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Perspective

PI3K(p110α) Inhibitors as Anti-Cancer Agents

Minding the Heart

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ABSTRACT

The central role of phosphatidylinositol 3-kinase (PI3K, p110α) signaling in allowing cancer cells to bypass normal growth-limiting controls has led to the development of PI3K(p110α) inhibitors. A challenge in targeting PI3K(p110α) relates to the diverse actions of the PI3K pathway in numerous cell types. Recent findings in mice deficient in PI3K(p110α) activity in the heart, demonstrate the critical role of this pathway in protecting the heart against pathological insults. Mice deficient in PI3K(p110α) displayed accelerated heart failure in response to dilated or hypertrophic cardiomyopathy. These results help explain the association of cardiomyopathy in cancer patients given tyrosine kinase inhibitors and raise concerns for the use of PI3K(p110α) inhibitors in cancer patients with cardiovascular risk factors. Interestingly, an inhibitor of the mammalian target of rapamycin (a downstream effector of PI3K), did not have adverse effects on the heart. A more complete understanding of the complex arms and interactions of the PI3K pathway will hopefully lead to the development of anti-cancer agents without cardiac complications.

THE PHOSPHATIDYLINOSITOL 3-KINASE SIGNALING PATHWAY

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate the hydroxyl group at position 3 of phosphatidylinositol (4,5) bisphosphate (PIP2) to produce the second messenger phosphatidylinositol (3,4,5) triphosphate (PIP3).1,2 PI3K isoforms are divided into three classes (I, II, III) and composed of several subunits.1,2 Class I PI3Ks are the best characterized and are subdivided into class IA and IB. Class IA PI3Ks consist of a catalytic subunit (p110α, p110β and p110δ) and a regulatory subunit (p85α, p55α, p50α, p56, and p55γ). They are activated by receptor tyrosine kinases e.g., insulin and insulin-like growth factor 1 receptors (IGF1R; Fig. 1). Other tyrosine kinase receptors like BCR-ABL and ErbB2, which new anti-cancer drugs target, also signal through the PI3K pathway.3,4 Class IB PI3K consists of the p110γ catalytic subunit and the p101 regulatory subunit and is activated by G-protein-coupled receptors (GPCRs; Fig. 1). Class I PI3Ks produce PIP3, a lipid second messenger that controls a wide range of cellular responses.5 Phosphatase and tensin homolog (PTEN) negatively regulates PI3K signaling by dephosphorylating PIP3 to PIP2. Akt is activated downstream of PIP3 to mediate physiologic processes. Substantial crosstalk exists with other signaling networks at all levels of the PI3K pathway.6

THE CENTRAL ROLE OF PI3K SIGNALING IN CARCINOGENESIS

It has been suggested that malignant growth requires six essential changes in cell physiology including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis.7 Mutations in the PI3K signaling pathway play critical roles in at least two of these oncogenic phenotypes (i.e., self-sufficiency in growth signals and evasion of apoptosis). Many inherited and acquired oncogenic mutations in PI3K signaling have been identified.8 For example, loss-of-function mutations of the tumour suppressor PTEN, are found in Cowden disease, a familial cancer syndrome, and a significant percentage of spontaneous cancers, leading to constitutive activation of class I PI3Ks.8,9 Activating mutations of PI3K(p110α) have also been associated with diverse forms of cancer at high frequency.10,11 Thus, uncontrolled activation of the PI3K(p110) pathway is a critical molecular mechanism by which cancer cells bypass normal growth-limiting controls. Consequently, the therapeutic potential of PI3K(p110α) inhibitors has generated great

KEY WORDS
phosphatidylinositol 3-kinase, cancer, heart, cardiomyopathy, receptor tyrosine kinase, mammalian target of rapamycin, Akt

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Inhibiting PI3K(p110α) in a Setting of Heart Disease

Cardiac function was not compromised in mice deficient in PI3K(p110α) under basal conditions, but the critical role of PI3K(p110α) in regulating physiological heart growth led us to believe that inhibiting PI3K(p110α) in the heart may have an adverse effect in the presence of pathologic stimuli. To test this hypothesis, we recently studied dnPI3K(p110α) transgenic mice in a setting of dilated or hypertrophic cardiomyopathy.\(^{26}\) DnPI3K(p110α) transgenic mice were genetically crossed to a transgenic mouse model of dilated cardiomyopathy (DCM)\(^{27}\) or subjected to pressure overload for 1 week (a surgically placed constriction of the ascending aorta increases the pressure work of the heart to induce hypertrophic cardiomyopathy).\(^{28}\) The transgenic mouse model of DCM has a mean lifespan of approximately 80 days in males. In a setting of reduced PI3K(p110α) activity, lifespan in the DCM model was reduced dramatically to ~40 days.\(^{26}\) In the model of pressure overload, cardiac function was significantly depressed in dnPI3K(p110α) transgenic mice but not control (non-transgenic) animals (Fig. 2A).\(^ {26}\) These data suggest that PI3K(p110α) is essential for maintaining cardiac function in response to a pathological cardiac insult and raises concerns for the use of PI3K(p110α) inhibitors in cancer patients with cardiovascular risk factors.

