymphocyte associated protein 4
CD25: interleukin-2 receptor α chain
PD-1: programmed death protein-1
PD-L1: programmed cell death ligand 1
PD-L2: programmed cell death ligand 2
IRAEs: immune-related adverse events
GITR: glucocorticoid-induced TNFR-related protein
TLR: toll-like receptors

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

Given the nature of this work as a literature review, it did not require institutional research ethics board (REB) approval or participant consent. This is because no primary data collection or direct interaction with human or animal subjects was involved; instead, the review is based on previously published and publicly accessible data, ensuring all ethical standards were adhered to.

Authors' Contributions

KT: all stages of the research process including conceptualizing and designing the study, selecting, and reviewing the relevant literature, synthesizing the information, critical analysis, and writing the manuscript.

Acknowledgements

The author is deeply grateful to Megan Hong, their mentor, whose wisdom and guidance have been indispensable in the process of writing this review. Her thoughtful input and enduring support are much appreciated.

Funding

This study was not funded.

References

[1] Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell. 2008;133(5):775–87. https://doi.org/10.1016/j.cell.2008.05.009
[2] Wei S, Kryczek I, Zou W. Regulatory T-cell compartmentalization and trafficking. Blood. 2006;108(2):426–31. https://doi.org/10.1182/blood-2006-01-0177
[3] Taylor A, Verhagen J, Blaser K, Akdis M, Akdis CA. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-beta: The role of T regulatory cells. Immunology. 2006;117(4):433–42. https://doi.org/10.1111/j.1365-2567.2006.02321.x
[4] Sojka DK, Huang YH, Fowell DJ. Mechanisms of regulatory T-cell suppression - A diverse arsenal for a moving target. Immunology. 2008;124(1):13–22. https://doi.org/10.1111/j.1365-2567.2008.02813.x
[5] Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117(5):1137–46. https://doi.org/10.1172/jci31405
[6] Kalim KW, Yang JQ, Modur V, Nguyen P, Li Y, Zheng Y, et al. Graded RhoA GTPase expression in Treg cells distinguishes tumor immunity from autoimmunity. Front Immunol. 2021;12:726393. https://doi.org/10.3389/fimmu.2021.726393

