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Review

T-Regulatory Link of the Immune System and Its Role in the Pathogenesis of Inflammation and Carcinogenesis of the Lungs

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Abstract: The lack of awareness among the general medical audience about the central link in the lung immune system—T-regulatory cells (Treg) and the existing contradictions on this issue necessitate consideration and analysis, which is the purpose of this work. An analysis of 63 full-text literary sources, selected from the primary information databases, was conducted. An assessment of Treg in maintaining immune status is provided, indicating that they play a central role in balancing proinflammatory and anti-inflammatory cytokines, thereby maintaining the body's homeostasis. Their primary function is reflected in the generally accepted paradigm underlying the diagnosis and treatment of immune system disorders, which consists of an immunosuppressive effect with complex, ambivalent manifestations. This effect limits inflammatory reactions, especially hyperergic ones, but simultaneously contributes to the suppression of the antitumor immune response and stimulation of carcinogenesis processes. A decrease in Tregs is associated with opposite effects that depend on the nature of the relationship between the tumor and inflammation, and requires immunoprecise therapeutic effects. By influencing Tregs, it is possible to target and effectively modulate the processes of inflammation and carcinogenesis in the lungs. The depletion of the T-regulatory cell population is directly proportional to antitumor activity and inflammation intensity, and inversely proportional to tumor progression and inflammation regression. The opinion of some researchers that depletion of Treg cells reduces inflammation is unfounded and contradicts the generally accepted paradigm.

Keywords: T-Regulatory Cells; Interleukin-2; Inflammation; Carcinogenesis

1. Introduction

1.1. T-Regulatory Cells Are the Leading Regulatory Link of the Immune System With Suppressive Action

Today, the central role of T-regulatory cells (Treg) in regulating the immune system's response to pathogenic factors and ensuring autotolerance and body homeostasis has been recognized relatively recently. It is essential for understanding the development and therapeutic control of the inflammatory process and tumors, which are leading issues in medicine, particularly in pulmonology. However, despite the successes in developing ideas about Treg and the existing paradigm, generally accepted at the level of the world community of scientists and based on a large number of studies reflected in a large array of works, awareness of the Treg problem is far from sufficient, along with the fact that in some educational institutions theoretical material on this problem is specifically presented and therapy using Treg is already beginning to occupy significant positions in the practice of doctors. At the same time, there are individual researchers (IR), relying on ideas and proposing approaches to therapeutic effects on

inflammation that contradict the generally accepted paradigm. All this obliges us to consider the Treg problem in more detail and draw a certain conclusion on its solution in the present, assessing its prospects for the future.

2. Material and Methods

A selection and subsequent analysis of publications posted on the PubMed, Embase, Cochrane, Index Medicus platforms, as well as the Clinical Trials.gov registry of clinical trials, was carried out using keywords and phrases, including T-regulatory cells, inflammation, cancer, COVID-19, modulation, ambivalence, Interleukin-2 (IL-2), immunotherapy, cytostatics, lungs.

The analysis included 63 full-text literature sources, mostly from the last 5 years, with narrowing at each stage. The selected data were then structured and used to prepare a review (**Figure 1**).

