REVIEW PAPER

Regulatory T cells in non-muscle invasive bladder cancer: Immune modulators, prognostic markers, and therapeutic targets

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Introduction Non-muscle invasive bladder cancer (NMIBC) is characterized by a high recurrence rate and variable response to intravesical Bacillus Calmette-Guérin (BCG) therapy. Regulatory T cells (Tregs), a specialized subset of CD4+ T lymphocytes expressing FOXP3, play a crucial role in shaping the tumor immune microenvironment by suppressing anti-tumor immune responses. Their presence in NMIBC has been associated with both immune evasion and, paradoxically, potential protective effects under specific conditions.

This review examines the role of Tregs in NMIBC, focusing on their impact on the tumor microenvironment, prognosis, and therapeutic potential.

Material and methods A literature review was conducted using PubMed to analyze studies on Tregs in NMIBC, including their immunosuppressive mechanisms and therapeutic targeting strategies.

Results Tregs suppress anti-tumor immunity through cytokine secretion (interleukin-10, tumor growth factor β), metabolic adaptations, and inhibition of CD8+ T cells. High FOXP3+ Treg levels are associated with increased recurrence and progression, particularly post-BCG. PD-L1+ Tregs contribute to BCG resistance, making them a potential target for immune checkpoint inhibitors and combination therapies.

Conclusions Tregs are key modulators of NMIBC progression and treatment response. Targeting their suppressive functions may enhance immunotherapy outcomes and improve patient prognosis.

Key Words: regulatory T cells ‹› FOXP3 ‹› non-muscle invasive bladder cancer ‹› BCG therapy ‹› immune suppression ‹› immunotherapy

INTRODUCTION

Bladder cancer is a significant global health concern, with approximately 610,000 new cases in 2022, an 7.1% increase from 2020 [1]. Non-muscle invasive bladder cancer (NMIBC) constitutes nearly 75% of all bladder cancer cases and is characterized by its high recurrence rate and potential for progression to muscle-invasive disease. The management of NMIBC poses substantial challenges due to its heterogeneity in clinical behavior and variable responses to standard therapies. The gold standard of management is transurethral resection of bladder tumors (TURBT), followed by intravesical therapies such as Bacillus Calmette-Guérin (BCG) [2]. BCG remains the most effective treatment for reducing recurrence and progression in high-risk NMIBC patients, yet over 20% of these either fail to respond or develop resistance to therapy [3, 4].

Regulatory T cells (Tregs) play a fundamental role in maintaining immune homeostasis and preventing autoimmunity through the suppression

of excessive immune responses. They are a specialized subpopulation of CD4+ T lymphocytes, distinguished primarily by the elevated expression of the FOXP3 (forkhead box protein P3) transcription factor and the α chain of the interleukin-2 (IL-2) receptor, known as CD25 [5]. Their role in cancer, however, is double-edged. In many malignancies, including ovarian, lung, and bladder cancer, a high Treg presence correlates with poor prognosis due to their suppression of anti-tumor immunity. Conversely, in colorectal cancer, Hodgkin's lymphoma, and gastric cancer, high Treg infiltration has paradoxically been associated with improved survival outcomes [6–8]. A high concentration of FOXP3+ T cells in tumor tissues may reflect significant immune cell infiltration and an active immune response, which could account for favorable outcomes. This context-dependent behavior reflects the complexity of Treg function across tumor types and underscores the importance of evaluating their role within specific tumor microenvironments. [6].

The significance of analyzing the tumor microenvironment (TME) in bladder cancer arise from the substantial infiltration of Tregs into the cancerous tissue [7]. In the TME, Tregs suppress antitumor immune responses during immune checkpoint blockade through multiple pathways, such as CTLA-4 (cytotoxic T lymphocyte antigen) mediated inhibition of antigen-presenting cells, depletion of IL-2, and secretion of immunosuppressive cytokines and molecules [5, 9, 10]. Human bladder carcinoma is highly infiltrated by Treg (FOXP3+) cells and inhibitory cytokines [11]. Although a high infiltration has been linked to reduced recurrence-free survival (RFS) and progression-free survival (PFS) following TURBT, some studies have reported contrasting findings, suggesting a potential positive association between Treg cell presence and survival outcomes [6, 7]. Additionally, the location of the Treg and the interaction with other immune components and cells within the bladder TME has gained attention [7]. This review aims to provide an updated synthesis of the role of Tregs in NMIBC, focusing on their biological functions within the TME, their prognostic significance, and emerging therapeutic strategies targeting their suppressive mechanisms.

