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mTOR in growth and protection of hypertrophying myocardium

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Abstract

Cell growth and survival are two indispensable processes that must be tightly regulated to sustain compensatory cardiac hypertrophy under conditions such as increased hemodynamic load to the heart. Pathways crucial for accelerating protein synthesis in the hypertrophying heart need to be well coordinated with protective pathways in which removal of deleterious proteins is critical for the survival of cardiomyocytes. In this context, our studies show that β3 integrin signaling and the associated activation of nonreceptor tyrosine kinases offer cardioprotective effects in pressure-overloaded (PO) myocardium via triggering both mTOR/Akt-mediated cell survival pathways and the ubiquitin/proteasome-mediated cellular clearance of proapoptotic proteins. Therefore, a thorough understanding of β3 integrin/ubiquitination/cell survival axis would reveal potential therapeutic targets to sustain or enhance the cardioprotective effect and prevent/delay maladaptive changes in PO myocardium. Towards this goal, we used *in vivo* animal models of PO cardiac hypertrophy and an *in vitro* cell culture model of insulin-stimulated adult cardiomyocytes to show that rapamycin, which is commonly used as immunosuppressant in transplanted patients, at appropriate doses and intermittent treatment conditions, could augment mTOR/Akt-mediated cardiomyocyte survival signaling and the associated ubiquitin process. Our overall aim is to establish that β3 integrin expressed specifically in cardiomyocytes is responsible for the PO-induced transient ubiquitination that contributes to cardiomyocyte survival and then determine how altering the two mTOR complexes, mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin-insensitive), could change the dynamics of PO-induced Ub and the associated cell survival mechanism in PO myocardium.

Biography

Dr. Dhan Kuppuswamy is an Associate Professor of Medicine, Cardiology Division at the Medical University of South Carolina (MUSC), Charleston, South Carolina. As a faculty member for 19 years, he is investigating how signals generated by integrins and the associated tyrosine kinases contribute to the growth and protection of hypertrophying myocardium. He got his PhD degree at the University of Madras, India and obtained postdoctoral training at Washington University, St. Louis. As a faculty at MUSC, he is actively involved in graduate school, mentored several PhD students and postdoctoral fellows. He has published more than 45 papers and does editorial service to multiple journals.