Why is PI3K so hard?

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Hyperactivation of the PI3K-AKT-mTOR signaling cascade occurs in a plethora of cancer types. Both preclinical data and clinical studies suggest that this pathway is a valid pharmacological target in selected patient populations. However, intrinsic and acquired drug resistance, together with emergence of intolerable side effects, limits the use of PI3K inhibitors in the clinic. There are at least two reasons that potentially explain why PI3K is so hard to tackle pharmacologically. One is the triggering of adaptive responses following treatments with PI3K inhibitors that can circumvent the antitumor activity of these agents. Upon blockade of the PI3K-AKT axis, these compensatory pathways can still sustain cell viability and proliferation, bypassing the pharmacological pressure. Hypothesis-based combinatorial strategies may prevent these molecular feedbacks and increase the efficacy of PI3K inhibitors. Another intrinsic limitation of these drugs is their limited therapeutic window. Ways to overcome this problem are a better selection of patients who are more likely to respond to these inhibitors and a better way to deliver these compounds specifically to the tumor microenvironment.

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