THE ROLE OF TREGS IN THE TUMOR MICROENVIRONMENT OF NON-MUSCLE INVASIVE BLADDER CANCER

Regulatory T cells are highly enriched within the tumor-infiltrating lymphocytes (TILs) of bladder cancer, primarily localizing to the stromal regions surrounding bladder tumors. Research indicates that Tregs comprise more than 20% of the CD4+ T cell population in TILs, a significantly higher proportion compared to adjacent normal bladder tissue or peripheral blood [12, 13]. This distinct distribution highlights their critical role in establishing an immunosuppressive tumor microenvironment, which facilitates tumor progression.

In non-muscle invasive bladder cancer, Tregs include both conventional CD4+FOXP3+ subsets, recognized for their potent immunosuppressive properties, and atypical subsets such as CD8+CD28−CD127loCD39+ cells. These atypical Tregs, though less common, exhibit robust suppressive activity and are instrumental in immune evasion strategies employed by the tumor [14, 15]. Tumor-driven mechanisms also induce phenotypic adaptations in Tregs, including upregulation of immune checkpoint molecules such as PD-L1, which further amplifies their suppressive functions, particularly during immunotherapy [16].

FOXP3, the hallmark transcription factor of Tregs, is indispensable for their immunosuppressive activity. Elevated levels of FOXP3+ Tregs are consistently observed in the TME of NMIBC, predominantly localized in stromal regions adjacent to cancerous lesions. This spatial distribution underscores their active role in shaping the immune landscape to favor tumor survival and progression [13, 17]. The stability of FOXP3 expression in these cells is maintained by epigenetic mechanisms, such as hypomethylation of the FOXP3 promoter and conserved non-coding sequence 2 (CNS2) regions. These epigenetic modifications are pivotal in ensuring a sustained suppressive phenotype, which is critical for their function in the TME [14, 18].

Regulatory T cells exert their immunosuppressive effects through the secretion of cytokines such as IL-10, TGF-β, and IL-35. These cytokines play critical roles in suppressing effector T cell activation, reducing IFN-γ production, and promoting immune tolerance. In non-muscle invasive bladder cancer (NMIBC), the elevated presence of these immunosuppressive cytokines creates a permissive environment that facilitates tumor growth [11, 14, 19]. Furthermore, Tregs contribute to tumor progression by promoting angiogenesis and stromal remodeling through the induction of VEGF-A secretion and the transformation of fibroblasts into cancer-associated fibroblasts (CAFs), which provide structural and functional support to the tumor microenvironment [20].

Tregs also suppress anti-tumor immune responses by inhibiting CD8+ cytotoxic T cells and Th17 cells, while interacting with tumor-associated mac-

rophages (TAMs) to sustain an immunosuppressive tumor microenvironment. The density of Tregs in tumors inversely correlates with CD8+ T cell activity, thereby undermining the body's natural immune defenses against the tumor. Additionally, tumor-driven production of TGF-β and IL-10 enhances Treg recruitment and stabilization, forming a self-reinforcing loop of immune suppression [12, 13].

Within the metabolically challenging hypoxic and glycolysis-driven TME, Tregs demonstrate remarkable adaptability by utilizing lactic acid as an energy source. This metabolic flexibility allows Tregs to maintain their suppressive functions, even as effector T cells are rendered metabolically disadvantaged. Moreover, Tregs express immune checkpoint molecules such as CTLA-4, LAG-3, and TIGIT, which interact with dendritic cells (DCs) to downregulate costimulatory molecules like CD80/CD86 and induce the production of immunosuppressive factors such as indoleamine 2,3-dioxygenase (IDO) [20]. Notably, FOXP3+ Tregs are more abundant in "hot" immune clusters (characterized by high immune activity), signifying elevated immunosuppressive activity in these tumors [4].

