

# Ca<sup>2+</sup> Oscillation Frequency Decoding in Cardiac Cell Hypertrophy: Role of Calcineurin/NFAT as Ca<sup>2+</sup> Signal Integrators

FRANCESCA GRISAN<sup>1</sup>, VALERIE ROBERT<sup>1</sup>, MATILDE COLELLA<sup>2</sup> AND TULLIO POZZAN<sup>1,3</sup>

<sup>1</sup>*Dept of Biomedical Sciences, CNR Institute of Neurosciences, University of Padua, Italy*

<sup>2</sup>*Dept of General and Environmental Physiology, University of Bari, Italy*

<sup>3</sup>*Venetian Institute of Molecular Medicine (VIMM), Padua Italy*

**ABSTRACT.** Various conditions were used to investigate the importance of Ca<sup>2+</sup> signalling in triggering hypertrophy in neonatal rat cardiomyocytes *in vitro*. An increase in cell size and sarcomere reorganization were induced by treatment with receptor agonists such as Angiotensin II, aldosterone and norepinephrine, as well as by a small rise in medium KCl concentration, a treatment devoid of direct effects on receptor signalling. Aldosterone effects were prevented by spironolactone and by Angiotensin II receptor antagonists. While Angiotensin II caused a small, transient rise of [Ca<sup>2+</sup>], aldosterone had no acute effect on Ca<sup>2+</sup> handling. All these hypertrophic treatments increased the frequency of spontaneous [Ca<sup>2+</sup>] oscillations, caused nuclear translocation of transfected nuclear factor of activated T cells (NFAT) and increased the expression of an NFAT sensitive reporter gene. Cyclosporine A inhibited hypertrophy and NFAT translocation, but not the increased oscillation frequency. It is concluded that calcineurin-NFAT can act as integrators of the Ca<sup>2+</sup> signal and that they can even decode alterations in the frequency of rapid Ca<sup>2+</sup> oscillations.

**KEYWORDS.** Ca<sup>2+</sup> signalling, triggering hypertrophy, Angiotensin II, aldosterone, norepinephrine, KCl, Ca<sup>2+</sup> oscillations, NFAT, calcineurin

**Address for correspondence:** Prof Tullio Pozzan, PhD, Venetian Inst Molecular Medicine, Dept. of Biomedical Sciences, Via G. Colombo 3, 35129, Padua, Italy. Tel +39 049 7923-231, Fax : +39 049 7923-260

Email: tullio.pozzan@unipd.it