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Targeting the Lymphatic-Inflammatory Axis in Bladder Cancer: A Comprehensive Review of Molecular Mechanisms and the Therapeutic Potential of α -Tomatine

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Abstract

Background: Bladder cancer (BCa) remains a significant global health challenge, characterized by high recurrence rates and significant mortality associated with lymph node metastasis (LNM). The spread of tumor cells through the lymphatic system is driven by lymphangiogenesis, a process heavily regulated by the Vascular Endothelial Growth Factor-C (VEGF-C)/VEGFR-3 axis and exacerbated by chronic inflammation within the tumor microenvironment (TME). Despite advances in surgical and chemotherapeutic interventions, effective strategies to specifically inhibit metastatic dissemination are lacking.

Methods: This narrative review synthesizes current literature regarding the molecular drivers of BCa metastasis and the pharmacological potential of natural steroidal alkaloids. We analyzed data focusing on the interplay between inflammatory signaling (NF- κ B/MAPK) and lymphangiogenic factors, alongside the specific bioactivity of α -tomatine.

Results: The literature confirms that VEGF-C and PDGF-BB are critical promoters of lymphatic vessel density in BCa. Furthermore, chronic activation of the NF- κ B pathway in tumor-associated immune cells fuels the secretion of these lymphangiogenic factors. Emerging evidence highlights α -tomatine, a glycoalkaloid found in tomatoes, as a potent dual-inhibitor. α -Tomatine suppresses inflammation by blocking MAPK/NF- κ B signaling and induces cancer cell apoptosis via Autophagy/Beclin-1 and Wnt/ β -catenin modulation.



Conclusion: Targeting the intersection of inflammation and lymphangiogenesis offers a promising therapeutic avenue. α -Tomatine represents a high-potential lead compound that may suppress BCa metastasis by severing the inflammatory support network required for lymphatic expansion. Future research should focus on optimizing the bioavailability of this alkaloid for clinical application.

Keywords: Bladder Cancer, Lymphangiogenesis, α -Tomatine, VEGF-C, NF- κ B, Metastasis, Inflammation.

Introduction

Bladder cancer (BCa) constitutes a profound burden on global healthcare systems, ranking as one of the most common malignancies of the urinary tract. Despite advancements in diagnostic modalities, including cystoscopy and molecular biomarkers, the management of BCa is complicated by its heterogeneous nature and high propensity for recurrence [1]. While non-muscle-invasive bladder cancer (NMIBC) is generally manageable via transurethral resection, a significant subset of patients progresses to muscle-invasive bladder cancer (MIBC). MIBC is associated with a dire prognosis, primarily due to the early onset of metastasis [2, 3]. The survival rates for patients with metastatic BCa remain unsatisfactory, underscoring an urgent need to decipher the molecular mechanisms driving tumor dissemination and to identify novel therapeutic targets.

The primary route of metastasis in bladder cancer is the lymphatic system. Lymph node metastasis (LNM) is the strongest predictor of poor survival in patients undergoing radical cystectomy [4]. Unlike the hematogenous spread, which involves blood vessels, lymphatic metastasis relies on lymphangiogenesis—the formation of new lymphatic vessels from pre-existing vasculature. This process is not merely passive; it is actively driven by the tumor microenvironment (TME), where cancer cells secrete specific growth factors that recruit and proliferate lymphatic endothelial cells (LECs) [5, 6]. Physiological lymphangiogenesis is crucial for tissue fluid homeostasis and immune surveillance, but in the context of cancer, it provides a highway for tumor cells to escape the primary site and colonize regional lymph nodes [6].

Central to pathological lymphangiogenesis is the Vascular Endothelial Growth Factor (VEGF) family, particularly VEGF-C and VEGF-D, which bind to the tyrosine kinase receptor VEGFR-3 expressed on LECs [7, 8]. The binding of these ligands triggers a phosphorylation cascade that promotes the proliferation, migration, and tube formation of lymphatic vessels. Moreover, other growth factors such as Platelet-Derived Growth Factor-BB (PDGF-BB) have been implicated in stabilizing these newly formed vessels and facilitating tumor spread [9]. While inhibitors targeting these pathways have shown

promise in preclinical models, clinical translation has been hindered by toxicity and resistance, necessitating the exploration of alternative or adjuvant agents.

