GDF-11 prevents cardiomyocyte hypertrophy by maintaining the sarcoplasmic reticulum-mitochondria communication

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Growth differentiation factor 11 (GDF11) is a novel factor with controversial effects on cardiac hypertrophy both in vivo and in vitro. Although recent evidence has corroborated that GDF11 prevents the development of cardiac hypertrophy, its molecular mechanism remains unclear. In our previous work, we showed that norepinephrine (NE), a physiological pro-hypertrophic agent, increases cytoplasmic Ca2+ levels accompanied by a loss of physical and functional communication between sarcoplasmic reticulum (SR) and mitochondria, with a subsequent reduction in the mitochondrial Ca2+ uptake and mitochondrial metabolism. In order to study the anti-hypertrophic mechanism of GDF11, our aim was to investigate whether GDF11 prevents the loss of SR-mitochondria communication triggered by NE. Our results show that: a) GDF11 prevents hypertrophy in cultured neonatal rat ventricular myocytes treated with NE. b) GDF11 attenuates the NE-induced loss of contact sites between both organelles. c) GDF11 increases oxidative mitochondrial metabolism by stimulating mitochondrial Ca2+ uptake. In conclusion, the GDF11-dependent maintenance of physical and functional communication between SR and mitochondria is critical to allow Ca2+ transfer between both organelles and energy metabolism in the cardiomyocyte and to avoid the activation of Ca2+-dependent pro-hypertrophic signaling

pathways.