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Bringing target-matched PI3King from the bench to the clinic

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Increased signaling through the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway occurs in diverse malignancies.[1] In cancer, the PI3K/AKT/mTOR pathway can be activated by mutations in several oncogenes such as *PIK3CA*, *PIK3R1*, *AKT*, *TSC1/2*, *LKB1* and *PTEN* (**Fig. 1**). Most activating mutations occur in the helical or kinase domain of the *PIK3CA* gene.

Preclinical models demonstrated that mutations in *PIK3CA* have oncogenic potential and can also be associated with sensitivity to PI3K/AKT/mTOR inhibitors.[2-4] In a human non-small cell lung cancer (NSCLC) xenograft model, *PIK3CA* mutation H1047R was associated with response to the dual PI3K and mTOR kinase inhibitor BEZ235.[3] Similarly, breast cells with the same mutation demonstrated reduced proliferation compared with breast cells with wild-type (wt) *PIK3CA*.[4] In addition, early clinical data from histology-independent protocols suggested that *PIK3CA* mutations could be associated with sensitivity to therapies targeting PI3K/AKT/mTOR signaling in subsets of patients with advanced cancers. The reported response rate of these patients in early-phase clinical trials was approximately 30%, which is less than that with some other molecularly matched therapies, but significantly more than the traditional response rates of 4% to 6% observed in this patient population.[5]

Preclinical models also demonstrated that *KRAS* mutations can be associated with resistance to PI3K/AKT/mTOR targeted therapies. A human NSCLC xenograft model with a *KRAS* G12D mutation demonstrated resistance to the dual PI3K and mTOR kinase inhibitor BEZ235, but had a good response to the MEK inhibitor AZD6244 or combination of BEZ235 and AZD6244.[3] Similarly, several cell lines with simultaneous *PIK3CA* and *KRAS* mutations demonstrated relative resistance to the pan-PI3K inhibitor PX-866, whereas cell lines with a *PIK3CA* mutation only were sensitive to it.[2] Finally, colorectal cancer cell lines with simultaneous *PIK3CA* and *KRAS* mutations demonstrated resistance to the mTOR inhibitor everolimus, which was eliminated by restoration of wt *KRAS* status, and those observations were confirmed in a human colon cancer xenograft model.[4] These data are particularly interesting because patients with *PIK3CA* mutations and advanced cancers are twice as likely to have simultaneous *KRAS* mutations (34% vs. 21%, p = 0.047).[1] Of note, in early-phase clinical trials enrolling patients with advanced cancers with *PIK3CA* and *KRAS* mutations in codon 12 or 13, treatment with PI3K/AKT/mTOR inhibitors led to lower response rates compared with patients without simultaneous *KRAS* mutations (response rate of 0% vs. 23%, p = 0.046).[6]

It is also plausible that not all *PIK3CA* mutations equally predict response to PI3K/AKT/mTOR inhibitors. Interestingly, observations from early clinical studies demonstrated that patients with advanced cancer and a H1047R mutation have higher response rates to PI3K/AKT/mTOR inhibitors than patients with other *PIK3CA* mutations (38% vs. 10%, p = 0.018).[1,6]

Early clinical experience suggests that single-agent PI3K/AKT/mTOR inhibitors are seldom effective compared with combinations (response rate of 0% vs. 29%, p = 0.002; progression-free survival of 3.1 vs. 1.8 months; p = 0.004).[6] There are several possible explanations for this. First, tumor heterogeneity might play role. It has been demonstrated that DNA isolated from three different areas of a small breast cancer sample had three different results for *PIK3CA* status (H1047R, wild-type, E542K, respectively).[7] Second, preclinical experiments in cell lines with *PIK3CA* mutations demonstrated that sensitivity to single-agent inhibition can be dependent on BIM (a pro-apoptotic Bcl-2 family protein) levels, because low levels of BIM prevent cancer cells from undergoing apoptosis in response to targeted therapy but not to chemotherapy.[8] Third, activation of collateral pathways through *KRAS* or other proteins (MET, MYC, etc.) is not effectively abrogated by inhibition of the single pathway.

PIK3CA mutations do not seem to have a common taxonomy across diverse tumor types except for an association with *KRAS* mutations, at least in some tumor types.[1] However, therapeutic targeting with PI3K/AKT/mTOR pathway inhibitors in cancers with an activated PI3K/AKT/mTOR pathway demonstrated efficacy in preclinical and early clinical experiments; this has implications for cancer treatment, because many drugs targeting the PI3K/AKT/mTOR signaling pathway are currently in clinical development.

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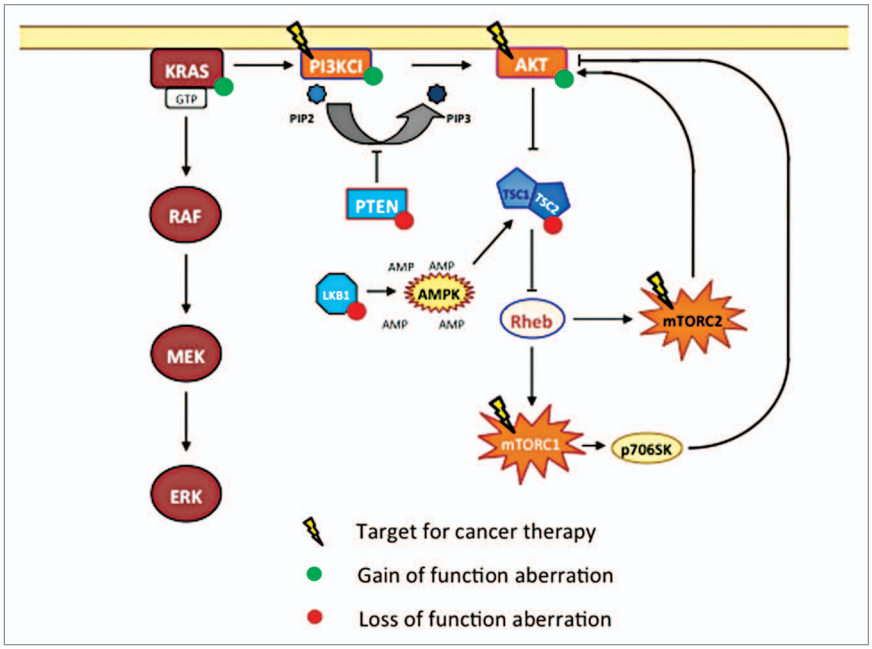

Figure 1. PI3K/AKT/mTOR pathway, targets for anticancer therapy and most common locations for gain-of-function aberrations (green) or loss-of-function aberrations (red).

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