Interestingly, Tregs can also play a protective role against tumor invasion when localized at the invasive margin of the tumor. They inhibit the expression of MMP2, a pro-invasive matrix metalloproteinase, in the TME. A strong inverse relationship has been observed between Treg frequency and MMP2 expression at the invasive tumor front, suggesting that Tregs can suppress tumor invasion. In vitro studies further confirmed that Tregs downregulate MMP2 mRNA and protein expression in both M2 macrophages and bladder cancer cells in a dose-dependent manner [18].

Treg cells and Bacillus Calmette-Guérin therapy

BCG therapy elicits a robust inflammatory response, activating effector T cells and macrophages to eliminate residual tumor cells. Paradoxically, Tregs are significantly enriched during BCG treatment, particularly PD-L1+ Tregs, which increase following BCG instillation and attenuate the therapeutic immune response [16]. Elevated levels of FOXP3+, CD25+, and PD-L1+ Tregs correlate with reduced recurrence-free survival after BCG therapy, as these cells suppress the activation of both CD4+ and CD8+ T cells, undermining BCG efficacy [13, 16, 21, 22]. The enrichment of PD-L1+ Tregs underscores the need for combination therapies to overcome immune resistance mechanisms [21, 22].

BCG therapy has been shown to enhance the CD4+/FOXP3+ ratio by 1.5–2 times, reflecting a favorable shift towards effector T cell dominance [23]. However, higher FOXP3/CD8 ratios in non-responders indicate a less favorable immune profile, emphasizing the importance of modulating Treg activity to improve therapeutic outcomes [24]. Tumors with high Treg infiltration often exhibit a Th2-dominated microenvironment, which suppresses the Th1-type immune responses critical for effective BCG-induced anti-tumor activity [21]. In high-risk NMIBC patients, recurrence was observed exclusively in those with elevated FoxP3+ Treg levels. While BCG therapy increased total CD3+ T cell numbers, the percentage of FoxP3+ Tregs decreased, suggesting an immunomodulatory effect on the tumor microenvironment [17].

Baseline Treg levels have been inconsistently linked to BCG response. While some studies suggest that high baseline Treg densities correlate with poor outcomes, others, such as Lim et al., found no significant differences in baseline CD4+FOXP3+ Treg levels between responders and non-responders. Post-BCG therapy, both CD4+FOXP3+ Tregs and non-Treg CD4+FOXP3− T cells increased in density, but the rise in non-Tregs was significant only in responders. This highlights the dynamic role of non-Treg immune subsets in predicting BCG responsiveness. Transcriptomic analyses revealed post-BCG enrichment of immune activation pathways, including CTLA-4, PD-L1, and TIM-3, which are associated with Treg-mediated immunosuppression. Despite this, active non-Treg CD4+FOXP3− cells and non-exhausted CD8+PD-1− T cells were more strongly associated with improved RFS, while non-responders exhibited elevated levels of exhausted CD8+PD-1+ T cells [25]. Immunohistochemistry and RNA sequencing confirmed that Tregs did not exhibit significant changes in density post-BCG, and their suppressive activity remained intact in non-responders [22].

To mitigate Treg-mediated immune suppression, combining BCG with immune checkpoint inhibitors targeting PD-1/PD-L1 or CTLA-4 has been proposed. Such strategies aim to restore effector T cell activity and enhance the therapeutic efficacy of BCG [16]. Table 1 summarizes the key findings about the role of Treg cells in BCG therapy.

PROGNOSTIC VALUE OF TREG CELLS IN NON-MUSCLE INVASIVE BLADDER CANCER

Treg levels and clinical outcomes

Elevated levels of regulatory T cells are strongly associated with poor clinical outcomes in non-muscle

