

Role of the JNK Pathway in Bladder Cancer

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Abstract: Bladder cancer, one of the most frequently diagnosed cancers worldwide, is associated with high morbidity and mortality and a poor prognosis. The bladder cancer types include 1) non-muscle invasive bladder cancer (NMIBC) and 2) muscle invasive bladder cancer (MIBC). Metastases and chemoresistance in MIBC patients are the leading causes of the high death rate. c-Jun N-terminal kinase (JNK) is an important factor for the undifferentiated state of cancer cells. JNK belongs to the mitogen-activated protein kinases (MAPKs) family; it is activated by various extracellular stimuli, such as stress, radiation, and growth factors and mediates diverse cellular functions, such as apoptosis, autophagy, proliferation, invasion, and migration by mediating AKT (Akt strain transforming), ATG (Autophagy related), mTOR (Mammalian target of rapamycin), and caspases 3, 8, and 9. This review describes the JNK-related functions, mechanisms, and signaling in bladder cancer.

Keywords: bladder cancer, JNK, proliferation, apoptosis, metastasis, chemoresistance, autophagy

Introduction

Bladder cancer (BC) is the second most common genitourinary malignancy worldwide.^{1,2} Over 430,000 men and women in the world and 74,000 in the USA are diagnosed with BC every year—and the incidence is four times higher in men than women. Urinary BC ranks fourth in the number of estimated new cases in the USA.³ Most BCs are urothelial carcinomas developing in the urinary bladder and derived from the stratified epithelium (also known as urothelium). About 20% of BC patients are younger than 75. The occurrence of new BC cases increases steadily with age. Reported risk factors for BC include cigarette smoking, older age, male gender, white race, occupational exposure to certain chemicals, radiation to the pelvis, use of medications (such as cyclophosphamide), chronic bladder infection, and family history.⁴

BC cases can be grouped by morphology and basement membrane invasion. There are three morphology types: (1) papillary, (2) sessile, and (3) mixed; most BCs are urothelial carcinomas with basement membrane invasion. Moreover, BC cases are classified into two groups: (1) non-muscle invasive bladder cancer (NMIBC, mostly low-grade BC) and (2) muscle invasive bladder cancer (MIBC, high-grade BC).^{5–7} Most NMIBC cases (50–70%) recur and 10–15% progress to invasion; the five-year-survival rate of NMIBC cases is above 90%. Meanwhile, MIBC has a poor prognosis with a low five-year-survival rate and tends to progress to metastasis.⁸ NMIBC is not life-threatening, while MIBC is clinically aggressive and produces lymph node, liver, lung, bone, and brain metastases. Invasion and metastases have increased the death rate of BC every year.⁹ Resistance to chemotherapy, cell adhesion molecule production, protease secretion, and angiogenesis at the tumor sites have been studied as main reasons of metastatic BCs. Thus, the molecular mechanism of metastasis is insufficiently studied.^{10–12}

Besides metastasis occurrence, early diagnosis is critical for treating BC. Asymptomatic patients are frequently diagnosed from a routine checkup, and patients with urinary tract malignancies often experience hematuria and irritative voiding symptoms.¹³ Regarding standardized BC diagnosis, the gold standards of diagnostic procedures are cystoscopy and urine cytology. Cystoscopy is invasive and expensive and can cause urinary tract infections. However, cystoscopy method might

miss a small flat tumor site and involves the risk of urethral injury, urinary tract infection due to instrumentation. Painless hematuria (blood or blood clot in urine) is the most common BC symptom. Less typical symptoms include frequent urination and painful urination. Meanwhile, advanced BC can cause pelvic pain, bone pain, and back pain.^{14–16}

JNK (c-Jun N-terminal kinase, also called stress-activated protein kinase or stress-activated MAP kinase, SAPK) plays pivotal roles in BC. JNK belongs to the mitogen-activated protein kinase (MAPK) family and participates in various cellular processes, including cell proliferation, apoptosis, angiogenesis, differentiation, metastasis, invasion, and inflammation.^{17–19} Numerous cell stimuli activate JNK through autophosphorylation.²⁰ Such stimuli include cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), and environmental stress factors, such as redox stress, radiation, and osmotic stress. JNK can suppress or promote tumor development. Continued abnormal functioning of JNK leads to various diseases such as cancers.²¹ JNK is a highly complex multi-functional protein associated with various signaling proteins, such as p38 and nuclear factor kappa B (NF- κ B); crosstalks between these proteins are critical for cancer programming. JNK, p38, and NF- κ B share upstream kinases and may act as synergistic regulators for cancer cell survival.²² Besides, autophagy activates JNK, counteracting apoptosis signaling and promoting cancer cell survival.²³ Additionally, JNK-mediated prosurvival autophagy promotes chemotherapy resistance in cancer cells.²⁴ Moreover, the cell proliferation mechanism based on the regulation of JNK mediates cancer cell survival.²⁵

