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PI3K inhibitors as novel cancer therapies: Implications for cardiovascular medicine

Gavin Y Oudit
Universityof Alberta, Canada

The diverse effects mediated by PI3K/PTEN signaling in the heart clearly support an important biological and pathophysiological role for this signaling cascade. Phosphoinositide 3-kinases (PI3Ks) are a family of evolutionary conserved lipid kinases that mediate many cellular responses to physiological and pathophysiological stimuli. The PI3K signaling cascade ¬¬has fundamental roles in cell growth, survival and motility; increased PI3K activity is an important and common contributor to tumorigenesis and cancer progression. Class I PI3K can be activated by either receptor tyrosine kinase(RTK)/cytokine receptor activation (class IA) or G-protein coupled receptors (GPCR) (class I_B) leading to the generation of PtdIns (3,4,5)P_3 and recruitment and activation of Akt/protein kinase B (PKB), 3'-phosphoinositide-dependent kinase-1 (PDK1), or monomeric G-proteins and phosphorylation of a wide range of downstream targets including glycogen synthase kinase 3' (GSK3'), mTOR (mammalian target of rapamycin), p70S6 kinase, endothelial nitric oxide synthase (eNOS) and several anti-apoptotic effectors. Class IA (PI3Kα, βand δ) and class IB (PI3Kα) PI3Ks mediate distinct phenotypes in the heart under negative control by the 3'-lipid phosphatase PTEN (phosphatase and tensin homologue deleted on chromosome ten) which dephosphorylates PtdIns(3,4,5)P3 to generate PtdIns(4,5)P_2. PI3Kα, PI3Kγ and PTEN are expressed in cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells where they modulate cell survival, hypertrophy, contractility, metabolism and mechanotransduction. The PI_3K/PTEN signaling pathways are involved in a wide variety of diseases including myocardial hypertrophy and contractility, heart failure and preconditioning. Inhibition of PI3Kalpha/tyrosine kinase signaling has emerged as novel cancer therapies which can result in a growing epidemic of chemotherapy-induced cardiotoxicity.

Biography

Oudit completed his BSc, MD and Ph.D. at the University of Toronto where he completed his clinical training in internal medicine and adult cardiology. He graduated from the Clinician-Investigator program where he was a CIHR and Heart and Stroke Post-Doctoral Fellow. In 2008, he joined the University of Alberta as a staff cardiologist and as a clinician-scientist with the Mazankowski Alberta Heart Institute. Oudit has been the recipient of numerous awards and scholarships including the Distinguish Clinician-Scientist Award from the CIHR. He is a principal investigator on three grants including HSFC, CIHR and the AHFMR Clinician-Investigator Award and a co-investigator on three other grants. He has authored 5 book chapters, 105 publications in medium to high impact journals in both basic and clinical research. Oudit's very active participation in these key areas reflects his genuine commitment and dedication to the field of cardiology. His main research interest is in the fundamental mechanisms of end-stage heart disease with the aim to develop new therapies for heart failure.

gavin.oudit@ualberta.ca