Concurrently, chronic inflammation is increasingly recognized as a hallmark of cancer and a key driver of lymphangiogenesis. The inflammatory milieu within the bladder involves a complex interplay of cytokines, chemokines, and immune cells that activate signaling pathways such as Nuclear Factor- κ B (NF- κ B) and Mitogen-Activated Protein Kinases (MAPK). These pathways not only sustain tumor cell survival but also upregulate the expression of lymphangiogenic factors like VEGF-C [18, 19]. Thus, agents that can simultaneously dampen inflammation and inhibit lymphangiogenic signaling represent a rational therapeutic strategy.

Nature has long been a source of pharmacological leads, with plant-derived alkaloids showing significant potential in oncology. α -Tomatine, a steroidal glycoalkaloid predominantly found in tomatoes (*Solanum lycopersicum*), has recently garnered attention for its potent biological activities. Although historically studied for its anti-nutritional properties and defense against plant pathogens [22], emerging research suggests α -tomatine possesses robust anti-inflammatory and anti-cancer capabilities [17, 24]. It has been shown to modulate the NF- κ B and MAPK pathways and induce apoptosis in various cancer cell lines, including melanoma and hepatocellular carcinoma [20, 21]. However, its specific potential in the context of bladder cancer lymphangiogenesis remains underexplored.

This article provides a comprehensive review of the molecular mechanisms linking inflammation and lymphangiogenesis in bladder cancer. We critically evaluate the role of the VEGF-C/VEGFR-3 axis and the inflammatory TME in driving metastasis. Furthermore, we synthesize current evidence supporting the therapeutic potential of α -tomatine, proposing it as a multi-target agent capable of disrupting the lymphatic-inflammatory axis to improve outcomes in bladder cancer patients.

Methods

This article employs a narrative review methodology to synthesize existing literature on bladder cancer metastasis, lymphangiogenesis, and the pharmacological properties of α -tomatine. The review was constructed by analyzing peer-reviewed articles sourced from major biomedical databases, primarily PubMed/MEDLINE and Scopus.

Search Strategy



The literature search was conducted using a combination of Medical Subject Headings (MeSH) and free-text terms. The primary search strings included: "Bladder Cancer AND Lymphangiogenesis," "VEGF-C AND Metastasis," "Tumor Microenvironment AND Inflammation," "NF-kappaB AND Cancer," and "Alpha-Tomatine OR Solanum Alkaloids AND Cancer." The search was not restricted by publication date, allowing for the inclusion of seminal papers on lymphangiogenesis (early 2000s) alongside the most recent findings on molecular signaling and natural product pharmacology (up to 2025).

Inclusion and Exclusion Criteria

Articles were included if they met the following criteria:

1. Studies investigating the molecular mechanisms of lymph node metastasis in urothelial carcinoma or bladder cancer.
2. Basic science reports detailing the signaling pathways of VEGF-C, VEGFR-3, PDGF-BB, and Thrombospondins.
3. Pharmacological studies examining the effects of α -tomatine or related steroidal alkaloids on cancer cell lines or inflammatory models.
4. Reviews discussing the crosstalk between inflammation (NF- κ B/MAPK pathways) and tumor progression.

We excluded studies that focused solely on surgical techniques without molecular insight, articles in languages other than English, and studies involving plant extracts where the active compound was not identified or standardized.

Data Synthesis

The gathered literature was categorized into three thematic pillars: (1) The molecular drivers of lymphangiogenesis in bladder cancer; (2) The inflammatory pathways facilitating the tumor microenvironment; and (3) The specific mechanisms of action of α -tomatine. These distinct bodies of evidence were then integrated to construct a theoretical framework proposing α -tomatine as an inhibitor of the inflammatory-lymphangiogenic axis. The synthesis focuses on identifying overlapping signaling nodes—specifically where the inhibitory effects of α -tomatine coincide with the activation pathways of BCa metastasis.