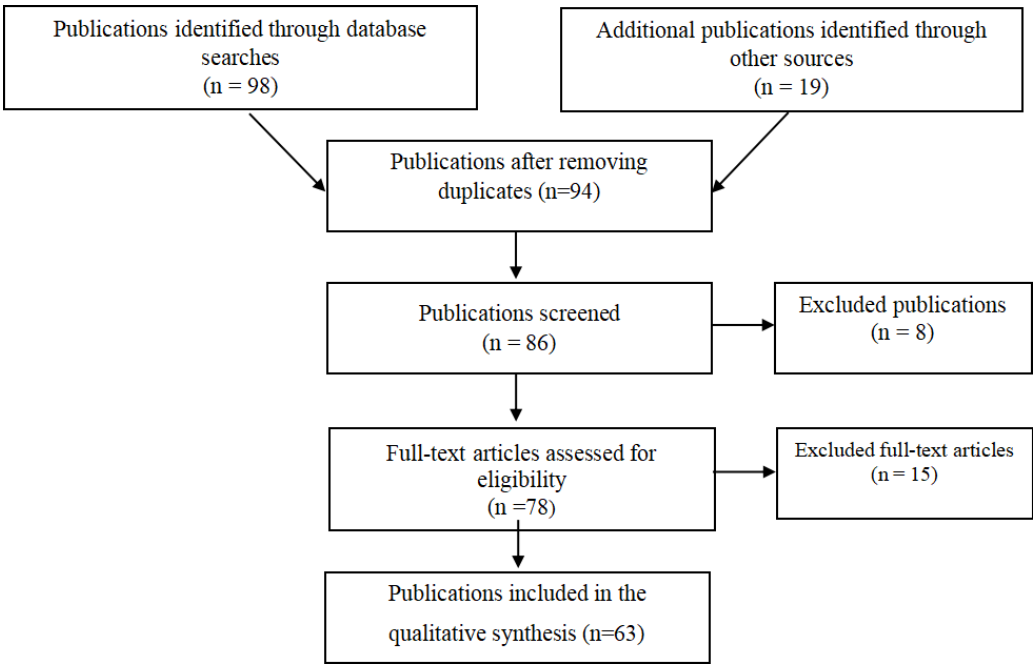

Figure 1. Scheme of publication selection.

3. Brief Background on the Development of Ideas on the Problem of Treg and Their Role in Inflammation and Carcinogenesis

According to the generally accepted paradigm in the world, based on a huge number of research results reflected in a large body of literature, Tregs are a subpopulation of cells that specialize in suppressing immunity. Tregs, being powerful immunosuppressors, contribute to the strict control over the inflammatory process, especially in acute conditions, by limiting and reducing it, thereby protecting the body from inflammatory and autoimmune diseases, as well as enhancing regenerative processes in the epithelial tissue of the lungs [1]. Their main function is to regulate the strength and duration of the immune response by controlling the function of T-effector cells (Teff), which include T-helpers and T-killers, as well as the production of cytokines. Most Tregs are generated in the thymus and were originally characterized as CD4+CD25+ T cells, which account for 5–10% of peripheral CD4+ T cells in humans [2]. More recently, the FOXP3 protein has been identified as a transcription factor that regulates the transcription of genes responsible for T cell differentiation and the expression of cytokines and other factors involved in immune suppression. Therefore, these cells are often referred to as FOXP3 regulatory T cells (FOXP3+CD4+CD25+). Tregs include three main populations: thymus-derived Tregs, previously called natural Tregs, are differentiated from two subsets of CD4 single-positive precursors, which are characterized as CD25+ Foxp3; Tregs of peripheral origin are induced following antigen stimulation of naïve T cells in peripheral lymphoid tissues, particularly at environmental interfaces in the lung, gut, and skin; *in vitro* generated Tregs are derived from naïve CD4+ T cells stimulated with

anti-CD3 in the presence of IL-2 and TGFβ. Although no marker distinguishes between these three populations, Foxp3 expression is important for their suppressive function [3].

The study of Tregs began in the 1970s, when it was discovered that they could suppress immune responses [4]. However, due to the lack of a molecular marker, studies of this cell population were stopped and only in the 1990s, with the discovery of a subpopulation of CD4 + T cells that originate from the thymus and express high levels of IL-2Rα (CD25), capable of protecting thymectomized mice from autoimmunity, information about them gained significant momentum [5]. Numerous studies have been conducted, yielding results that indicate the decisive role of Tregs in maintaining immune homeostasis by preventing hyperinflammatory reactions and autoimmunity [6]. This initiated interest in the T-regulatory link and provided the basis for utilizing Tregs in the treatment of inflammatory diseases and autoimmune processes, as well as for leveling the graft-versus-host reaction and slowing transplant rejection by increasing their number and/or activity [6–8]. The first results on enhancing Tregs by adoptive transfer were obtained back in 2009 [9]. The effect of increasing Tregs is so significant that it can be used to control the immune response and tolerance to transplantation, which are crucial for improving transplant survival in the early stages of transplantation. At the same time, a significant reduction in the use of traditional immunosuppressants is ensured, which have significant side effects that counteract the treatment results [10]. We emphasize that significant positive results have been obtained with the therapeutic use of Tregs in the treatment of respiratory diseases. This applies to patients with severe bronchial asthma, characterized by an uncontrolled course, various autoimmune diseases, and conditions marked by a hyperergic systemic inflammatory response, which may lead to the development of the so-called cytokine storm, as seen, for example, in COVID-19 [11,12].