Table 1. *The role of Treg cells in BCG therapy*

Study	Year	Findings
Pichler et al. [21]	2016	High Treg infiltration promotes a Th2-dominated immune microenvironment, suppressing Th1-type responses critical for BCG efficacy Elevated Tregs are associated with higher recurrence rates post-BCG therapy
Miyake et al. [13]	2017	Elevated levels of FOXP3+ Tregs correlate with poor RFS and PFS in NMIBC patients undergoing BCG therapy Tregs suppress CD4+ and CD8+ T cell activation, reducing BCG therapy efficacy
Kates et al. [23]	2017	BCG therapy increases the CD4+/FOXP3+ ratio by 1.5–2 times in responders, indicating a favorable immune profile for therapeutic success
Chevalier et al. [16]	2018	PD-L1+ Tregs increase following BCG therapy, attenuating therapeutic immune responses Elevated FOXP3+ Tregs correlate with reduced RFS, suggesting immune resistance mechanisms
Murai et al. [17]	2018	Recurrence observed exclusively in patients with elevated FoxP3+ Treg levels. BCG therapy increased total CD3+ T cells but decreased the percentage of FoxP3+ Tregs, indicating a shift in the immune microenvironment FoxP3+ Tregs were more abundant in tumor tissue compared to normal bladder tissue, highlighting their role in tumor progression
Eich et al. [24]	2018	Higher FOXP3/CD8 ratios observed in non-responders indicate a less favorable immune profile
Kates et al. [22]	2019	High baseline FOXP3+ Tregs associated with poor BCG response No significant reduction in Treg density post-BCG therapy among non-responders; their suppressive activity persists Active non-Treg CD4+FOXP3– and non-exhausted CD8+PD-1– T cells correlate with improved RFS, while non-responders show immune exhaustion. Transcriptomic analyses reveal enrichment of immune activation pathways (e.g., CTLA-4, PD-L1, TIM-3) in non-responders
Lim et al. [25]	2021	Found no significant differences in baseline CD4+FOXP3+ Treg levels between responders and non-responders Post-BCG therapy, both CD4+FOXP3+ Tregs and non-Treg CD4+FOXP3– T cells increased, but non-Tregs significantly increased in responders. Elevated levels of exhausted CD8+PD-1+ T cells in non-responders highlight immune exhaustion as a key factor in therapy failure

BCG – Bacillus Calmette-Guérin; NMIBC – non-muscle invasive bladder cancer; PFS – progression-free survival; RFS – recurrence-free survival

invasive bladder cancer. High densities of FOXP3+ Tregs predict significantly shorter recurrence-free survival and progression-free survival in NMIBC patients undergoing BCG therapy [13]. A T effector/Treg ratio below 1 is also highly correlated with early recurrence, underscoring the critical role of immune balance in preventing disease relapse [14]. Tregs are more prevalent in high-grade and T1 tumors compared to lower-grade or pTa tumors, highlighting their contribution to tumor aggressiveness and immune evasion [12]. Moreover, CD25+ lymphocyte levels are significantly elevated in pT1 tumors, linking their presence to more advanced disease stages [26].

Elevated Treg levels have been associated with higher recurrence rates, although their direct link to progression to muscle-invasive bladder cancer (MIBC) remains unclear. Tregs' immunosuppressive role may primarily impair local immune surveillance, thus facilitating recurrence without necessarily driving progression [21]. Additionally, Tregs suppress anti-tumor immunity by downregulating effector T cell subsets, such as IFN-γ+ and IL-17+ cells, and promoting immune evasion in residual tumor micro-foci. Their subclinical infiltration into normal-appearing bladder tissue creates a permissive microenvironment that fosters recurrence [14].

Analysis of immune clusters in recurrent tumors showed divergent patterns of Treg involvement. Tumors initially classified in the "hot cluster" maintained high immune activity, including elevated levels of FOXP3+ Tregs, PD-L1, and other immune checkpoint molecules, indicating persistent immune modulation. Conversely, “cold-cluster” tumors that recurred after BCG therapy exhibited reduced levels of FOXP3+ Tregs and CD8+ T cells, suggesting immune exhaustion or suppression [4].

CD25+ lymphocyte presence has been specifically linked to stage progression in NMIBC. Patients with CD25+ cell levels exceeding 0.2% demonstrated significantly higher hazard ratios for stage progression, underlining their prognostic significance [26]. Moreover, high infiltration of FOXP3+ Tregs in NMIBC tumors has been associated with increased recurrence rates following transurethral resection of bladder tumors [17].