Key cancer recurrence factors include signaling pathway regulating proteins, such as p38/MAPK, transforming growth factor-beta (TGF- β), TWIST (Twist-related protein 1), NF- κ B, Src (Proto-oncogene tyrosine-protein kinase Src), AKT, and JNK.^{1,26–30} This review provides a comprehensive summary of the specific JNK signaling pathway function in BC (Table 1 and Figure 1). It aims to improve the understanding of the JNK signaling pathway's role in cancer growth mechanisms, such as tumorigenesis, apoptosis, autophagy, chemotherapy resistance, and metastasis (invasion and migration).

The Diverse Function of JNK Signaling Pathway in BC Tumorigenesis

Tumorigenesis is the dynamic, complicated cancer formation process. It occurs in three stages: initiation, progression, and metastasis.^{31,32} Malignant cancer cells exhibit abnormal features such as uncontrolled cell proliferation, cell death signal

Table 1 Function of JNK in Bladder Cancer

Category	JNK Function	Corresponding References
Tumorigenesis	Phosphorylate AP-1 proteins Involved in AKT1 binding to JIP1	[32–40]
Cell proliferation	Regulate cell death and cell survival through FAS and TNF Inhibit JNK-enhanced bladder cancer cell apoptosis Inhibit cell growth via p21WAF1 activation Activate caspase-9, -8, and -3 Mediate apoptosis by regulating TGF- β 1	[2,41–49]
Metastasis	Increase miR-200c transcription Decrease migration by inhibiting SOD2-induced JNK activation	[50–61]
Chemoresistance	Increase chemosensitivity through p53	[39,61,75,76]
Autophagy	Induce Bcl-2/Beclin-1 complex breakdown Activate autophagic reaction Attenuate gemcitabine-induced JNK activation through HMGB1 knockdown	[1,24,61–70]
Metabolism and Immune escape	Regulate lipid metabolism through MEX3C Enhance immune response by suppressing PD-L1	[71–74]

Abbreviations: AP-1, Activator protein 1; AKT, Akt strain transforming; JIP1, JNK-interacting protein 1; FAS, Fas Cell Surface Death Receptor; TNF, Tumor necrosis factor; JNK, c-Jun N-terminal kinases; p21WAF1, cyclin-dependent kinase inhibitor 1; TGF- β 1, Transforming growth factor beta 1; SOD, Superoxide dismutase; Bcl-2, B-cell lymphoma 2; HMGB1, High mobility group box 1 protein, also known as high-mobility group protein; MEX3C, Mex-3 RNA Binding Family Member C; PD-L1, Programmed death-ligand 1.

C. Apoptosis signal-regulating kinase 1 (ASK1) mediates TNF- α , and oxidative stress activates JNK/p38 and apoptosis. Besides, TNF- α regulates the apoptosis signaling pathway through the JNK/p38 pathway.⁴⁴

Besides TNF- α , reactive oxygen species (ROS), such as H₂O₂, also activate JNK and p38.⁴⁵ ROS can severely damage DNA, leading to apoptosis. In human BC cells, sanguinarine (a benzophenanthridine alkaloid isolated from plants belonging to the Papaveraceae family) activated JNK in a ROS-dependent manner. However, treating these cells with a JNK inhibitor did not reverse the sanguinarine-induced cell death. Similarly, ROS-induced JNK activation was reported in T24, EJ, and 5637 cells.⁴⁶ In T24 cells, vitamin K2 induced mitochondria-related apoptosis via ROS-induced JNK/p38 MAPK signaling pathway activation. Vitamin K2 induced cytochrome C release from mitochondria to the cytosol and turned on the caspase cascade, resulting in mitochondria-related apoptosis.⁴⁷ In addition, actein strongly activated p38 and JNK by phosphorylation and inactivated autophagy-related proteins, such as AKT/mTOR.²