[7] Ren B, Cui M, Yang G, Wang H, Feng M, You L, et al. Tumor microenvironment participates in metastasis of pancreatic cancer. Mol Cancer. 2018;17(1):108. https://doi.org/10.1186/s12943-018-0858-1
[8] Wang X, Lang M, Zhao T, Feng X, Zheng C, Huang C, et al. Cancer-FOXP3 directly activated CCL5 to recruit FOXP3(+)Treg cells in pancreatic ductal adenocarcinoma. Oncogene. 2017;36(21):3048–58. https://doi.org/10.1038/onc.2016.458
[9] Pastille E, Wasmer MH, Adamczyk A, Vu VP, Mager LF, Phuong NNT, et al. The IL-33/ST2 pathway shapes the regulatory T cell phenotype to promote intestinal cancer. Mucosal Immunol. 2019;12(4):990–1003. https://doi.org/10.1038/s41385-019-0176-y
[10] Shang B, Liu Y, Jiang SJ, Liu Y. Prognostic value of tumor-infiltrating FoxP3+ regulatory T cells in cancers: a systematic review and meta-analysis. Sci Rep. 2015;5:15179. https://doi.org/10.1038/srep15179
[11] Su S, Liao J, Liu J, Huang D, He C, Chen F, et al. Blocking the recruitment of naive CD4(+) T cells reverses immunosuppression in breast cancer. Cell Res. 2017;27(4):461–82. https://doi.org/10.1038/cr.2017.34
[12] Dejaco C, Duftner C, Grubeck-Loebenstein B, Schirmer M. Imbalance of regulatory T cells in human autoimmune diseases. Immunology. 2006;117(3):289–300. https://doi.org/10.1111%2Fj.1365-2567.2005.2317.x
[13] Ha TY. The role of regulatory T cells in cancer. Immune Netw. 2009;9(6):209–35. https://doi.org/10.4110%2Fin.2009.9.6.209
[14] Do JS, Visperas A, Sanogo YO, Bechtel JJ, Dvorina N, Kim S, et al. An IL-27/Lag3 axis enhances Foxp3+ regulatory T cell-suppressive function and therapeutic efficacy. Mucosal Immunol. 2016;9(1):137–45. https://doi.org/10.1038/mi.2015.45
[15] Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci. 2019;20(23). https://doi.org/10.3390/ijms20236008
[16] Elliott RL, Blobe GC. Role of transforming growth factor beta in human cancer. J Clin Oncol. 2005;23(9):2078–93. https://doi.org/10.1200/jco.2005.02.047
[17] Zhang SM, Liang J, Xia JP, Li L, Zheng L, Wang YL, et al. Interleukin 35: Protective role and mechanism in type 1 diabetes. Cent Eur J Immunol. 2013;48(1):48–53. https://doi.org/10.5114/ceji.2023.125043
[18] Wainwright DA, Balyasnikova IV, Chang AL, Ahmed AU, Moon KS, Auffinger B, et al. IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. Clin Cancer Res. 2012;18(22):6110–21. https://doi.org/10.1158/1078-0432.ccr-12-2130
[19] Collison LW, Delgoffe GM, Guy CS, Vignali KM, Chaturvedi V, Fairweather D, et al. The composition and signaling of the IL-35 receptor are unconventional. Nat Immunol. 2012;13(3):290–9. https://doi.org/10.1038%2Fni.2227
[20] Crane CA, Ahn BJ, Han SJ, Parsa AT. Soluble factors secreted by glioblastoma cell lines facilitate recruitment, survival, and expansion of regulatory T cells: Implications for immunotherapy. Neuro Oncol. 2012;14(5):584–95. https://doi.org/10.1093/neuonc/nos014
[21] Schlecker E, Stojanovic A, Eisen C, Quack C, Falk CS, Umansky V, et al. Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J Immunol. 2012;189(12):5602–11. https://doi.org/10.4049/jimmunol.1201018
[22] Tan MC, Goedegebuure PS, Belt BA, Flaherty B, Sankpal N, Gillanders WE, et al. Disruption of CCR5-dependent homing of regulatory T cells inhibits tumor growth in a murine model of pancreatic cancer. J Immunol. 2009;182(3):1746–55. https://doi.org/10.4049/jimmunol.182.3.1746
[23] Iellem A, Mariani M, Lang R, Recalde H, Panina-Bordignon P, Sinigaglia F, et al. Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. J Exp Med. 2001;194(6):847–53. https://doi.org/10.1084/jem.194.6.847
[24] Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? Cancer Sci. 2019;110(7):2080–9. https://doi.org/10.1111/cas.14069
[25] Muthuswamy R, Urban J, Lee JJ, Reinhart TA, Bartlett D, Kalinski P. Ability of mature dendritic cells to interact with regulatory T cells is imprinted during maturation. Cancer Res. 2008;68(14):5972–8. https://doi.org/10.1158%2F0008-5472.CAN-07-6818
[26] Angelin A, Gil-de-Gomez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. Cell Metab. 2017;25(6):128–93. https://doi.org/10.1016/j.cmet.2016.12.018
[27] Gao F, Tang Y, Liu WL, Zou MZ, Huang C, Liu CJ, et al. Intra/extracellular lactic acid exhaustion for synergistic metabolic therapy and immunotherapy of tumors. Adv Mater. 2019;31(51):e1904639. https://doi.org/10.1002/adma.201904639
[28] Li XB, Gu JD, Zhou QH. Review of aerobic glycolysis and its key enzymes - New targets for lung cancer therapy. Thorac Cancer. 2015;6(1):17–24. https://doi.org/10.1111/1759-7714.12148

[29] Shim H, Dolde C, Lewis BC, Wu CS, Dang G, Jungmann RA, et al. c-Myc transactivation of LDH-A: Implications for tumor metabolism and growth. Proc Natl Acad Sci. 1997;94(13):6658–63. https://doi.org/10.1073/pnas.94.13.6658