However, it is necessary to consider the ambivalence of the Treg action, as it has been established that the enhancement of Treg, which suppresses immunity, including antitumor immunity, along with a decrease in inflammation, contributes to the development and progression of tumors due to the weakening of Tef. An imbalance between Tef and Tregs in the tumor microenvironment, favoring the enhancement of Tregs, can also occur due to their recruitment and preferential transcriptional and metabolic adaptation to the tumor microenvironment [13]. The opposite effect occurs with the depletion of Tregs, which promotes an increase in Tef activity and, consequently, the initiation and enhancement of immune responses, causing an antitumor effect [14, 15]. However, as noted above, the initiating effect also concerns the enhancement of inflammation and an increase in the likelihood of autoimmune reactions. Thus, the depletion of Tregs, in contrast to the inflammation that it aggravates, increases the activity of antitumor cells and blocks carcinogenesis processes, making it an effective strategy for cancer immunotherapy [16]. At the same time, when treating a tumor by influencing Tregs, it is necessary to consider the presence or absence of a connection between the tumor and inflammation, which significantly affects its development, as well as the nature of the inflammation itself [17–19]. Thus, on the one hand, data is indicating that Tregs accumulate in tumors and, as noted above, by suppressing immune responses, promote their growth. On the other hand, data have been obtained showing that in the case of bacterial inflammation that promotes carcinogenesis, they, by suppressing it, can cause a favorable outcome of cancer. This is explained by the dual role of Tregs, which reveals their connection with a poor prognosis in some types of cancer, but with a favorable outcome in others [20]. Recent technological advances have significantly expanded our understanding of the connection between tumors and inflammation, particularly through the indirect influence of Tregs, which are associated with both tumor progression and the effectiveness of anticancer therapy. It has been established that chronic inflammation, by attracting Tregs over time but depleting Teff, causes immunosuppression, providing an inflammatory tumor microenvironment favorable for carcinogenesis. In contrast, acute inflammation causes a more powerful antitumor immune response, leading to tumor suppression [21]. Chronic inflammation, which occurs due to long-term exposure to infection, various exogenous pathogenic factors associated with smoking, and environmental triggers, causes DNA damage and stimulates cell proliferation [22, 23]. It occurs at all stages of tumor development and plays a significant role in the formation of an inflammatory and immunosuppressive tumor microenvironment due to the influx of Tregs. The role of chronic inflammation, which promotes a long-term increase in Tregs and depletion of Teffs, which significantly reduces antitumor activity, can also be confirmed by the results of a comprehensive study of the relationship between Treg-mediated risk in COPD and lung cancer using a two-stage Mendelian randomized analysis and scRNA-seq data integration and single-cell sequencing analysis [24]. A significant degree of association with the risk of lung cancer of diseases such as COPD and bronchial asthma, including in the absence of exogenous risk factors, including smoking, is also evidence of a significant role in carcinogenesis of chronic airway inflammation inherent in these

diseases and causing the influx of Tregs and a suppressive effect, which contributes to the development and progression of the tumor. This is convincingly evidenced by the data of a stable and reliable meta-analysis based on a fairly large sample [25]. Moreover, the annual incidence of lung cancer is approximately 5 times higher among patients with COPD compared to the general population, and 45–63% of lung cancer patients worldwide suffer from COPD [26,27]. In recent years, advances in sequencing have enabled the identification of a diverse microbiome of microflora in the respiratory tract providing a deeper understanding of its role in the development and progression of inflammation and lung cancer, which is closely linked to Tregs. It was determined that dysbiosis increases susceptibility to infection and chronic inflammation. However, it does not directly cause oncogenesis, but forms the tumor microenvironment. Violation of the balance between immigration and elimination of opportunistic bacteria under the influence of various exogenous and endogenous pathogenic factors can lead to an imbalance in the microbiota, the presence and prevalence of pathogenic bacteria and the development of chronic inflammation, which triggers the above-described immunosuppressive mechanism of Tregs, significantly contributing to carcinogenesis and tumor progression [28]. At the same time, the intestinal mucosa model demonstrated that the microbiome is necessary for the induction and support of Tregs, thereby determining the balance between Tregs and Teffs [29]. On the other hand, it is well known that Treg also plays a major role in tolerance to commensal microbiota [30]. This reflects not only the evolution of immunological mechanisms for respiratory protection against external pathogens, but also their coevolution with resident microbes in a harmonious relationship [31].

Thus, the role of Tregs in the development of inflammation and tumors is significant and can be manifested in different ways, indicating a potential that requires clarification and may form the basis for therapeutic intervention.

Acute inflammation, in contrast to chronic inflammation, activates Teff and dendritic cells, exhibiting an anticancer function [32]. However, suppose the acute inflammatory reaction is not resolved in time, it can transform into chronic inflammation, resulting in an immunosuppressive environment with a large number of immunosuppressive cells, including Tregs, which directly suppress the cytotoxic functions of natural killer (NK) cells and CD8+ cytotoxic T lymphocytes through the expression and production of various factors such as PD-L1, B7-H4, and β-galactoside-binding protein (βGBP), which suppress anti-tumor immune responses, thereby promoting immune evasion of tumor cells and tumor development and progression [33].