Furthermore, JNK affects apoptosis by regulating TGF- β 1 in urological, prostate cancer (PC3), and BC (T24) cells. TGF- β 1 participates in the apoptotic process of various cell types. In PC3 and T24 cells, it activates JNK and other stress-activated kinases, and JNK acts as a direct tumor suppressor on invasive prostate cancer and BC cells by inducing apoptosis and inhibiting cell proliferation.⁴⁸ Besides TGF- β 1, AATBC (apoptosis-associated transcript in bladder cancer, also known as LOC284837) down-regulation modulated JNK activity and affected BC cell apoptosis. Additionally, the JNK inhibitor SP600125 attenuated the pro-apoptotic ability of AATBC down-regulation, clearly indicating that AATBC modulates BC cell death through JNK signaling.⁴⁹ Cordycepin, an organic component found in garlic, activated JNK by phosphorylation, causing T24 cell apoptosis. It also inhibited cancer cell growth and p21WAF1-mediated G2/M phase cell cycle arrest.³⁰ JNK inhibition suppressed cleaved caspase-3, poly-ADP ribose polymerase, caspase-8, and caspase-9 in actein treated BC cells. Actein triggered autophagy and apoptosis by cleaving caspase-3, PARP (Poly (ADP-ribose) polymerase), caspase-8, and caspase-9. N-acetyl cysteine (NAC) significantly reversed the expression of apoptosis-related proteins. Thus, JNK plays critical roles in the apoptosis process in cancer cells, acting both as an anti- and pro-apoptotic protein by mediating FAS, TNF, p21WAF1, and TGF- β 1.

Metastasis (Migration and Invasion)

Metastases are responsible for a considerable part (nearly 90%) of the yearly worldwide cancer-associated deaths. Metastases come from cancer cells escaping the primary tumor mass and colonizing other body parts.^{50,51} Metastases occur when cancer cells acquire migratory and invasive capabilities⁵² because of basement membrane and extracellular matrix degradation. Extracellular matrix hydration through matrix metalloproteinase-2 (MMP-2) and MMP-9 secretion is critical in the metastasis process.^{53,54} Cell migration implies multiple processes: cell-cell adhesion loss, membrane protrusion in the direction of movement, de-adhesion from the extracellular matrix, forward re-adhesion, and actin cytoskeleton contraction to drive the cell body forward.

Less than 30% of all BC patients are diagnosed with MIBC, the most life-threatening BC type lacking effective treatment options. At the molecular level, MIBC is heterogenous, with genomic instability and a high genomic mutation rate.⁵⁵ JNK participates in tumorigenesis, notably in the metastasis and invasion of multiple cancers.^{56–59} In gastric cancer cells, JNK regulates fascin1 expression through TGF- β 1 and the ERK (extracellular-signal-regulated kinase) signaling pathway. Specific MAPK signaling pathway inhibitors PD98059 (ERK inhibitor) and SP600125 (JNK 1/2/3 inhibitor) suppressed fascin1 expression.⁵⁶ In isoliquiritigenin-treated prostate cancer cells, JNK regulated cellular invasion and migration ability. SP600125 treatment suppressed uPA (Urokinase-Type Plasminogen Activator), VEGF (Vascular endothelial growth factor), MMP, and TIMP-1 (Tissue inhibitor matrix metalloproteinase-1) secretion and DNA binding activity.⁵⁷ In colon cancer cells, JNK modulated cancer progression and metastasis via epithelial-mesenchymal transition. Chemokine ligand 7 (CCL7) interacts with CC chemokine receptor 3 (CCR3), promoting cellular proliferation, invasion, and migration via the ERK and JNK signaling pathways.⁵⁸ In osteosarcoma cells, nobiletin exerted anti-migratory effects through the ERK and JNK signaling pathways. Cotreating U2OS and HOS cells with nobiletin and ERK and JNK inhibitors suppressed DNA the binding activity of NF- κ B, cAMP response element-binding protein, and specificity protein 1 (SP-1). In addition, the co-treatment reduced the migration and invasion ability of U2OS cells.⁵⁹