[30] Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell. 2022; 40(2):201–18. https://doi.org/10.1016/j.ccell.2022.01.001

[31] Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell. 2015;162(6):1229–41. https://doi.org/10.1016/j.cell.2015.08.016

[32] Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? Trends in Biochemical Sciences. 2016;41(3):211–8. https://doi.org/10.1016%2Fj.tibs.2015.12.001

[33] Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature. 2021;591(7851):645–51. https://doi.org/10.1038/s41586-020-03045-2

[34] Hossain F, Al-Khami AA, Wyczechowska D, Hernandez C, Zheng L, Reiss K, et al. Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. Cancer Immunol Res. 2015;3(11):1236–47. https://doi.org/10.1158/2326-6066.cir-15-0036

[35] Kempkes RWM, Joosten I, Koenen HJPM, He X. Metabolic pathways involved in regulatory T cell functionality. Frontiers in Immunology. 2019;10. https://doi.org/10.3389/fimmu.2019.02839

[36] Wang W, Zou W. Amino acids and their transporters in T cell immunity and cancer therapy. Mol Cell. 2020 Nov 5;80(3):384–95. https://doi.org/10.1016/j.molcel.2020.09.006

[37] Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, et al. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. J Immunol. 2010;185(2):1037–44. https://doi.org/10.4049/jimmunol.0903586

[38] Malek TR, Castro I. Interleukin-2 receptor signaling: At the interface between tolerance and immunity. Immunity. 2010;33(2):153–65. https://doi.org/10.1016/j.immuni.2010.08.004

[39] Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016 Feb;39(1):98–106. https://doi.org/10.1097/coc.0000000000000239

[40] Jie HB, Gildener-Leapman N, Li J, Srivastava RM, Gibson SP, Whiteside TL, et al. Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients. Br J Cancer. 2013;109(10):2629–35. https://doi.org/10.1038/bjc.2013.645

[41] Tekguc M, Wing JB, Osaki M, Long J, Sakaguchi S. Treg-expressed CTLA-4 depletes CD80/CD86 by trogocytosis, releasing free PD-L1 on antigen-presenting cells. Proceedings of the National Academy of Sciences. 2021;118(30):e2023739118. https://doi.org/10.1073/pnas.2023739118

[42] Osinska I, Stelmaszczyk-Emmel A, Polubiec-Kownacka M, Dziedzic D, Domagala-Kulawik J. CTLA-4 on regulatory T cells - Regulation of local immune response in lung cancer. European Respiratory Journal. 2015;46(suppl 59):PA532. https://doi.org/10.1007/s00262-016-1930-6

[43] Tang AL, Teijaro JR, Njau MN, Chandran SS, Azimzadeh A, Nadler SG, et al. CTLA4 expression is an indicator and regulator of steady-state CD4+ FoxP3+ T cell homeostasis. J Immunol. 2008 Aug 1;181(3):1806–13. https://doi.org/10.4049/jimmunol.181.3.1806

[44] Ha D, Tanaka A, Kibayashi T, Tanemura A, Sugiyama D, Wing JB, et al. Differential control of human Treg and effector T cells in tumor immunity by Fc-engineered anti–CTLA-4 antibody. Proceedings of the National Academy of Sciences. 2019;116(2):609–18. https://doi.org/10.1073/pnas.1812186116

[45] Han Y, Liu D, Li L. PD-1/PD-L1 pathway: Current researches in cancer. Am J Cancer Res. 2020; 10(3): 727–42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136921/

[46] Rana J, Biswas M. Regulatory T cell therapy: Current and future design perspectives. Cell Immunol. 2020 Oct;356:104193. https://doi.org/10.1016/j.cellimm.2020.104193

[47] Ohue YA-O, Nishikawa HA-O. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? Cancer Science. 2019;110(7):2080–9 https://doi.org/10.1111/cas.14069

[48] Goswami TK, Singh M, Dhawan M, Mitra S, Emran TB, Rabaan AA, et al. Regulatory T cells (Tregs) and their therapeutic potential against autoimmune disorders - Advances and challenges. Human Vaccines & Immunotherapeutics. 2022;18(1) https://doi.org/10.1080/21645515.2022.2035117