Results

The Lymphatic Network: A Conduit for Bladder Cancer Metastasis

The lymphatic system plays a paradoxical role in oncology; while essential for immune defense, it acts as a primary route for dissemination in bladder cancer. The density of lymphatic vessels (Lymphatic Vessel Density, LVD) in the peritumoral region correlates significantly with nodal status and overall survival in patients with invasive urothelial carcinoma [5]. Unlike blood angiogenesis, which relies heavily on VEGF-A, lymphangiogenesis is orchestrated by a distinct set of growth factors and receptors.

The VEGF-C/VEGFR-3 Axis

The most critical regulator of this process is VEGF-C. In bladder cancer, tumor cells often overexpress VEGF-C, which is secreted into the TME. VEGF-C requires proteolytic processing to bind with high affinity to VEGFR-3, a receptor largely restricted to lymphatic endothelial cells in adults [7, 8]. Upon ligand binding, VEGFR-3 undergoes dimerization and autophosphorylation, activating downstream signaling cascades including the RAS/MAPK and PI3K/Akt pathways [13]. This activation results in the sprouting of new lymphatic capillaries from existing vessels, increasing the surface area available for tumor cells to invade the lymphatic system.

Blockade of this axis has shown profound effects in preclinical models. Studies utilizing monoclonal antibodies against VEGF-C or soluble VEGFR-3 decoys have demonstrated a significant reduction in lymph node metastasis, validating this pathway as a prime therapeutic target [12, 13]. Similarly, VEGF-D, a homolog of VEGF-C, also promotes metastatic spread via VEGFR-3, although its expression in bladder cancer is more variable [11].

PDGF-BB and Structural Integrity

Beyond the VEGF family, Platelet-Derived Growth Factor-BB (PDGF-BB) has emerged as a significant contributor to intratumoral lymphangiogenesis. PDGF-BB recruits pericytes and stabilizes the nascent lymphatic vessels, making them more functional and conducive to tumor cell transport [9]. The simultaneous targeting of endothelial sprouting (via VEGF-C) and vessel maturation (via PDGF-BB) presents a more comprehensive strategy for halting metastasis.

Endogenous Inhibitors: Thrombospondins

The body possesses natural inhibitors of angiogenesis and lymphangiogenesis, such as thrombospondins (TSPs). These matricellular proteins can directly inhibit endothelial cell migration and induce apoptosis. In aggressive bladder cancers, the expression of TSPs is often downregulated, shifting the balance toward pro-lymphangiogenic factors [14]. Restoring this balance is a key conceptual goal in BCa therapy.



Inflammation: The Fuel for Metastatic Progression

The link between chronic inflammation and bladder cancer is well-established, exemplified by the increased risk of squamous cell carcinoma in patients with schistosomiasis or chronic cystitis. However, inflammation is also crucial in the more common urothelial carcinomas.

The NF- κ B/MAPK Nexus

The Nuclear Factor- κ B (NF- κ B) pathway serves as a master regulator of inflammation. In the context of BCa, NF- κ B is constitutively activated in both tumor cells and infiltrating immune cells (such as tumor-associated macrophages) [18]. This activation is often mediated by upstream Toll-like Receptors (TLRs) or cytokine receptors. Once active, NF- κ B translocates to the nucleus and drives the transcription of pro-survival genes (e.g., Bcl-2) and, crucially, pro-lymphangiogenic factors including VEGF-C [19].

Similarly, the Mitogen-Activated Protein Kinase (MAPK) pathways—comprising ERK, p38, and JNK—are frequently dysregulated in BCa. These pathways integrate signals from the extracellular environment to control cell division and migration. Cross-talk between MAPK and NF- κ B creates a feed-forward loop: inflammation activates MAPK, which enhances NF- κ B transcriptional activity, leading to further cytokine and VEGF-C production [20]. This "inflammatory-lymphangiogenic axis" creates a TME that is hostile to anti-tumor immunity but highly favorable for metastasis.