JNK also acts as a key migration and invasion regulator in BC. Metastatic cells express higher JNK levels than non-metastatic cells. Superoxide dismutase 2 (SOD2) activates JNK, and SOD2 inhibition promotes migration and invasion in T24 cells. SOD2 is a critical factor in BC cell migration regulation. It reduces CDC2 and Rac1 protein expression and decreases migration by inhibiting JNK activation in T24 cells.⁵¹ Programmed cell death 4 (PDCD4) and SRY (sex determining region Y)-box 2 (SOX2) also modulate JNK activation.^{60,61} PDCD 4 is a tumor suppressor localized in the nucleus and involved in tumor progression and prognosis in various human cancers. PDCD 4 inhibited human BC cells invasion and reversed the epithelial-mesenchymal transition by activating the JNK/c-Jun signaling pathway.⁶⁰ Cheliensisin A, a styryl-lactone isolated from *Goniothalamus cheliensis* Hu, inhibited human BC cells by activating the MAPK/JNK/c-Jun cascade and increased microRNA 200c (miR-200c) levels via SOX2 protein translation inhibition.⁶¹ These results indicate that JNK promotes invasion and migration—and, therefore, metastasis—via miR-200c and SOD2.

Autophagy

Autophagy (meaning “self-eating” or “self-digestion”) is a process discovered more than 40 years ago. It consists in capturing and degrading intracellular components to maintain cellular homeostasis; autophagy defects can lead to various diseases, such as cancer, aging, or lysosomal disorders. Autophagy protects cells from endoplasmic reticulum stress, ontological development, microbial infection, and diseases involving protein aggregation. It starts with the formation of a double-membrane vesicle (known as an autophagosome) near the cargo macromolecules (organelles or regions of the cytosol) under cellular stress conditions, such as nutrient deprivation (caloric restriction), oxidative stress, hypoxia, protein aggregation, and molecular toxicity.⁶² First, stress inactivates mTOR, initiating ATG (autophagy-related gene) 1 (an Ulk1 and Ulk2 homolog) kinase activation. Next, Atg1/Ulk1–2 activation induces Atg13 and FIP200 phosphorylation and Ulk (Unc-51 like autophagy activating kinase) proteins autophosphorylation. The activated and phosphorylated Atg13-Ulk-FIP200 (focal adhesion kinase family-interacting protein of 200 kDa) complex then recruits other Atg proteins, forming an autophagosome. Autophagosomes then fuse with lysosomes to form autophagolysosomes, and proteases degrade their components. Autophagosomes can be named according to the targeted organelle. For instance, a phagosome targeting mitochondria is a mitophagosome, and one targeting the peroxisome is a pexophagosome. For lysosome degradation, selective autophagy (or chaperone-mediated autophagy) occurs. In this case, the lysosome fuses with targeted proteins within the cytoplasm.

The role of autophagy in cancer remains unclear and somewhat controversial.^{63,64} mTORC2 indirectly suppresses autophagy by activating mTORC1. Previous studies reported that mTORC1 inhibition increases the autophagic reaction.⁶⁵ LC3B (1A/1B-light chain 3) and p62 are widely used autophagy markers. During autophagy, LC3B-I (the cytosolic form) is converted to LC3B-II (the lipidated form) and becomes an integral part of the autophagosome membrane.⁶⁶ JNK is one of the regulators of autophagy inducers in diverse cancers.^{67,68}

In ovarian cancer, neferine induced autophagy by forming autophagosomes and converting LC3B-I to LC3B-II. Moreover, neferine activated the p38 MAPK and JNK signaling pathways. In addition, JNK and p38 MAPK specific inhibitors attenuated neferine induced LC3B-II accumulation in A2780 and HO8910 cells.⁶⁹ In BC cells, epirubicin, an anthracycline drug, induced JNK phosphorylation, leading to Bcl-2/Beclin-1 complex breakdown and autophagy initiation. Tea polyphenols suppressed epirubicin-induced JNK-mediated autophagy through the JNK/Bcl2 (B-cell lymphoma 2)/Beclin-1 signaling pathway.⁷⁰ Furthermore, blocking JNK suppressed the autophagic reaction and increased apoptosis. In T24 and BIU-87 cells (human BC cell lines), HMGB1 (High mobility group box 1 protein) knockdown attenuated gemcitabine-induced JNK and ERK activation. Gemcitabine affects BC cell apoptosis and induces a cytoprotective autophagic reaction that involves HMGB1-mediated JNK and ERK signaling pathway activation.¹ Besides, activated JNK inhibits gemcitabine-induced apoptosis via an autophagy suppression mechanism. A JNK inhibitor effectively blocked gemcitabine-induced autophagy by suppressing LC3B-II.²⁴ Thus, JNK regulates autophagy through Bcl, Beclin-1, and HMGB1.