[49] Bayati F, Mohammadi M, Valadi M, Jamshidi S, Foma AM, Sharif-Paghaleh E. The therapeutic potential of regulatory T cells: Challenges and opportunities. Front Immunol. 2021 Jan 15:11:585819. https://doi.org/10.3389/fimmu.2020.585819

[50] Jago CB, Yates J Fau - Câmara NOS, Câmara No Fau - Lechler RI, Lechler Ri Fau - Lombardi G, Lombardi G. Differential expression of CTLA-4 among T cell subsets. Clin Exp Immunol. 2004 Jun;136(3):463–71. https://doi.org/10.1111/j.1365-2249.2004.02478.x

[51] Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. J Exp Med. 2004;199(7):971–9. https://doi.org/10.1084/jem.20031579

[52] Long SA, Buckner JH. CD4+FOXP3+ T regulatory cells in human autoimmunity: More than a numbers game. J Immunol. 2011;187(5):2061–6. https://doi.org/10.4049/jimmunol.1003224

[53] Grant CR, Liberal R, Mieli-Vergani G, Vergani D, Longhi MS. Regulatory T-cells in autoimmune diseases: Challenges, controversies and--yet--unanswered questions. Autoimmun Rev. 2015;14(2):105–16. https://doi.org/10.1016/j.autrev.2014.10.012

[54] Göschl L, Scheinecker C, Bonelli M. Treg cells in autoimmunity: From identification to Treg-based therapies. Semin Immunopathol. 2019;41(3):301–14. https://doi.org/10.1007/s00281-019-00741-8

[55] Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. Nat Immunol. 2018;19(7):665–73. https://doi.org/10.1038/s41590-018-0120-4

[56] Carbone F, De Rosa V, Carrieri PB, Montella S, Bruzzese D, Porcellini A, et al. Regulatory T cell proliferative potential is impaired in human autoimmune disease. Nat Med. 2014;20(1):69–74. https://doi.org/10.1038/nm.3411

[57] Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001;27(1):20–1. https://doi.org/10.1038/83713

[58] Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and activity of Anti–PD-L1 antibody in patients with advanced cancer. New England Journal of Medicine. 2012;366(26):2455–65. https://doi.org/10.1056/nejmoa1200694

[59] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of Anti–PD-1 antibody in cancer. New England Journal of Medicine. 2012;366(26):2443–54. https://doi.org/10.1056/nejmoa1200690

[60] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with Ipilimumab in patients with metastatic melanoma. New England Journal of Medicine. 2010;363(8):711–23. https://doi.org/10.1056/nejmoa1003466

[61] Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving Nivolumab. Journal of Clinical Oncology. 2014;32(10):1020–30. https://doi.org/10.1200/jco.2013.53.0105

[62] Weber JS, Dummer R, De Pril V, Lebbé C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab. Cancer. 2013;119(9):1675–82. https://doi.org/10.1002/cncr.27969

[63] Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. Journal of Clinical Oncology. 2012;30(21):2691–7. https://doi.org/10. 1200/jco.2012.41.6750

[64] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. New England Journal of Medicine. 2015;372(26):2521–32. https://doi.org/10.1056/nejmoa1503093

[65] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. New England Journal of Medicine. 2015;372(4):320–30. https://doi.org/10.1056/nejmoa1412082

[66] Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558–62. https://doi.org/10.1038/nature13904

[67] Johnston RL, Lutzky J, Chodhry A, Barkin JS. Cytotoxic T-lymphocyte-associated antigen 4 antibody-induced colitis and its management with infliximab. Digestive Diseases and Sciences. 2009;54(11):2538–40. https://doi.org/10.1007/s10620-008-0641-z

[68] Hamid O, Robert C, Daud A, Hodi FS, Hwu W-J, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti–PD-1) in melanoma. New England Journal of Medicine. 2013;369(2):134–44. https://doi.org/10.1056/nejmoa1305133

