Phosphoinositide 3-kinase (PI3K, p110α) and adaptive growth in the heart

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PI3Ks are important signalling proteins in numerous cell types. PI3Ks catalyse the phosphorylation of lipids in the cell membrane, leading to the generation of second messengers such as phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P_3). There are three major classes of PI3Ks (classes I-III). These are determined based on amino acid sequence, homology of the lipid-kinase domains, and specificity for substrate binding. Class I PI3Ks consist of a 110kDa catalytic subunit (p110) complexed with a regulatory subunit, and can be divided into two subclasses: I_A and I_B. Class I_A PI3Ks (p110α, p110β and p110δ) associate with the regulatory proteins p85α, p85β and p55γ (as well as spliced variants of p85α), while p110γ (class I_B PI3K) is regulated by p101. p110α, β and γ are expressed in the heart and vasculature, while p110δ is found predominantly in leukocytes.

Transgenic and knockout mouse models have provided a powerful approach for understanding the specific roles of different PI3K isoforms in the heart. Studies in cardiac-specific PI3K transgenic mice have demonstrated that the p110α isoform of PI3K is critical for developmental and exercise-induced heart growth (physiological cardiac hypertrophy). Unlike pathological cardiac hypertrophy (heart growth in response to chronic pressure or volume overload e.g. hypertension, valve disease), physiological hypertrophy is characterised by normal cardiac structure and function, and does not lead to heart failure. Mice expressing a cardiac-specific constitutively active (ca) form of PI3K(p110α) displayed a 6.5 fold increase in PI3K(p110α) activity, which was associated with a 20% increase in heart size compared with control mice (non-transgenics). Mice expressing a dominant negative (dn) PI3K mutant displayed a 77% decrease in PI3K activity, and had 20% smaller hearts compared with non-transgenics. Importantly, caPI3K and dnPI3K mice showed no signs of cardiomyopathy (such as fibrosis) and had normal cardiac function and lifespan under basal conditions. dnPI3K mice showed a blunted response to exercise (a stimulus that induces physiological heart growth), but not to pressure overload (a pathological stimulus that leads to maladaptive heart growth, cell death and fibrosis), suggesting that PI3K(p110α) is critical for physiological, but not pathological, induced cardiac growth. These studies were later confirmed using a knockout approach. Deletion of class I_A PI3Ks from cardiac myocytes in mice led to a reduction in heart size that was similar in magnitude to that observed in dnPI3K mice. Knockout mice also showed a blunted cardiac hypertrophic response to exercise training.

Genetic mouse models have also highlighted the potential of targeting the PI3K(p110α) pathway in a setting of cardiac disease. This pathway is important for maintaining cardiac function and has anti-fibrotic and anti-apoptotic actions. In general, heart failure research and therapy has concentrated on identifying and inhibiting pathological processes. An alternative approach may be to identify and activate genes elevated during physiological cardiac hypertrophy, such as PI3K(p110α). Of note, given PI3K(p110α) has numerous actions in numerous cell types an on-going challenge is to find a means by which the PI3K(p110α) pathway can specifically be activated in cardiac myocytes.