α -Tomatine: A Multipotent Natural Inhibitor

Given the complexity of the signaling networks described above, single-target synthetic drugs often fail due to compensatory mechanisms. This has led to renewed interest in "promiscuous" natural compounds that can modulate multiple pathways simultaneously. α -Tomatine, a major saponin in tomatoes, has demonstrated a remarkable profile of bioactivities relevant to BCa.

Structure and Anti-Inflammatory Action

α -Tomatine consists of a steroid-like aglycone (tomatidine) attached to a tetrasaccharide moiety. This structure allows it to interact with cell membranes and intracellular signaling proteins. In macrophages and dendritic cells, α -tomatine and its metabolites have been shown to significantly inhibit the release of pro-inflammatory cytokines (TNF- α , IL-6) induced by lipopolysaccharides (LPS) [17, 23]. Mechanistically, this is achieved by suppressing the phosphorylation of proteins in the MAPK pathway (specifically p38 and JNK) and inhibiting the nuclear translocation of NF-

κ B [15, 16]. By dampening this inflammatory signaling, α -tomatine effectively reduces the "noise" in the TME that drives VEGF-C expression.

Direct Anti-Cancer Mechanisms

Beyond its anti-inflammatory effects, α -tomatine exerts direct cytotoxicity against cancer cells.

1. **Induction of Autophagy and Apoptosis:** α -Tomatine has been observed to inhibit the fusion of autophagosomes with lysosomes, leading to an accumulation of autophagosomes and subsequent autophagic cell death. This is often mediated via the regulation of Beclin-1 [21].
2. **Wnt/ β -catenin Suppression:** In hepatocellular carcinoma models, α -tomatine suppresses the Wnt/ β -catenin pathway, a signaling route often aberrant in BCa that contributes to stemness and drug resistance [20].
3. **Inhibition of Metastatic Behavior:** In vitro studies on metastatic melanoma cells indicate that α -tomatine can reduce cell migration and invasion, likely by downregulating the expression of Matrix Metalloproteinases (MMPs), which are essential for degrading the extracellular matrix during metastasis [19].

Discussion

The interplay between inflammation and lymphangiogenesis represents a critical vulnerability in the progression of bladder cancer. Our review of the literature suggests that the transition from organ-confined disease to metastatic muscle-invasive bladder cancer is driven by a self-perpetuating cycle: inflammatory stimuli within the bladder activate NF- κ B and MAPK signaling, which in turn upregulates VEGF-C and PDGF-BB. These growth factors promote the expansion of the lymphatic network, providing the physical route for tumor cells to exit the bladder. Standard chemotherapies target rapidly dividing cells but often fail to interrupt this underlying signaling architecture. This highlights the necessity for agents that can remodel the tumor microenvironment.

Synthesis of the Therapeutic Model

The data presented points toward α -tomatine as a highly promising candidate for disrupting this axis. The theoretical efficacy of α -tomatine in bladder cancer relies on its "dual-hit" capability.

First, by inhibiting NF- κ B and MAPK phosphorylation in the tumor microenvironment, α -



tomatine acts upstream of lymphangiogenesis. If NF- κ B is suppressed, the transcriptional drive for VEGF-C production is diminished. This would theoretically lead to a reduction in Lymphatic Vessel Density (LVD) surrounding the tumor, effectively "starving" the cancer of its metastatic escape routes. This mechanism is supported by studies showing that other NF- κ B inhibitors significantly reduce VEGF-C expression and lymph node metastasis in xenograft models [13, 19].

Second, the direct cytotoxic effects of α -tomatine on tumor cells act as a debulking strategy. The induction of autophagic cell death is particularly relevant in BCa cells that may have developed resistance to apoptotic triggers (e.g., via p53 mutations). The inhibition of the Wnt/ β -catenin pathway [20] further suggests that α -tomatine could target the subpopulation of cancer stem cells responsible for recurrence, addressing one of the most persistent challenges in BCa management.