Taking into account these factors, the individual characteristics of the oncological process in a particular patient, as well as the pharmacodynamics and pharmacokinetics of the drugs used, which is largely determined by their dosage, allows for a selective effect on Tregs, using the effect of their suppression or enhancement, which is necessary for a therapeutic effect on a tumor and/or inflammatory process. For example, this effect can be illustrated using the case of IL-2, which will be discussed below. This approach forms the basis of immunoprecision therapy, which ensures the selectivity of action and achieves a targeted effect, thereby increasing the effectiveness of both anti-inflammatory and antitumor therapies and reducing or eliminating systemic and corresponding side effects.

4. Main Mechanisms of Immune Suppression by T Regulatory Cells

Treg, a subset of T lymphocytes that control the balance between immune activation and tolerance, originates from two main sources: natural Tregs produced by the thymus and peripheral Tregs induced during immune priming. They are the first line of immunological defense against uncontrolled inflammation and viral infections, suppressing CD4+ and CD8+ Tregs and reducing the infiltration of Tef: NK cells, eosinophils, and neutrophils [34,35]. As we have already mentioned, Tregs comprise several subsets, each of which is functionally suppressive and has different mechanisms of action, enabling control of the immune response [3,36]. The suppressive effect is achieved through a complex of mechanisms that can be grouped into four groups: 1) production of anti-inflammatory cytokines such as interleukin 10 (IL-10), IL-35, and transforming growth factor beta (TGF-β), which inhibit the production of proinflammatory cytokines and suppress the activation and proliferation of TEF; 2) inhibition of TEF cytolysis through the production of Treg granzyme A and granzyme B (grzB/A)-dependent and perforin-dependent killing mechanisms; 3) metabolic disturbances that include apoptosis mediated by cytokine deprivation of the high-affinity IL-2 α receptor (CD25), cyclic AMP (cAMP)-mediated inhibition generated by CD39 and/or CD73 and adenosine purinergic receptor (A2A) expression – mediated immunosuppression of Teff and enhancement of the suppressive capacity of Tregs; 4) interactions with dendritic cells (DCs), which modulates their function and maturation, such as lymphocyte activating gene 3 (LAG3; also known as CD223) – MHC class II-mediated suppression of DC

maturation and cytotoxic T lymphocyte antigen-4. (CTLA4)-CD80/CD86-mediated induction of indoleamine 2,3-dioxygenase (IDO), which is an immunosuppressive molecule, by DCs. We will not detail each mechanism, as this is beyond the scope of this work and is limited by its volume; instead, we will refer to the works where they are well described [36,37].

Regulation of immune responses in the lungs during viral infections is crucial for preventing hyperinflammation, pulmonary failure, and acute respiratory distress syndrome, in which there is a decrease in Tregs. This is especially true in patients with severe acute respiratory syndrome infected with SARS-CoV-2, in whom a decrease in the number and function of Tregs has been observed, which is an important pathogenetic link [38].

A decrease in Tregs can be caused by a number of factors, such as the influence of severe inflammatory reactions that contribute to the destabilization of Tregs, excluding their ability to express Foxp3p and immunosuppressive functions, transforming them into Tef; an increase in IL-6 levels, which promotes the differentiation of CD4+ Tregs into proinflammatory Th17 cells, and also inhibits the expression of Tregs, leading to an imbalance in the Treg/Th17 ratio towards inflammation; the presence of hypoxia, which can activate the factor induced by it - 1α, binding to Foxp3, which IL-2 expresses, and thereby interfere with the differentiation of Tregs, and others [39,40]. It has been established that in patients with COVID-19, Tregs play a role in reducing inflammation and suppressing the cytokine storm. This is indicated by the fact that patients with a large number of these cells have a milder course of the disease. In recovering patients, the expression of the transcription factor FoxP3, which is their most informative molecular marker, was significantly higher in circulating Tregs than in uninfected individuals [41]. Along with this, a clear correlation was found between an excessive immune response and a lower level of Tregs, which leads to the development of uncontrolled inflammation and a poor prognosis of the disease [42]. This is confirmed by a significant decrease in Tregs in critically ill patients and their comorbidity with respiratory distress syndrome and COVID-19, and their increase in mild and severe cases of SARS-CoV-2 [43]. As the disease progresses, Tregs help suppress inflammation. Therefore, the degree of Treg recruitment to the lungs of COVID-19 patients may determine the severity of the disease. It is critical to properly understand the role of Treg in patients with uncontrolled inflammation, particularly in COVID-19, to help develop and use methods that somehow enhance Treg in these patients to reduce the level of hyperinflammation and tissue damage. Taking into account the analysis of the development of hyperinflammation and the immune system's response to it, using COVID-19 as an example, we summarized and schematically reflected the role of Treg in this process in **Figure 2**, depending on the phase and severity of the disease.

