Abstract: 3S

Cardiac protein phosphatases: more than an 'off' switch for protein kinases

Kate L Weeks

Department of Anatomy & Physiology, University of Melbourne, Parkville 3010

Heart failure continues to place an enormous burden on the Australian healthcare system. Improved understanding of the signalling pathways that contribute to cardiac remodelling and dysfunction during heart failure pathogenesis may lead to the development of novel therapies to treat this debilitating and deadly condition.

Protein phosphorylation is a fundamental mechanism regulating the heart's response to hemodynamic overload. Much research has focussed on the role of protein kinases (e.g. protein kinases C & D, Ca2+/calmodulin-dependent protein kinase II, G protein-coupled receptor kinases) in medicating cardiac hypertrophy, remodelling and dysfunction in cardiovascular disease settings. Relatively little is known about the function of protein phosphatases, which counteract the activity of protein kinases by dephosphorylating protein substrates. Our work has identified the protein phosphatase 2A (PP2A) family as an important family of signalling proteins that are responsive to neurohormonal stimuli. Within cardiac myocytes, regulatory subunits target PP2A phosphatase activity to specific substrates within distinct subcellular compartments to regulate processes involved in calcium handling, myofilament contractility, metabolism and gene transcription. Our research combines mouse models with omics approaches to determine the function of key PP2A species in the heart, and to explore the therapeutic potential of phosphatases as drug targets in preclinical models of heart failure.