[69] Fadel F, Karoui KE, Knebelmann B. Anti-CTLA4 Antibody–induced lupus nephritis. New England Journal of Medicine. 2009;361(2):211–2. https://doi.org/10.1056/nejmc0904283

[70] Berthod G, Lazor R, Letovanec I, Romano E, Noirez L, Mazza Stalder J, et al. Pulmonary Sarcoid-like granulomatosis induced by ipilimumab. Journal of Clinical Oncology. 2012;30(17):e156–9. https://doi.org/10.14740%2Fjmc4038

[71] Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155–64. https://doi.org/10.1016/s1470-2045(09)70334-1

[72] Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte–associated antigen 4. Journal of Clinical Oncology. 2006;24(15):2283–9. https://doi.org/10.1200/jco.2005.04.5716

[73] Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol. 2011;8(3):151–60. https://doi.org/10.1038/nrclinonc.2010.223

[74] Polak L, Turk JL. Reversal of immunological tolerance by cyclophosphamide through inhibition of suppressor cell activity. Nature. 1974;249(458):654–6. https://doi.org/10.1038/249654a0

[75] Ercolini AM, Ladle BH, Manning EA, Pfannenstiel LW, Armstrong TD, Machiels JP, et al. Recruitment of latent pools of high-avidity CD8(+) T cells to the antitumor immune response. J Exp Med. 2005;201(10):1591–602. https://doi.org/10.1084/jem.20042167

[76] Ghiringhelli F, Menard C, Puig PE, Ladoire S, Roux S, Martin F, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol Immunother. 2007;56(5):641–8. https://doi.org/10.1007/s00262-006-0225-8

[77] Chen CA, Ho CM, Chang MC, Sun WZ, Chen YL, Chiang YC, et al. Metronomic chemotherapy enhances antitumor effects of cancer vaccine by depleting regulatory T lymphocytes and inhibiting tumor angiogenesis. Mol Ther. 2010;18(6):1233–43. https://doi.org/10.1038%2Fmt.2010.34

[78] Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. J Immunol. 1999;163(10):5211–8.

[79] Rech AJ, Vonderheide RH. Clinical use of anti-CD25 antibody daclizumab to enhance immune responses to tumor antigen vaccination by targeting regulatory T cells. Ann N Y Acad Sci. 2009;1174:99–106. https://doi.org/10.1111/j.1749-6632.2009.04939.x

[80] de Vries IJ, Castelli C, Huygens C, Jacobs JF, Stockis J, Schuler-Thurner B, et al. Frequency of circulating Tregs with demethylated FOXP3 intron 1 in melanoma patients receiving tumor vaccines and potentially Treg-depleting agents. Clin Cancer Res. 2011;17(4):841–8. https://doi.org/10.1158/1078-0432.ccr-10-2227

[81] Morse MA, Hobeika AC, Osada T, Serra D, Niedzwiecki D, Lyerly HK, et al. Depletion of human regulatory T cells specifically enhances antigen-specific immune responses to cancer vaccines. Blood. 2008;112(3):610–8. https://doi.org/10.1182/blood-2008-01-135319

[82] Valzasina B, Guiducci C, Dislich H, Killeen N, Weinberg AD, Colombo MP. Triggering of OX40 (CD134) on CD4(+)CD25+ T cells blocks their inhibitory activity: A novel regulatory role for OX40 and its comparison with GITR. Blood. 2005;105(7):2845–51. https://doi.org/10.1182/blood-2004-07-2959

[83] Piconese S, Valzasina B, Colombo MP. OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection. J Exp Med. 2008;205(4):825–39. https://doi.org/10.1084/jem.20071341

[84] Hirschhorn-Cymerman D, Rizzuto GA, Merghoub T, Cohen AD, Avogadri F, Lesokhin AM, et al. OX40 engagement and chemotherapy combination provides potent antitumor immunity with concomitant regulatory T cell apoptosis. J Exp Med. 2009;206(5):1103–16. https://doi.org/10.1084/jem.20082205