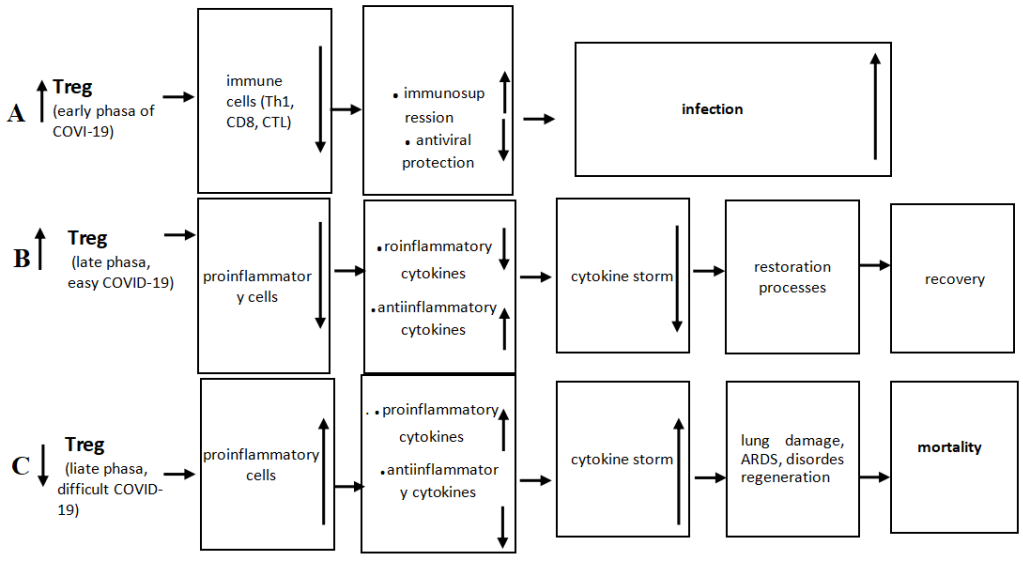

Figure 2. The role of Tregs in the pathogenesis of COVID-19 in different phases of the disease.

Notes: up arrow: increase/activation; down arrow: reduction/suppression.

5. Interleukin 2 Is an Important Promoter of the T-Regulatory Function of the Immune System

It should be emphasized that since the end of the last century, IL-2 has been identified as a growth factor for Treg. The latter, performing a promoter role, promotes the generation, survival, and functional activity of Treg, it enhances Fas activation, induces cell death, and inhibits the development of inflammatory Th17 cells [44]. It was subsequently established that, in the absence of, as well as against the background of blocking IL-2 or its receptor, a profound deficiency in the suppressor role of Treg is observed, leading to defective control of Teff and increased inflammation [45,46]. That is, it has two opposing functions or pleiotropy: maintaining Treg and simultaneously controlling and stimulating immune responses.

In this case, the question of the relationship between the role of Treg and IL-2 immediately arises, which of them is more significant, and through which is it more appropriate to regulate inflammation? Let us consider this from different aspects. First, for clarity, we will use an analogy from set theory–Euler-Venn diagrams. It should be noted that the role of the key link of the immune system, Treg, is subordinate (**Figure 3a**), while the role of IL-2 with its characteristics is subordinate (**Figure 3b**).

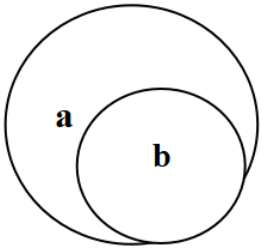

Figure 3. Scheme of relationships between the sphere influence. a: T-regulatory link, subordinating; b: IL-2.