Regulation of Tumor Cell Metabolism and Immune Escape

Genome instability and mutations in oncogenes and tumor suppressor genes are enabling characteristics of cancer.⁷¹ Mex-3 proteins are associated with numerous cancers. For instance, MEX3C (Mex-3 RNA Binding Family Member C) is related to fatty acid metabolism in BC through the MAPK/JNK signaling pathway. MEX3C overexpression increases the

accumulation of lipids and triglycerides in BC cells.⁷² As cancers grow in the host, immune escape occurs as the final phase of cancer immunoediting, facilitating death signal modulation and escape for cancer cells.⁷³ JNK plays a crucial part in the immune escape in BC by modulating PD-L1 expression. Inhibiting JNK suppressed PD-L1 and enhanced the immune response of BC.⁷⁴

Chemoresistance

Chemotherapy is the main treatment for most cancer patients, and BC is a chemosensitive malignant tumor. Several patients show positive responses at the beginning of treatment; however, repeating treatments may progressively become ineffective. This drug resistance is a significant obstacle to the successful cure of BC patients. Thus, identifying the chemoresistance mechanism is paramount to predict treatment outcome, develop effective chemotherapeutic agents, and cure BC patients. The poor prognosis and mortality of BC are mostly due to chemoresistance-related recurrence.⁶¹ Many cisplatin-resistant cancers seem unaffected by other chemotherapies. Therefore, chemotherapy resistance is a critical obstacle to BC treatment. Unfortunately, there is no consensus on how to manage cisplatin-resistant BC.⁷⁵ Inhibiting JNK can increase the sensitivity of hepatocellular carcinoma cells to cisplatin. Cisplatin-resistant hepatocellular carcinoma cells overexpress the MDR1 (Multidrug resistance) gene, encoding for the drug efflux protein Pgp (P-glycoprotein 1). In addition, this acquired resistance involved JNK over-activation. These results indicate that the MDR1 gene is closely linked to cisplatin resistance via the JNK signaling pathway.⁷⁶

In T24 cells, JNK down-regulation promoted mitomycin C chemoresistance by decreasing p53 stability. JNK2 protects p53 from MDM2 (Murine double minute 2 homolog)-mediated degradation by phosphorylating p53 on Thr81. Moreover, JNK2 down-regulation attenuated mitomycin C-induced BC cell death.³⁹ Thus, the activity of JNK critically affects chemotherapy efficacy by regulating p53. However, the role of JNK in cancer chemoresistance remains controversial.

Conclusions

JNK signaling pathway research has made major advances in recent years. The current paper provides a comprehensive overview of the relationship between JNK and BC. BC is a global burden, and MIBC treatment remains a major challenge because of the migratory and invasive characteristics, deregulated cell proliferation, chemoresistance, and cell death evasion of cancer cells. This study reports the involvement of the JNK signaling pathway in BC. The JNK signaling pathway is deeply associated with many cancer growth factors. For instance, AKT-mediated JNK activation promotes tumorigenesis; however, JNK, as a double-edged sword, can also suppress tumorigenesis. As a tumor suppressor, activated JNK initiates apoptotic signaling, killing cancer cells.

In metastasis, JNK modulates diverse factors like PDCD4, micro RNAs, and SOX2. JNK also regulates the chemosensitivity to multiple anticancer drugs. Additionally, the JNK signaling pathway manages autophagy-related genes maintaining homeostasis. The mechanisms involving JNK in autophagy and cancer need deeper research. Furthermore, inhibiting JNK significantly increases cisplatin sensitivity. Based on these reported papers, JNK is one of important molecules in BC, since JNK is involved in many categories (tumorigenesis, cell proliferation, metastasis, autophagy, chemoresistance, metabolism, and immunity of cancer). The current body of knowledge shows that targeting the JNK pathway could lead to the discovery of new therapies and biomarkers; however, the present study highlights the necessity of further investigating the mechanisms linking the JNK signaling pathway and tumorigenesis, cell proliferation, metastasis, chemoresistance, and autophagy in BC.

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Disclosure

The authors declare no conflict of interest.

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