[85] Davis EJ, Martin-Liberal J, Kristeleit R, Cho DC, Blagden SP, Berthold D, et al. First-in-human phase I/II, open-label study of the anti-OX40 agonist INCAGN01949 in patients with advanced solid tumors. J Immunother Cancer. 2022;10(10). https://doi.org/10.1136/jitc-2021-004235

[86] Turk MJ, Guevara-Patiño JA, Rizzuto GA, Engelhorn ME, Sakaguchi S, Houghton AN. Concomitant tumor immunity to a poorly immunogenic melanoma is prevented by regulatory T cells. J Exp Med. 2004;200(6):771–82. https://doi.org/10.1084/jem.20041130

[87] Stephens GL, McHugh RS, Whitters MJ, Young DA, Luxenberg D, Carreno BM, et al. Engagement of glucocorticoid-induced TNFR family-related receptor on effector T cells by its ligand mediates resistance to suppression by CD4+CD25+ T cells. J Immunol. 2004;173(8):5008–20. https://doi.org/10.4049/jimmunol.173.8.5008

[88] Ko K, Yamazaki S, Nakamura K, Nishioka T, Hirota K, Yamaguchi T, et al. Treatment of advanced tumors with agonistic anti-GITR mAb and its effects on tumor-infiltrating Foxp3+CD25+CD4+ regulatory T cells. J Exp Med. 2005;202(7):885–91. https://doi.org/10.1084/jem.20050940

[89] Piha-Paul SA, Geva R, Tan TJ, Lim DW, Hierro C, Doi T, et al. First-in-human phase I/Ib open-label dose-escalation study of GWN323 (anti-GITR) as a single agent and in combination with spartalizumab (anti-PD-1) in patients with advanced solid tumors and lymphomas. J Immunother Cancer. 2021;9(8). https://doi.org/10.1136/jitc-2021-002863

[90] Sutmuller RP, Morgan ME, Netea MG, Grauer O, Adema GJ. Toll-like receptors on regulatory T cells: expanding immune regulation. Trends Immunol. 2006;27(8):387–93. https://doi.org/10.1016/j.it.2006.06.005

[91] Yang Y, Huang CT, Huang X, Pardoll DM. Persistent Toll-like receptor signals are required for reversal of regulatory T cell-mediated CD8 tolerance. Nat Immunol. 2004;5(5):508–15. https://doi.org/10.1038/ni1059

[92] Peng G, Guo Z, Kiniwa Y, Voo KS, Peng W, Fu T, et al. Toll-like receptor 8-mediated reversal of CD4+ regulatory T cell function. Science. 2005;309(5739):1380–4. https://doi.org/10.1126/science.1113401

[93] Conroy H, Marshall NA, Mills KH. TLR ligand suppression or enhancement of Treg cells? A double-edged sword in immunity to tumours. Oncogene. 2008;27(2):168–80. https://doi.org/10.1038/sj.onc.1210910

[94] Cherfils-Vicini J, Platonova S, Gillard M, Laurans L, Validire P, Caliandro R, et al. Triggering of TLR7 and TLR8 expressed by human lung cancer cells induces cell survival and chemoresistance. J Clin Invest. 2010;120(4):1285–97. https://doi.org/10.1172/jci36551

[95] Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 2011;334(6062):1573–7. https://doi.org/10.1126/science.1208347

[96] Blackburn MR, Vance CO, Morschl E, Wilson CN. Adenosine receptors and inflammation. Handb Exp Pharmacol. 2009(193):215–69. https://doi.org/10.1007/978-3-540-89615-9_8

[97] Casares N, Rudilla F, Arribillaga L, Llopiz D, Riezu-Boj JI, Lozano T, et al. A peptide inhibitor of FOXP3 impairs regulatory T cell activity and improves vaccine efficacy in mice. J Immunol. 2010;185(9):5150–9. https://doi.org/10.4049/jimmunol.1001114

[98] Yuan Q, Bromley SK, Means TK, Jones KJ, Hayashi F, Bhan AK, et al. CCR4-dependent regulatory T cell function in inflammatory bowel disease. J Exp Med. 2007;204(6):1327–34. https://doi.org/10.1084/jem.20062076