Naturally, the resulting effect on Treg is also predetermined to be predominant. Moreover, in this case, the most effective approach will obviously be the direct route–direct administration of Treg–while the next most important will be the indirect route through the effect on IL-2. Secondly, it is necessary to consider the high selective sensitivity of Treg to IL-2, which allows for the use of IL-2 to initiate Treg in such low doses that any potential effect on Teff, which could cause their initiation and increase inflammation, is absent [47–49]. This creates the fundamental basis for therapeutic effects using IL-2, as mentioned earlier. Here, there is some analogy with the use of ultra-low doses of cytostatics, proposed by IR. These IRs explain their effect by the exclusion of toxic effects and side effects while reducing the proinflammatory effect of IL-2 on Tef. However, this not taken into account the basic position that suppression of IL-2R promotes a decrease in the main link of the immune system, Treg, and an exacerbation of inflammation and the development of autoimmune reactions, in contrast to the use of low doses of IL-2, which, given the above-described selective sensitivity of Treg to IL-2, promotes an increase in Treg and a decrease in inflammation. In support of judgment on the pathogenetic positive significance of IL-2 build-up, we note that it exerts its pleiotropic effects by binding to cell surface receptor complexes, which consist of three subunits [49]. Heterotrimeric association of all three subunits (IL-2Rα/β/γc) forms a high-affinity IL-2R complex [44]. Tregs have a specialized intracellular signaling response to IL-2, and dysfunction of IL-2 signaling disrupts the work of Tregs. Tregs are highly sensitive to low levels of IL-2 in the environment, in part due to their constitutive and high expression of the high-affinity IL-2 receptor complex (IL-2Rα/β/γc). Tregs have both a competitive advantage for IL-2 and a lower threshold for IL-2 signaling. They are highly sensitive to low levels of IL-2 in the environment, in part due to their constitutive and high expression of the high-affinity IL-2 receptor complex (IL-2Rα/β/γc). This allows Tregs to sequester extracellular IL-2 from the environment (a process known as the IL-2 flux suppression mechanism), thereby limiting Teff growth while promoting a more suppressive Treg phenotype [50]. Tregs have been shown to undergo IL-2-mediated STAT5 phosphorylation at approximately 10-fold lower IL-2 concentrations than conventional memory T cells or T cell blasts induced to express high levels of surface IL-2Rα and activation; IL-2-dependent gene responses can occur at IL-2 concentrations 100-fold lower than those of Teff [51]. This suggests an increased sensitivity to IL-2 signaling that is independent of the high-affinity IL-2 receptor. Together, these features

provide a biological basis for the therapeutic effects of low doses of IL-2, which are too low to induce activation of resting Tef and provide exogenous IL-2-mediated therapeutic effects through Treg enhancement. Extensive clinical trials on Tregs induction with a low dose of IL-2 were conducted in 14 autoimmune and inflammatory diseases, including systemic ulcerative colitis, atherosclerosis, rheumatoid arthritis, and sclerosing cholangitis, convincingly supporting the argument for the therapeutic effect of this approach. At the same time, the expansion and activation of Tregs occurred in all patients without the activation of T-eff, and no serious side effects were associated with the treatment [52].

Thus, the use of IL-2 can be very effective for treating inflammation, including in bronchopulmonary pathology, particularly in patients with COPD and bronchial asthma. In these cases, the indirect influence of Treg inhibits the progression of the disease and optimizes remodeling processes [53,54].

Considering the aspects of the influence of Tregs on the pathophysiology of inflammation, it is worth noting that a similar situation regarding the role of Tregs in inflammation and their correction by influencing Tregs also occurs in the intestinal inflammatory process, which aligns with the generally accepted paradigm, thereby confirming it once again. Thus, a number of studies have shown that the transfer of Tregs to mice with ulcerative colitis is sufficient to resolve the inflammatory response and restore normal intestinal architecture [55]. This once again indicates that Tregs and their enhancement are key mechanisms for preventing and controlling, excessive inflammation in lung and intestinal diseases. Studies in this regard constitute a global trend, and their results indicate the therapeutic value of using Tregs and significant prospects. At the same time, one cannot fail to mention the fact that Tregs have a significant similar therapeutic potential and prospects for a whole range of autoimmune diseases, including type 1 diabetes mellitus, autoimmune hepatitis, rheumatoid arthritis, systemic sclerosis, and Sjogren's disease, which tend to develop against the background of Tregs depletion [56,57]. Thus, the obtained results of the analysis of the works in the present study give reason to believe that Tregs depletion is directly proportional to antitumor activity and inflammation intensity, and inversely proportional to tumor progression and inflammation regression.

From the position of the generally accepted paradigm, according to which the role of Tregs in inflammation and tumors is different and their enhancement in the first case is aimed at stopping the inflammatory process, and in the second it promotes tumor progression (Figure 4), the ideas of IR are not consistent with it. They are based on the fact that the selective depletion of Tregs is necessary to stop both inflammatory and tumor processes. In other words, they view Tregs as having a unidirectional role in suppression, which is particularly facilitated by the use of cytostatics [58–61]. At the same time, despite the differences in basic views and, accordingly, different effects on Tregs using pharmacological agents, the results of this effect are equally positive, which does not align with the fundamental concept of the role of Tregs in controlling innate and adaptive immunity, and causes a corresponding assessment. Perhaps this is due to artifacts of the methodological and interpretative plans, the presence of the "placebo effect" as a result of the use of practically homeopathic doses of the drug used with an initial 100-fold dilution of its suspension and a subsequent 10-fold decrease in the dose due to its inhalation administration [62]. However, it has been shown that small doses do not stop, but increase inflammation [63].

