Ca2+/Calmodulin-dependent kinase II delta B is essential for Cardiomyocyte Hypertrophy and complement factors gene expression, after TLR-4 stimulation *in vitro*

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Background: The immune system leads to interface between several other systems and tissues including cardiovascular system. Cardiac response may be initiated by Toll-like receptors (TLRs) [pathogen-related molecular (PAMPs) or damage-related (DAMPs)], through the complement system (SC) or by both combined responses. In the inflammatory process, C3a component of SC is released in large amounts and binds to the C3aR receptor, which we have already known that is influenced by the activation of TLRs, inducing the transcription of inflammatory factors through the translocation of nuclear transcription factor kappa B (NF-kB) to the nucleus.

Aims: The aim of this study was to evaluate the participation of the complement system in the development of TLR4-induced cardiac hypertrophy through CamKIIδ pathway in primary culture of cardiomyocytes.

Methods: Cells obtained by primary culture of cardiomyocytes from neonates Wistar rats. There were three main treatments: control cells untreated, cells treated with TLR4 agonists (HSP60 and LPS) and cells treated with siRNA of CamKIIδ prior to the TLR4 agonists treatment. Real time PCR were utilized to analyze gene expression of markers of cardiac hypertrophy, complement components, inflammatory cytokines and NF-kB.

Results: The mRNA expression of cardiac hypertrophy biomarkers (BNP and alpha-actin) showed a significantly increase when cardiomyocytes were treated only with LPS and HSP60 ($p<0.05$). It was reverted when the CamKIIδ was silenced. The same pattern was observed in the complement system components: C3 and Cfb mRNA expression were increased after TLR4-agonists treatments however it was attenuated after CamKIIδ silencing when compared to control groups. Even though the NF-kB mRNA levels are significantly increase after the LPS and HSP60 treatment, we could observe an attenuation after the CamKIIδ silencing but it did not revert the expression to similar to control group ($p<0.05$). Concerning the inflammatory cytokines (IL-6 and TNF-alpha), they have a significantly increase compared to control groups ($p<0.05$), however it did not change with the siRNA treatment.

Conclusion: We show that stress stimulus induced by HSP60 promotes cardiomyocyte hypertrophy, accompanied by initiation of inflammatory response via complement system. Whereas silencing CaMKIIδ is sufficient to prevent the hypertrophic growth and i it is not to prevent the inflammation. Findings presented here complement actual understanding on CaMKII mechanisms behind inflammation mediated cardiomyopathies.

Speaker Biography

Marcela Sorelli Carneiro Ramos is graduated in Biomedicine (2001), completed a PhD (2006) and Post-Doctoral (2008) in the Department of Cell Biology and Development of the Institute of Biomedical Sciences of the University of São Paulo. The research developed in this period, addressed the role of the Renin-Angiotensin System in the thyroid hormone-induced cardiac hypertrophy, as well the effect of thyroxine on global gene expression modulation. Nowadays, the research line aim to study the impact of the inflammatory response and immune system on the cardiovascular changes observed in the Cardiorenal Syndrome. She is an Associate Professor at the Federal University of ABC and has experience in cell and molecular biology, cardiovascular physiology, inflammation and renal failure.

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