[99] Hirahara K, Liu L, Clark RA, Yamanaka K, Fuhlbrigge RC, Kupper TS. The majority of human peripheral blood CD4+CD25highFoxp3+ regulatory T cells bear functional skin-homing receptors. J Immunol. 2006;177(7):4488–94. https://doi.org/10.4049/jimmunol.177.7.4488

[100] Bayry J, Triebel F, Kaveri SV, Tough DF. Human dendritic cells acquire a semimature phenotype and lymph node homing potential through interaction with CD4+CD25+ regulatory T cells. J Immunol. 2007;178(7):4184–93. https://doi.org/10.4049/jimmunol.178.7.4184

[101] Davies MN, Bayry J, Tchilian EZ, Vani J, Shaila MS, Forbes EK, et al. Toward the discovery of vaccine adjuvants: coupling in silico screening and in vitro analysis of antagonist binding to human and mouse CCR4 receptors. PLoS One. 2009;4(11):e8084. https://doi.org/10.1371/journal.pone.0008084

[102] Conforti R, Ma Y, Morel Y, Paturel C, Terme M, Viaud S, et al. Opposing effects of toll-like receptor (TLR3) signaling in tumors can be therapeutically uncoupled to optimize the anticancer efficacy of TLR3 ligands. Cancer Res. 2010;70(2):490–500. https://doi.org/10.1158/0008-5472.can-09-1890

[103] Colombo MP, Piconese S. Regulatory-T-cell inhibition versus depletion: the right choice in cancer immunotherapy. Nat Rev Cancer. 2007;7(11):880–7. https://doi.org/10.1038/nrc2250

[104] Bayry J, Tchilian EZ, Davies MN, Forbes EK, Draper SJ, Kaveri SV, et al. In silico identified CCR4 antagonists target regulatory T cells and exert adjuvant activity in vaccination. Proc Natl Acad Sci U S A. 2008;105(29):10221–6. https://doi.org/10.1073/pnas.0803453105

[105] Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. Cancer Metastasis Rev. 2011;30(1):83–95. https://doi.org/10.1007/s10555-011-9281-4

[106] Hipp MM, Hilf N, Walter S, Werth D, Brauer KM, Radsak MP, et al. Sorafenib, but not sunitinib, affects function of dendritic cells and induction of primary immune responses. Blood. 2008;111(12):5610–20. https://doi.org/10.1182/blood-2007-02-075945

[107] Finke JH, Rini B, Ireland J, Rayman P, Richmond A, Golshayan A, et al. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. Clin Cancer Res. 2008;14(20):6674–82. https://doi.org/10.1158/1078-0432.ccr-07-5212

[108] Desar IM, Jacobs JH, Hulsbergen-vandeKaa CA, Oyen WJ, Mulders PF, van der Graaf WT, et al. Sorafenib reduces the percentage of tumour infiltrating regulatory T cells in renal cell carcinoma patients. Int J Cancer. 2011;129(2):507–12. https://doi.org/10.1002/ijc.25674

[109] Busse A, Asemissen AM, Nonnenmacher A, Braun F, Ochsenreither S, Stather D, et al. Immunomodulatory effects of sorafenib on peripheral immune effector cells in metastatic renal cell carcinoma. Eur J Cancer. 2011;47(5):690–6. https://doi.org/10.1016/j.ejca.2010.11.021

[110] Adotevi O, Pere H, Ravel P, Haicheur N, Badoual C, Merillon N, et al. A decrease of regulatory T cells correlates with overall survival after sunitinib-based antiangiogenic therapy in metastatic renal cancer patients. J Immunother. 2010;33(9):991–8. https://doi.org/10.1097/cji.0b013e3181f4c208

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Megan Hong, Liliane Kreuder
Article Dates: Received Jul 29 23; Accepted Oct 10 23; Published Mar 11 24

Citation
Please cite this article as follows:
Torabiardakani K. The role of regulatory T cells (Tregs) in tumorigenesis: A comprehensive literature review. URNCST Journal. 2024 Mar 11: 8(3). https://urncst.com/index.php/urncst/article/view/517
DOI Link: https://doi.org/10.26685/urncst.517