

# Aberrant PI3K Signaling Pathway in Urinary Bladder Cancer



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## Abstract

In India UBC is the fifth most common cancer in men. UBC is categorized into non-invasive and muscle-invasive types. Recurrence and multifocality are the two common features of UBC. PI3K pathway is known as the survival pathway and it inhibits the apoptotic proteins. Some studies have revealed its potential role in bladder cancer progression and survival. In UBC this pathway is constitutively expressed. The mutations in downstream proteins of PI3K pathway include PTEN, PI3KCA, Akt and TSC1. These mutated genes are responsible for the severity of the disease.

**Keywords:** Bladder cancer; PI3K; Akt; mTOR; PTEN; Cell cycle inhibitors; Apoptosis; Cell signaling

**Abbreviations:** UBC: Urinary Bladder Cancer; PI3K: Phosphatidylinositol 3-kinase.

## Introduction

Urinary Bladder Cancer (UBC) ranks ninth among all cancers and is one of the common cancers worldwide with highest incidence in industrialized countries. According to American Cancer Society in 2015, there will be 74,000 (about 56,320 men and 17,680 women) new cases of UBC and 16,000 (about 11,510 men and 4,490 women) people will die of this disease in USA [1]. In India it is the fifth most common cancer among men with incidence rate of 5.8cases/100,000 person year according to Delhi based registry. But in females incidence is much lower (1.5cases/100,000 person year) [2]. It is an outcome of multi-factorial process that includes genetic and/or non-genetic risk factors, thus influencing the progression, angiogenesis, metastasis and invasion of the bladder cancer cells. Genetic risk factors include personal or family history of cancer, deletions on chromosome 3, 8, 9, 11, 13, 17 [3] and mutations in several genes such as CCND1 [4], FGF3 [4,5], FGF4 [4], GST-M1, NAT2 [5,6] HRAS [7,8], KRAS, NRAS, FGFR3, PIK3CA [8], PTEN [9]. While non-genetic factors include occupational exposure to carcinogenic substances like aromatic amines and polycyclic aromatic hydrocarbons [10,11], smoking habits [12,13], some drugs like diabetic medications [14] or chronic bladder

inflammation [15]. It has been found that both the genetic and non-genetic risk factors have cumulative effect in the occurrence of UBC like polymorphism in glutathione S-transferase and N-acetyl transferase gene in cigarette smokers modulates the risk [16,17]. UBC is pathologically classified into transitional cell carcinoma (90%) and the remaining (10%) into squamous cell carcinoma, adenocarcinoma, sarcoma and rare variety like small cell carcinoma [18]. Approximately 70-75% of UBCs [19] are non-invasive which are treated by transurethral resections but they have a tendency to recur and progress into invasive & metastatic carcinomas which limits the 5year survival rate to 69% [20]. The remaining 25-30% of UBCs [19] are muscle-invasive at the time of first detection but they become more aggressive & metastatic later which results in sharp depreciation of 5 year survival rate from 34% to 6% respectively [20]. Thus recurrence and multifocality are the two common features of UBC.

## Phosphatidylinositol 3-kinase (PI3K) signaling pathway

It is a significant cell signaling pathway that regulates various cellular functions like cell growth, proliferation and survival.

The two main features of PI3K pathway are anti-apoptosis and cell proliferation which are achieved by inhibition of apoptotic as well as cell division regulatory proteins respectively. But in a wide range of cancers this pathway is expressed continuously without its feed-back regulation. The various components of this pathway include PTEN, AKT, PI3K and mTOR which prove to be therapeutic targets in many Phase I clinical trials. Several studies have reported alterations in PI3K pathway in UBC. The mutation rates of genes in this pathway include PI3KCA (24% of superficial tumors) [8], PTEN (24–58% of high grade tumors) [9], AKT (2.7%) [21] and TSC1 (>50%) [22] gene. Thus it is worthwhile to study the cell signaling pathway which governs cell survival i.e. PI3K pathway. As recurrence and multifocality are the two common features of UBC therefore targeting PI3K pathway will be beneficial in reducing mortality rate.

## Discussion

UBC has high recurrence rate which necessitates researches to study its molecular pathogenesis and develop novel targets for effective treatment. As PI3K signaling pathway is involved in uncontrolled cell proliferation in UBC therefore it possesses potential for therapeutic target. The most common alteration of PI3K pathway include mutations in catalytic subunit PI3KCA, Akt and loss of PTEN. The mutation in PI3KCA has been found to be significantly associated with superficial tumors [8]. Akt activity remains elevated in bladder cancer cells as examined in UM-UC-3 and T24 cell lines [23]. Apart from mutations in genes micro-RNA too have role in targeting this pathway. It has been found that down regulation of microRNA-126 fails to inhibit PI3K pathway and thus promotes cell invasion in bladder cancer cell line [24]. The germline mutations in PI3K pathway have found to be predicting prognosis in higher stages of UBC. Chen M et al. [25] studied 20 genes of PI3K pathway out of which only three single nucleotide polymorphism of AKT2 rs3730050, PIK3R1 rs10515074, and RAPTOR rs9906827 genes were associated with the survival of UBC patients. PTEN is a tumor suppressor and regulates PI3K pathway. Few studies on immunohistochemistry have reported a decreased protein expression of PTEN in UBC [26]. Some bladder cancer cells uptake Bacille Calmette-Guerin while some are resistant to it. The uptake of BCG is mediated by PI3K pathway [27].

## Conclusion

From this review we conclude that PI3K pathway plays a crucial role in pathogenesis of bladder cancer. The alterations in this pathway will benefit in developing targeted therapy.

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