In superficial bladder cancer (NMIBC), the presence of FOXP3+ tumor-infiltrating lymphocytes was significantly associated with disease progression in univariate analysis. However, this association lost significance in multivariate analysis, suggesting that other factors such as tumor stage and grade may play more prominent roles in disease progression [27]. Interestingly, higher expres-

sion of FOXP3+ Tregs in peritumoral lymphocytes correlated with a reduced risk of tumor grade progression at subsequent biopsies. Tumors with an FOXP3/CD8 ratio >1 in intratumoral lymphocytes demonstrated reduced risk for tumor grade progression. This finding contrasts with prior studies that linked FOXP3+ Tregs to higher recurrence rates, indicating that their prognostic role may vary depending on the specific immune context [24]. Table 2 summarizes the key findings about the prognostic value of Tregs in NMIBC.

Biomarker potential

The FOXP3/CD8 ratio has emerged as a robust prognostic biomarker in NMIBC. A high FOXP3/CD8 ratio indicates a dominance of regulatory T cells over cytotoxic CD8+ T cells, correlating with poor survival outcomes and a more immunosuppressive tumor microenvironment. Conversely, a low FOXP3/CD8 ratio reflects a favorable immune profile with robust anti-tumor immunity, often linked to improved clinical outcomes [28]. High Treg infiltration within the TME often correlates with resistance to immunotherapy and poor clinical outcomes. Their presence can serve as a biomarker for immune suppression and disease progression in NMIBC [20].

CD25+ Tregs have demonstrated particular utility as predictive biomarkers for Bacillus Calmette-Guérin therapy failure. High levels of CD25+ cells, alongside FOXP3+ Tregs, are strongly associated with suboptimal responses to BCG, making them valuable for identifying patients at high risk of recurrence or progression [21]. These markers can guide clinicians in tailoring treatment strategies for NMIBC patients.

Additionally, the spatial clustering of FOXP3+ Tregs with other immune markers, such as PD-L1 and CD8+, provides critical insights into the immune landscape. Such clustering has been shown to stratify patients based on their risk of recurrence and progression, offering a more nuanced approach to risk assessment [4]. Additionally, the percentage of FOXP3+ Tregs in TURBT specimens may serve as a biomarker to identify patients at higher risk of recurrence and guide therapeutic decisions [17].

THERAPEUTIC IMPLICATIONS OF TREGS IN NON-MUSCLE INVASIVE BLADDER CANCER

Targeting Tregs directly

Direct depletion of Tregs through anti-FOXP3 or anti-CD25 monoclonal antibodies has demonstrated promise in preclinical models by reducing immune suppression. However, these strategies carry a significant risk of inducing autoimmunity due to the loss of peripheral tolerance maintained by Tregs [11]. To circumvent this, alternative approaches have been developed to impair Treg function without complete depletion, such as blocking TGF-β and IL-10 pathways. These strategies aim to reduce immune suppression while preserving overall immune homeostasis, making them a safer option for clinical applications [20].

Enhancing the efficacy of BCG therapy in NMIBC may also involve modulating Treg infiltration or function. Strategies to disrupt Treg recruitment

Table 2. *Prognostic value of Treg cells in NMIBC*

Study	Year	Findings
Chi et al. [12]	2010	Tregs more prevalent in high-grade and T1 tumors, indicating immune evasion and aggressiveness
Tsai et al. [27]	2014	FOXP3+ TILs associated with progression in univariate analysis but not in multivariate analysis
Parodi et al. [14]	2015	T effector/Treg ratio <1 correlates with early recurrence Subclinical Treg infiltration facilitates recurrence
Pichler et al. [21]	2016	Elevated Tregs associated with recurrence, but no clear link to progression to MIBC
Miyake et al. [13]	2017	High densities of FOXP3+ Tregs predict significantly shorter RFS and PFS in NMIBC patients undergoing BCG therapy
Murai et al. [17]	2018	High FOXP3+ Treg infiltration correlates with increased recurrence after TURBT
Eich et al. [24]	2018	FOXP3/CD8 ratio >1 in intratumoral lymphocytes linked to reduced risk of grade progression High FOXP3+ Tregs correlated with recurrence
Lillesand et al. [26]	2020	CD25+ lymphocytes elevated in pT1 tumors; levels > 0.2% linked to stage progression
Kamitani et al. [4]	2024	Divergent Treg involvement in recurrent tumors: “hot cluster” retained high FOXP3+ Tregs; “cold cluster” showed immune suppression

