COMMENTARY

Elucidating the Role of *PIK3CA* in Early-Stage Bladder Tumorigenesis

*New Insights from a Novel Transgenic Mouse Model*

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More than 70% of bladder cancers are nonmuscle invasive bladder cancers.\(^1\) Despite the high prevalence of nonmuscle invasive bladder cancers, there are significant gaps in our understanding of the early stages of bladder tumorigenesis. A landmark study by Shuman et al\(^2\) addresses this critical knowledge gap, focusing on the role of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit \(\alpha\) (*PIK3CA*)--activating mutations, identified across different stages of bladder cancer as one of the most prevalent oncogenic mutations.

To investigate the role of *PIK3CA* mutations in urothelial carcinogenesis, the researchers developed a *Upk2-Cre*/*Pik3ca* mouse model, expressing one or two R26-*Pik3ca* alleles specifically in the urothelium. They crossbred R26-*Pik3ca* H1047R mice with *Upk2-Cre* mice, which express Cre recombinase specifically in the urothelium. The H1047R mutation was chosen because of its frequent occurrence as an activating mutation.

The *Upk2-Cre/Pik3ca* mice demonstrated increased levels of nuclear phosphorylated Akt and elevated phosphorylation of AKT at the T308 and S473 residues, indicative of persistent downstream signaling that led to hyperplasia and nuclear atypia of the urothelium. After confirming the functionality of these mutations, it was observed that mice with one or two alleles of H1047R mutated *Pik3ca* at 6 months had increased urothelial thickness compared with controls. Interestingly, these mice also showed high levels of forkhead box A1 (*Foxa1*) and peroxisome proliferator-activated receptor \(\gamma\) (*Ppary*), and low levels of keratin 5/6 (*Krt5/6*) and keratin 14 (*Krt14*), exhibiting a luminal profile that is similar to most early-stage nonmuscle invasive bladder cancers in humans.

Unexpectedly, *Pik3ca* mutant mice did not show increased susceptibility to N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) exposure, necessitating further studies to understand the impact of *Pik3ca* mutation on carcinogen susceptibility and urothelial regeneration following carcinogen-induced injury. Given the variability in susceptibility among different mouse strains to BBN-induced carcinogenesis, future studies will need to account for these differences.

Another surprising revelation emerged from the single-sample gene set enrichment analysis of human muscle-invasive bladder cancer (The Cancer Genome Atlas). Examining *PIK3CA* mutant tumors after adjusting for activating mutations in other *PIK3CA*-AKT pathway genes revealed no significant increase in pathway activation due to *PIK3CA* mutations. These data suggest that *PIK3CA* mutations potentially initiate pathway activation and urothelial tumorigenesis, but over time, the more aggressive muscle-invasive bladder cancers evolve to have less oncogenic addiction to *PIK3CA* mutations.

This important study has established a novel precancerous transgenic mouse model driven by a common activating *Pik3ca* mutation, highlighting the crucial need for models that simulate early-stage bladder cancer, especially those representing therapeutically actionable targets. By advancing our understanding of early bladder

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tumorigenesis, this research opens new avenues for the development of preventive and therapeutic strategies for bladder cancer.

Disclosure Statement

None declared.

References