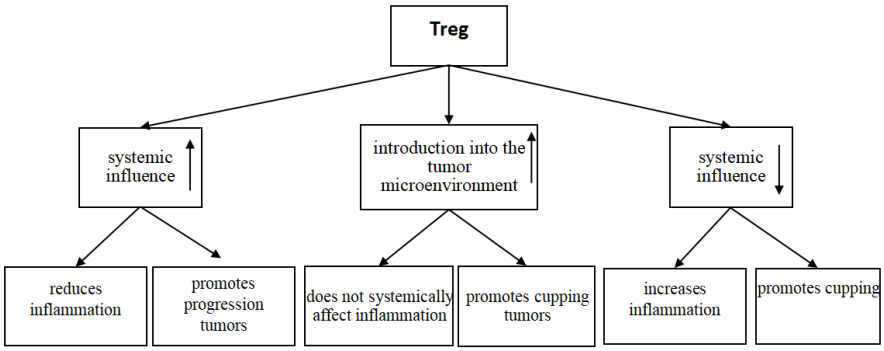

Figure 4. Comparative assessment of Treg function modulation strategies and pathways of its implementation in inflammatory and tumor processes.

Note: arrow up: enhancement; arrow down: decrease, depletion.

Given the important multifaceted role of the Treg link in immune homeostasis and the specific features of its mechanisms, the possibility of its differentiated use to influence it for targeted therapy purposes, carried out through various innovative methods and approaches, is obvious. This will be discussed in the next article. Here we will touch upon only one more important issue. Thus, the significant role of Tregs in the functioning of the lung immune system and the pathogenesis of inflammation and tumor process undoubtedly provides for the possibility of therapeutic influence on Tregs and is inextricably linked with questions about the most optimal way of influencing them not only from the standpoint of pharmacokinetics and pharmacodynamics of drugs and the mechanisms of their interaction with Tregs, but also in terms of the routes of delivery of these agents. A specific therapeutic goal largely determines this and depends on a specific tissue or target organ and the required target effect. Moreover, if delivery to the blood is preferable for systemic effects, when the action reaches all tissues and organs, for example, in the case when cancer has spread to other organs and tissues, then direct action on the mucous membranes, in particular, the respiratory tract of the lungs, will prevail for modulation of local immune reactions and targeted action on the pathological process. Therefore, we will address this issue in more detail within the context of this work.

6. Delivery of Agents for Action on Treg, Optimization

As is known, inhalation delivery of drugs provides high concentrations directly in the respiratory tract, resulting in a decrease in possible systemic side effects, which are most pronounced with parenteral administration. In this case, natural biological barriers are bypassed, particularly the gastrointestinal tract, which inactivates the effect of active agents. It is also known that the effect of inhaled substances significantly depends on the site of their action. Effects on Treg in this regard are no exception, especially considering that their presence is inherent in mucous tissues [64]. Modifications of aerosol therapy according to the parameters of the breathing mode and inhaler operation are the simplest way to optimize inhalant deposition in the respiratory tract, which does not require the development of special forms, a fairly complex and costly technological process. Radioisotope studies have shown that various inhalation modes, including particle size, patient breathing mode, and inhaler operation, can ensure preferential deposition of inhalant [65,66]. The effectiveness of aerosol therapy for inflammation and tumors depends on the location and nature of the inflammation (acute or chronic, intensity, and inflammatory phenotype), as well as the presence or absence of inflammation itself, if it concerns a tumor. The target effect of drugs is important, considering the specific node that is to be affected. Thus, a more significant presence of Tregs and a potentially more significant role of Tregs are noted in the respiratory part of the lungs, where gas exchange occurs and where the immune system is most closely connected with the external environment [67]. This is especially the case when the pathological process is located in this part of the lungs, as is the case with acute respiratory distress syndrome or COVID-19. If the acute inflammation is of a hyperergic nature, as is the case with COVID-19, then the phase of the disease must be taken into account.

However, in general, inflammation, especially hyperergic inflammation, should be suppressed by initiating Tregs in various ways and approaches, including if it plays a role in the tumor microenvironment, contributing to its progress. If the role of inflammation itself is not significant, then it is advisable to use a strategy of depleting Tregs, which promotes an increase in the immune response and, accordingly, the anti-cancer activity of the immune system. That is, the approach should be strictly individualized, depending on the clinical characteristics of a particular patient and the appropriate choice of a particular treatment method that influences Tregs. However, delivery of an inhalant to the respiratory part is the most problematic, since many protective mechanisms prevent the penetration of exogenous material into this part of the lung of a physiological nature (for example, aerodynamic filtration due to the anatomical features of the respiratory tract, mucociliary clearance) and pathological changes (for example, various types of airway obstruction). It also depends on the physicochemical properties of the inhalant and other factors. This requires the use of certain methods and approaches to aerosol therapy. The effectiveness of aerosol therapy can be increased by converting the inhaled agent from a hydrophobic state, characterized by low bioavailability, to a hydrophilic state, which ensures its penetration through cell membranes [68,69]. Other solubilizers, such as propylene glycol or ethanol, are used for the same purpose [70]. However, solubilizers can have an irritating effect on the mucous membranes of the respiratory tract and cause hyperhydration [71], and can also suppress the activity of the cilia in the mucociliary apparatus of the respiratory tract [69,71]. These two factors, which worsen, respectively, the mucous and ciliary links of the mucociliary system, are important, as disturbances in mucociliary clearance significantly contribute to the de-