BCG – Bacillus Calmette-Guérin; MIBC – muscle invasive bladder cancer; NMIBC – non-muscle invasive bladder cancer; PFS – progression-free survival; RFS – recurrence-free survival; TILs – tumor-infiltrating lymphocytes; TURBT – transurethral resection of bladder tumors

to the tumor microenvironment or to diminish their immunosuppressive activity have shown potential in preclinical studies [13, 17, 21]. For instance, targeting the SENEX gene expression or promoting Treg apoptosis could mitigate their suppressive effects and enhance anti-tumor immune responses.
Cytokine modulation represents another promising avenue for rebalancing immune responses in NMIBC patients. Increasing IL-2 levels, which support effector T cell proliferation, or reducing levels of TGF-β1 and IL-10, key mediators of Treg-driven immune suppression, could restore immune balance and improve therapeutic outcomes [19]. Such cytokine-based interventions may also synergize with existing immunotherapies to further enhance their efficacy.

Combination therapies

Combining BCG with immune checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4 has shown significant promise in enhancing anti-tumor immunity by reducing Treg-mediated suppression and promoting effector T cell activation. Early clinical trials have highlighted the potential of these combination approaches to improve recurrence-free survival in high-risk NMIBC patients, particularly those with suboptimal responses to BCG monotherapy [16].
For tumors with low immune activity ("cold tumors"), additional strategies are required to bolster immune responsiveness. Fibroblast growth factor receptor (FGFR) inhibitors have demonstrated potential in complementing immunotherapy by enhancing immune cell recruitment and activation. This approach is particularly relevant for FGFR3-mutant NMIBC cases, which are often resistant to BCG therapy [4]. By increasing the immunogenicity of cold tumors, FGFR inhibitors can help convert these refractory cases into immunologically "hot" tumors, thereby improving response rates to combined treatments.
Additionally, combining BCG therapy with agents targeting Tregs and tumor-associated macrophages represents a novel therapeutic avenue. This dual-targeting approach aims to address the immunosuppressive components of the tumor microenvironment that contribute to therapeutic resistance. Preclinical studies have indicated that modulating both Tregs and TAMs can enhance BCG efficacy and improve overall patient outcomes [13]. As part of this narrative review Figure 1 summarizes the possible implementations of the Treg in NMIBC.

