Expression of mutant *Pik3ca* in murine urothelial cells provides a novel model of early stage bladder cancer

Lauren Shuman MS, Hironobu Yamashita PhD, Thomas Wildermuth BS,
Xue-Ru Wu MD, Joshua Warrick MD, David DeGraff PhD

Background

Despite the fact that approximately 70% of newly diagnosed bladder cancers are non-invasive tumors with high rates of recurrence, non-invasive bladder cancer is significantly understudied. In part, the general lack of appropriate models to validate the contribution of specific molecular drivers in bladder tumorigenesis is a significant issue. Activating mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) are a frequent event in early stage bladder cancer, yet an *in vivo* model for understanding these mutations in bladder cancer is not available.

Methods

To address this gap, we have created a novel *Upk2-Cre/Pik3ca*^{H1047R} mouse model which expresses one or two copies of mutant *Pik3ca*^{H1047R} in a urothelial-specific manner. Experimental and genetic control mice were aged for 6 or 12 months, and bladders were collected for analysis. Western blotting and immunohistochemistry was used to confirm the functionality of mutant *Pik3ca* as well as to characterize urothelial expression differences.

Results

Mutant *Pik3ca* activity was confirmed by immunohistochemistry for phospho-Akt(Ser473). At 6 months of age, mice carrying one or two copies of mutant *Pik3ca* developed urothelial hyperplasia. While mice with one copy of *Pik3ca*^{H1047R} failed to progress to frank malignancy, activation of two copies of mutant *Pik3ca* resulted in the development of papillary bladder cancer at 12 months of age. Increased proliferation of bladder urothelium was confirmed by measuring urothelial thickness as well as immunohistochemistry for Ki67. Consistent with human papillary bladder cancer, immunohistochemistry also revealed high expression of luminal markers Foxa1, Pparγ, and Gata3, as well as low expression of basal markers Krt5/6 and Krt14.

Conclusions

These data provide evidence of the establishment and characterization of *Upk2-Cre/Pik3ca*^{H1047R} mice as a novel, clinically relevant model of non-invasive bladder cancer.