PI3K(p110α) induced “good” physiological cardiac growth also appears to inhibit “bad” pathological growth and to protect the heart from failing. In contrast to the accelerated heart failure observed in dnPI3K transgenics subjected to dilated or hypertrophic cardiomyopathy, caPI3K transgenic mice with increased physiological heart growth were significantly protected in these models.\(^ {26}\) Transgenic expression of caPI3K increased the lifespan of mice with dilated cardiomyopathy by 15–20%. The increase was comparable to that found using angiotensin-converting enzyme inhibitors, a mainstay of clinical heart failure management.\(^ {27}\) The caPI3K transgensics also displayed a blunted hypertrophic response to pressure overload and less pathology than control mice.\(^ {26}\)

To understand how physiological signaling/growth inhibits pathological growth, we isolated myocytes from non-transgenic, caPI3K transgenic and dnPI3K transgenic hearts. caPI3K myocytes showed a blunted response to GPCR stimulation whereas dnPI3K myocytes showed an exaggerated response.\(^ {26}\) These data suggest that PI3K(p110α) can inhibit signaling molecules downstream of GPCR, and explains how inhibition of PI3K(p110α) could accentuate the unhealthy response to pathologic stimuli.

Paradoxical Effects of Mammalian Target of Rapamycin (mTOR) Inhibition in the Heart

Inhibitors of mTOR, a downstream target of PI3K/Akt and effector of the growth response, are also being developed as anti-cancer drugs. Encouraging results from clinical trials of mTOR inhibitors have emerged.\(^ {25}\) Somewhat surprisingly, rapamycin, an inhibitor of mTOR, had an opposite effect on cardiac function as that observed in PI3K deficient mice (i.e., dnPI3K). Rapamycin improved cardiac function in a setting of left ventricular hypertension and cardiac dysfunction\(^ {30}\) (Fig. 2B). Furthermore, rapamycin reduced cardiac fibrosis in response to pressure overload,\(^ {31}\) whereas inhibition of PI3K(p110α) resulted in more fibrosis, which adversely increases the stiffness of the myocardium.\(^ {26}\) The opposite effects of reductions in PI3K or mTOR activity on cardiac function highlight the biological complexity of targeting this pathway. While these results seem

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Figure 1. Schematic of signaling cascades in the heart. PI3K is activated by receptor tyrosine kinases (RTK) and G-protein-coupled receptors (GPCRs). In the heart, PI3K activated by RTK induces physiological cardiac hypertrophy, whereas PI3K activated by GPCRs participates in the depressed cardiac function associated with pathological hypertrophy. IGF, insulin-like growth factor 1; Ang II, angiotensin II; ET-1, endothelin 1; mTOR, mammalian target of rapamycin; ERK, extracellular signal-regulated kinase; PKC, protein kinase C.
Figure 2. (A) Cardiac function in non-transgenic (Ntg) or dnPI3K transgenic mice in response to a moderate model of pressure overload or the sham operation for 1 week. Cardiac function was assessed non-invasively by echocardiography by measuring fractional shortening. Moderate pressure overload does not induce cardiac dysfunction in Ntg after a period of one week. Data taken from McMullen et al.26 (B) Cardiac function in Ntg mice subjected to a severe model of pressure overload or the sham operation for 1 week. Mice were then treated with an mTOR inhibitor (rapamycin) or vehicle for 1 week. The severe model of pressure overload induces cardiac dysfunction in mice after 1 week. *P<0.05, †P<0.05 compared to Ntg mice treated sham or vehicle. Data from McMullen et al.30

contradictory, it may be due to feedback mechanisms when inhibiting mTOR. Inhibiting mTOR has been reported to result in feedback mechanisms when inhibiting Akt (Fig. 1), resulting in increased or decreased Akt activation depending on the exposure time.32,33 Interestingly, Akt appears to be differentially regulated in the heart. Myostatin, an inhibitor of cardiac growth, inhibited GPCR induced Akt phosphorylation but not receptor tyrosine kinase induced phosphorylation.34 Finally, Akt1 and 2, the predominant isoforms in the heart may mediate separate physiologic processes induced by PI3K. Akt1 seems to effect physiologic growth and the anti-hypertrophic response to pressure overload, whereas Akt2 may effect anti-apoptotic pathways in the heart.35,36 Rapamycin might affect a very specific arm of the PI3K signaling pathway that leaves intact the salutory effects of PI3K activation in the heart.

THE PROMISE OF A GOOD LIFE AFTER THE CANCER IS CURED

An incredible demand is placed upon the mammalian heart to pump an entire lifetime without any significant mechanism to replace injured or dead cells. Therefore, a robust mechanism must exist to ensure survival of cardiac myocytes when they are stressed. It is not surprising then, that cancer cells and the heart share the PI3K pathway as a molecular survival mechanism. Considered in this context, the association of heart failure in cancer patients given tyrosine kinase inhibitors, like trastuzumab and imatinib, is understandable. Trastuzumab-related cardiomyopathy has been linked with downregulation of ErbB2 signaling, and imatinib mesylate is thought to promote apoptosis and heart damage by inhibiting the non-receptor tyrosine kinase c-Abl.37,38 Obviously, one should not have to trade one disease for another that often has a worse prognosis.

Since dnPI3K transgenic animals have normal cardiac function until stressed, it seems prudent to minimize stressors on the heart in cancer but experimental animal models offer the promise that adding an mTOR inhibitor may actually benefit the stressed heart.

In summary, recent findings in mice with deficient or supranormal PI3K(p110α) activity in the heart demonstrate the vital role of this pathway in normal growth and protection against pathologic stress. The data explain the association of cardiomyopathy in patients given tyrosine kinase inhibitors as cancer chemotherapy and raise the concern that future PI3K(p110α) inhibitors may cause an even higher incidence of heart failure. Fortunately, as the complex arms and interactions of the PI3K pathway are better understood, hope is raised that the deleterious cardiac complications can be avoided. Thus, patients may be offered the dual promise of a cure for their cancer and a good life.

References