velopment of bronchopulmonary pathology [69,72]. Therefore, other water-based aerosol formulations have been proposed, including those using liposomes [73]. Optimization of drug delivery can also be achieved using nanocarriers. The use of such aerosols improves the degree of penetration and more controlled distribution of the drug in the respiratory tract, prolongs the release and action of the drug, reduces the frequency of dosing, and increases compliance with treatment [74]. At the same time, there is no excessive hydration of the mucous membrane of the epithelial lining of the respiratory tract, which has a negative effect on mucociliary clearance. The effectiveness of aerosols can be increased by preliminary restoration of bronchial patency and/or selection of the inhalation mode based on the patient's breathing parameters and the operation of the inhaler [65]. The more perfect the approach and the higher the possibility of achieving the desired deposition, the higher the provision of a high concentration of the drug in the "morbid locus", resulting in less of it being required and used accordingly. Using IL-2 as an example for affecting Treg, it can be noted that there are various methods for inhalation administration of IL-2 in its various variants, in the form of an aqueous or non-aqueous solution, or suspension, or in the form of a dry powder, for example, in the form of a stabilized pulmonary lyophilisate. Each of these formulations may additionally contain a surfactant in an amount sufficient to enhance the absorption of the formulation after inhalation. Such formulations are referred to as highly absorbable [75]. The use of IL-2 aerosol therapy and this approach to its use was not only not inferior in therapeutic efficacy, but also reliably increased it in inflammation and malignant tumors compared to the traditional, subcutaneous version of drug administration [76–78].

Of course, it would be logical to ask about the possibility of direct aerosol delivery of Tregs, which may be more effective than indirect action on them. This is usually achieved by introducing Tregs into the bloodstream, allowing them to distribute throughout the body and reach the site of the pathological process, where they perform their protective function. Analysis shows that the adaptive transfer of regulatory T cells (Treg) by inhalation is a completely real and effective approach in animal models, and studies are currently underway to study its feasibility in humans. In this case, by inhalation, Tregs, both natural and induced *in vitro*, can be transferred to the lungs to mitigate inflammation and hyperreactivity, thereby suppressing the Th2 reaction. Inhaled antigens can initiate the induction of Tregs specific to an allergen stimulus and promote long-term protection against bronchial asthma and other allergic pathologies, as convincingly demonstrated in animals and promising for prevention, which can be carried out at an early age [79,80].

The effect of adoptive transfer of *in vitro* induced Treg cells by inhalation is comparable to that of natural Treg cell infusion and may be a promising therapeutic approach for the prevention and treatment of severe asthma [81]. It has been convincingly shown that the adoptive transfer of Tregs by inhalation significantly reduces hyperinflammation caused by viruses and fungi.

Thus, the route of action on Tregs is fundamentally important. It should be noted that the optimal action on this key link of the immune system is direct, rather than through the blood, and occurs by inhalation, given its predominant localization in the respiratory sections of the lungs, which are the least accessible. This requires the use of certain methods and approaches to aerosol therapy, which is very promising in this regard.

7. Conclusion

Thus, Tregs, being an important part of the pulmonary immune system, are necessary for its balanced functioning and maintenance of homeostasis. Their main function, according to the generally accepted paradigm, is to limit inflammation, which may underlie various inflammatory diseases of the bronchopulmonary system, primarily in severe, uncontrolled bronchial asthma, COVID-19, and autoimmune pathology, as well as in the intestinal system, particularly in ulcerative colitis. Strengthening Tregs can act as a protective mechanism in counteracting an excessive inflammatory response, while a decrease in their function contributes to the development of uncontrolled inflammation and autoimmune reactions. However, this can also have a significant therapeutic effect on carcinogenesis. Modern immunological methods for correcting inflammation and carcinogenesis are based on modulating Treg function, which can be achieved through various means, including direct and indirect methods of influencing it. Treatment methods for inflammation in the lungs, based on the use of alkylating cytostatics, including melphalan and cyclophosphamide, do not fit into the generally accepted paradigm. By promoting the depletion of Tregs, especially at low doses, they have a negative effect on it.

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Conflicts of Interest

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