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PIK3CA Mutations in Bladder Cancer: A Brief Review

ABSTRACT

The Phosphoinositide 3-kinase (PI3Ks) pathway plays a crucial role in cell growth, proliferation and survival as part of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, which deregulation is related to a broad range of cancers. The best known genetic alterations are PTEN loss, AKT mutations and activating point mutations at PI3K. Mutations in PIK3CA, the gene encoding the p110α catalytic subunit of PI3K, were identified as novel mechanisms of inducing oncogenic PI3K signaling and have been reported in many human cancer types including urothelial tract. In this review, we summarize the current knowledge about the role of PIK3CA in bladder cancer and its potential practical applications.

INTRODUCTION: THE PI3K PATHWAY

Phosphoinositide 3-kinases (PI3K) are a class of enzymes that phosphorylate a series of membrane phospholipids playing a crucial role in cell growth, proliferation and survival as part of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, which deregulation is related to many types of cancer [1].

PI3K type A is an important second messenger of tyrosine kinase receptors (TKR) as EGFR, FGFR, PDGFR, IGFR and Her2 while type B is related to protein G receptors. Numerous growth factors, mitogens, hormones and nutrients promotes the generation of phosphatidylinositol triphosphate (PIP3) that activates the PI3K/AKT/mTOR pathway, while phosphatase and tensin homologue (PTEN) down-regulates the pathway by dephosphorylation of PIP3, preventing AKT activation (Figure 1). The best known genetic alterations of this pathway are loss of the tumor suppressor PTEN, amplification of genomic region containing AKT and activating point mutations at PI3K [1].

Activation of protein G receptors or TKRs recruit PI3K complex to the membrane via the p85 regulatory subunit [1,2]. PI3Ks are heterodimers comprised of a regulatory subunit (p85) and a catalytic subunit (p110); in quiescent cells, the regulatory subunit keeps the catalytic subunit in a low activity state. When p85 subunit binds to phosphorylated tyrosine, either directly or via insulin receptor substrate adapter proteins, it relieves the inhibition of p110α subunit. The activation of p110α subunit phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP_2) to phosphatidylinositol-3,4,5-trisphosphate (PIP_3), which is a critical second messenger that recruits AKT. PTEN antagonizes this process by dephosphorylating PIP3 so that it inhibits activation of AKT. When AKT is activated, the pathway continues to influence many cellular processes that promote cell cycle progression, cell growth, energy metabolism and resistance to apoptosis.

MUTATIONS IN *PIK3CA*

Activating mutations in *PIK3CA*, the gene encoding the p110α catalytic subunit of PI3K, were identified as novel mechanisms of inducing oncogenic PI3K signaling [1,2]. The mutations can occur in any of the four domains: the adaptor-binding domain (ABD), C2 domain, helical domain and catalytic domain. The hot spot mutations occur in the helical domain in exon 9 (E542 and E545) and in the kinase domain in exon 20 (H1047). Mutations in the *PIK3CA* gene have been reported in many human cancer types including breast, endometrium, colorectal, ovarian and urothelial tract (http://www.sanger.ac.uk/genetics/CGP/cosmic).

PIK3CA IN UROTHELIAL CARCINOMA

Urothelial carcinoma has an interesting and well characterized molecular profile in a way that low-grade, noninvasive tumors and high grade, muscle-invasive tumors progress through different pathways, which results in different biological behaviors. The formers show high frequency in *FGFR3* mutation, whereas *TP53* mutations are associated with muscle-invasive tumors [1]. Mutations in the PI3K pathway have also been identified, and these include mutations in *AKT1*, *TSC1, PTEN* and *PIK3CA* [1].

PIK3CA mutations in bladder cancer most commonly occur in the helical domain. This spectrum differs from what happens in other cancers, in which the most common mutation occurs in the kinase domain. A previous study showed kinase domain mutations to be dependent on p85 binding and, conversely, helical domain mutations to require RAS binding [1]. Platt et al suggest that the predominance of helical domain mutations in bladder tumors may be determined by selective pressures relating to the cellular context [8].

Significant proportion of bladder tumors harbor *PIK3CA* mutations, ranging from 13% to 27% [1–5], related to low-grade and non-invasive tumors, including papillary urothelial neoplasm of low malignant potential (PUNLMP). López-Knowles et al found *PIK3CA* mutations in 13% of urothelial carcinomas and in 26% of 43 cases of PUNLMP [7]. Other groups have confirmed this finding reporting 17% to 26% of *PIK3CA* mutations mainly in low grade, non-invasive (pTa) urothelial carcinomas [7–9]. Based on this, *PIK3CA* mutation has been studied as a possible new prognostic factor. Lindgren et al classified urothelial carcinoma in two groups defined by gene expression, and found that *PIK3CA* mutations are significantly more frequent in the subtype of tumor related to a better prognosis [14]. However, Kompier *et al* found that *PIK3CA* mutations are not independent predictors of tumor recurrence, tumor progression, or disease specific survival [9]. So, additional data are required before using this molecular characteristic as a prognostic marker in urothelial cancer.

In breast cancer, *PIK3CA* mutation has been related to resistance to Her2-target drugs as well as hormonal agents [15]. There is no data in the literature concerning *PIK3CA* mutation as a predictor of response to drugs in urothelial cancer.

The knowledge of the role of PI3K/AKT/mTOR pathway and *PIK3CA* mutations in the development of urothelial carcinoma opens a new window for cancer treatment. There are numbers of agents available that affect the PI3K pathway including monoclonal antibodies, tyrosine kinase inhibitors, PI3K inhibitors, AKT inhibitors, rapamycin analogs, and mTOR catalytic inhibitors. Also, multiple PI3K inhibitors are currently under development, including pure PI3K inhibitors, compounds that block both PI3K and mTOR pathways (dual inhibitors), pure catalytic mTOR inhibitors, and inhibitors that block AKT that could be included in the arsenal to treat bladder cancer in a near future.

CONCLUSION

The significance of *PIK3CA* mutation in urothelial carcinoma is still in debate. Although some studies found an association between the presence of the mutation and tumor grade, data are limited. The role of *PIK3CA* mutations as prognosticators of outcome or predictors of therapeutic response needs further evaluation. The development of new target drugs related to the PI3K/AKT/mTOR pathway opens a new window of opportunity to treat bladder cancer.

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