Phosphatidylinositol-3-kinases (PI3K) were discovered more than 20 years ago, and it was soon apparent that they were members of a small family of kinases that included not only lipid kinases but also some protein kinases such as mTOR. The family is subdivided into 4 classes, and it was clear quite quickly that the 4 members of class I PI3K (p110γ, p110α, p110β, and p110δ) were activated downstream of receptor tyrosine kinases and G protein–coupled receptors, the latter being via allosteric effects of βγ subunits of heterotrimeric G-proteins (1). This results in increased production of the membrane lipid phosphatidylinositol 3,4,5-triphosphate (PIP3), which in turn activates a wide range of cellular responses that promote cell growth and reduce apoptosis. The importance of PI3K in such cell signaling pathways raised interest from cancer researchers, which increased greatly when it was found that more than 15% of all tumors contain activating mutations in the PIK3CA gene, which codes for p110α (2). In addition, PTEN—the phosphatase thought to be responsible for degrading PIP3—is a very common tumor suppressor gene. As a result, there has been intense activity in developing inhibitors of PI3K as potential anticancer drugs, and a number of such molecules are currently in clinical trials.

One important question is how each of the PI3K isoforms contributes to tumor development and whether isoform-selective therapies might be able to achieve therapeutic effects while minimizing potential side effects caused by inhibiting all isoforms. The most obvious target isoform is p110α. Indeed, inhibiting p110α alone can reduce the growth of tumors containing PIK3CA mutations (3), but this approach is not effective in all solid tumors. No oncogenic mutations have been identified in the other class I PI3K isoforms; however, p110β-selective inhibitors have proven effective in the clinic in certain forms of leukemia (4).

There is less evidence that inhibiting p110β might be therapeutically beneficial in treating cancer, although this isoform is interesting because it can be activated by both growth factor receptors and G protein–coupled receptors and its overexpression is capable of transforming cells (5). Knockdown of PIK3CB (coding for p110β) has been shown to block transformation of cells, although this was only observed in PTEN-deficient cell types (6). In agreement with this, reduction in functional p110β reduces the incidence of tumors in PTEN-deficient mice (7). Previous biochemical studies have also shown that the known p110β-selective inhibitor TGX-221 blocks activation of PKB/Akt in PTEN-deficient cells (6, 8). In this issue of Cancer Discovery, Ni and colleagues (9) now show that KIN-193 has very good pharmacokinetic properties and as such is suitable for in vivo inhibitor with a p110β-selective inhibitor as an antiproliferative agent, it would potentially minimize the side effects caused by pan-PI3K inhibitors and p110α-selective inhibitors (10). However, although sub-nM and 30- to 50-fold selective inhibitors of p110β enzyme have been described (6–8), they have not shown high antiproliferative potency in cell line assays, and, to date, no one has shown that a p110β inhibitor can be effective in an animal cancer model. Ni and colleagues (9) now show that KIN-193 has very good pharmacokinetic properties and as such is suitable for in vivo xenograft studies, in which they demonstrate for the first time that a small-molecule p110β inhibitor can block the progression of tumors derived from cell lines deficient in PTEN. The cytostatic effect is similar to that seen with p110α inhibitors in xenografts of PIK3CA mutant cells and the result adds to the growing evidence that inhibiting different PI3K isoforms has different effects in different tumor types.

However, there are still a number of questions remaining. For example, why are very high levels of KIN-193 required to achieve a cytostatic effect? Similar observations have been made with the use of p110β-selective inhibitors in other PTEN-deficient cell models (6, 8, 9, 11). One explanation for this is crossover with other targets for the drugs, as is suggested in the work of Ni and colleagues (9). In support of this, it has been shown that the combination of a p110β inhibitor with a p110α-selective inhibitor can together block activation of Akt in some PTEN-deficient tumors.
cell lines when neither inhibitor alone is capable of doing this (3). Together, this suggests that the effect of inhibiting combinations of class I PI3K warrants further investigation. Also, it is important to note that inhibition of p110β alone is not able to block activation of Akt in all PTEN-negative cell lines (3). The reason for this discrepancy with KIN-193 remains to be resolved, but it is notable that all the cell lines that responded to KIN-193 not only lacked PTEN but were also deficient for p53 (www.sanger.ac.uk/genetics/CGP/cosmic/), raising the possibility that more than simple loss of PTEN might be required to make cells responsive to p110β inhibitors. Although much remains to be learned, the beta-testing performed by Ni and colleagues (9) is likely to revive interest in p110β inhibitors as potential anticancer agents.

Disclosure of Potential Conflicts of Interest

Both P.R. Shepherd and W.A. Denny have served as consultants to Pathway Therapeutics.

Authors’ Contributions

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