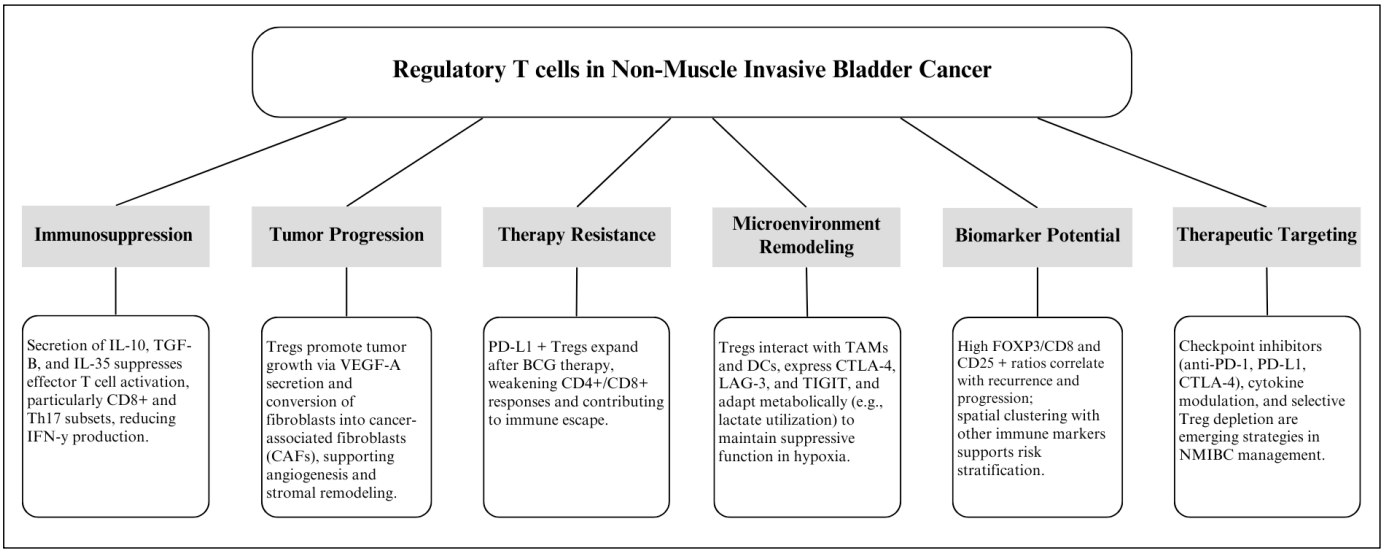

Figure 1. *Mechanisms by which regulatory T cells (Tregs) influence tumor biology and therapeutic response in non-muscle invasive bladder cancer (NMIBC).*
Tregs contribute to tumor immune evasion and progression through multiple mechanisms: (1) suppressing effector T cell activation (particularly CD8+ and Th17 cells) via immunosuppressive cytokines such as IL-10, TGF-β, and IL-35; (2) promoting tumor growth through VEGF-A secretion and stromal remodeling via cancer-associated fibroblasts (CAFs); (3) attenuating Bacillus Calmette-Guérin (BCG) therapy efficacy through expansion of PD-L1+ Tregs; (4) reshaping the tumor microenvironment by interacting with tumor-associated macrophages (TAMs) and dendritic cells (DCs) and utilizing metabolic adaptations; and (5) serving as prognostic biomarkers, with FOXP3/CD8 and CD25+ Treg levels correlating with recurrence, progression, and resistance to immunotherapy. These pathways highlight multiple therapeutic opportunities, including immune checkpoint inhibition, cytokine modulation, and targeted Treg depletion.

FUTURE DIRECTIONS IN IMMUNOTHERAPY TARGETING TREGS IN BLADDER CANCER

The future of uro-oncology is increasingly centered around personalized immunotherapeutic approaches, especially for NMIBC, where recurrence and resistance to intravesical BCG therapy remain substantial challenges [3, 21, 22]. One approach involves immune checkpoint blockade. Tregs in bladder tumors often express PD-L1, CTLA-4, and other inhibitory molecules. Trials combining BCG with checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4) are ongoing, with early results indicating enhanced immune activation and improved recurrence-free survival in high-risk NMIBC patients [16, 22].

Another promising avenue is selective Treg targeting. While broad depletion of Tregs using anti-CD25 antibodies can induce autoimmunity, refined methods aim to inhibit Treg suppressive function without eliminating their entire population. This includes blocking immunosuppressive cytokines like IL-10 and TGF-β, or modulating FOXP3 expression stability through epigenetic interference [11, 20]. Additionally, cytokine modulation is being explored to tip the immune balance toward effector T cells. Administration of low-dose IL-2 to preferentially expand CD8+ T cells, or inhibition of TGF-β signaling, are being evaluated to diminish Treg-driven suppression while enhancing cytotoxic responses [19]. From a tumor biology standpoint, spatial transcriptomics and single-cell RNA sequencing offer promising tools to dissect Treg heterogeneity within the bladder tumor microenvironment. Such techniques will support biomarker discovery and enable precise immune profiling, informing the selection of immunotherapeutic regimens [4, 24]. Emerging alternative therapies are also relevant. Hyperthermic intravesical chemotherapy (HIVEC) and novel intravesical agents are gaining attention for patients with BCG failure [29].

CONCLUSIONS

Regulatory T cells play a central role in the immune landscape of NMIBC, shaping tumor progression, therapy resistance, and patient outcomes. Their immunosuppressive functions, mediated by cytokines, cell-cell interactions, and metabolic adaptations, present both challenges and opportunities for therapeutic intervention. By leveraging Tregs as biomarkers and therapeutic targets, future research and clinical strategies can improve disease management and enhance patient survival. A concerted focus on Treg heterogeneity, mechanisms of immune resistance, and innovative combination therapies is essential for advancing NMIBC treatment paradigms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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