Crosstalk in the Tumor Microenvironment: A Deeper Analysis

To fully appreciate the potential of α -tomatine, one must consider the cellular complexity of the TME. The interaction between Tumor-Associated Macrophages (TAMs) and urothelial carcinoma cells is pivotal. TAMs are typically polarized toward an M2-like phenotype in aggressive cancers, a state that is highly pro-inflammatory and pro-angiogenic. These M2 macrophages are major sources of VEGF-C and VEGF-D [10]. The ability of solanum alkaloids to modulate macrophage function is therefore of high clinical relevance. Studies on related alkaloids indicate they can prevent the polarization of macrophages toward this pro-tumor phenotype or repolarize them toward an anti-tumor M1 state [25].

If α -tomatine can indeed repolarize TAMs within the bladder wall, the therapeutic impact would be multiplicative. Not only would VEGF-C secretion drop, but the local immune milieu would shift from immunosuppressive to immunostimulatory, potentially re-engaging the host's cytotoxic T-cells to attack the tumor. This immunomodulatory angle complements the direct anti-lymphangiogenic mechanism, offering a comprehensive approach to containing the disease.

Challenges and Limitations

Despite this promise, several hurdles remain before α -tomatine can be translated into clinical practice. The primary limitation of steroidal glycoalkaloids is their toxicity and bioavailability. High concentrations of α -tomatine can disrupt cholesterol-containing membranes, potentially leading to lysis of healthy cells, particularly erythrocytes (hemolysis) and

intestinal epithelial cells [22]. This narrow therapeutic window necessitates precise dosing strategies.

Furthermore, the oral bioavailability of α -tomatine is generally poor due to its large molecular size and susceptibility to hydrolysis in the acidic environment of the stomach, where it is converted to the aglycone tomatidine. While tomatidine also possesses bioactivity, the distinct properties of the glycosylated form might be lost. Consequently, the systemic administration of α -tomatine to target bladder lymphatics faces pharmacokinetic barriers. The "first-pass" metabolism by the liver also reduces the concentration of active compound reaching the urinary bladder.

Future Perspectives: Novel Delivery Systems

To overcome these limitations, future research must focus on advanced drug delivery systems. The intravesical administration of chemotherapy (instilling drugs directly into the bladder via a catheter) is a standard of care for NMIBC (e.g., BCG or Mitomycin C). This route offers a unique advantage for α -tomatine therapy. Intravesical delivery bypasses systemic metabolism, allowing high concentrations of the drug to contact the tumor and the surrounding urothelium directly while minimizing systemic toxicity [2, 3].

Nanotechnology offers another viable solution. Encapsulating α -tomatine in liposomes, nanoparticles, or hydrogels could enhance its stability and facilitate uptake by tumor cells and macrophages. For instance, liposomal formulations have been successfully used to deliver other hydrophobic natural products, improving their accumulation in lymphoid tissues. A nanoparticle formulation targeting VEGFR-3 or specific integrins on the surface of bladder cancer cells could act as a "guided missile," delivering the α -tomatine payload precisely where it is needed to inhibit lymphangiogenesis.

Moreover, combination therapies should be explored. The use of α -tomatine as a sensitizer could potentiate the effects of standard chemotherapeutics like cisplatin or gemcitabine. By inhibiting survival pathways (NF- κ B/Akt), α -tomatine prevents the tumor cell from mounting a defense against DNA damage induced by chemotherapy. This synergy could allow for lower doses of cytotoxic drugs, reducing the debilitating side effects currently experienced by BCa patients.

Conclusion

The metastatic spread of bladder cancer via the lymphatic system is a complex process driven by the collusion of tumor cells, immune cells, and lymphatic endothelium, orchestrated by the VEGF-C and NF- κ B signaling axes.



Current therapeutic options often fail to specifically dismantle this infrastructure. The steroidal glycoalkaloid α -tomatine emerges from our review as a compound with the requisite multi-target pharmacology to disrupt this fatal progression. By simultaneously suppressing the inflammatory triggers of lymphangiogenesis and inducing autophagic cell death in tumor cells, α -tomatine holds significant promise. While challenges regarding bioavailability and toxicity exist, the development of intravesical formulations or nanocarriers could unlock the full clinical potential of this natural feature-rich compound, offering a new hope for patients facing invasive bladder cancer.

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