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AVVISO DI SEMINARIO

SEMINAR ANNOUNCEMENT

Cellular cAMP microdomains visualized in real time by fluorescent biosensors

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11:30 – 13:30

Monterotondo CNR Seminar Room, Building 21

Highlights

Cyclic adenosine monophosphate (cAMP) regulates numerous physiological functions by acting in subcellular microdomains. Cardiac actions of cAMP include but are not limited to the modulation of contractility, pathological growth (hypertrophy) and remodelling. This is achieved at least in part, by local pools of cAMP formed around calcium handling proteins such as L-type calcium channels located in T-tubules or caveolin-rich membrane structures as well as calcium release and reuptake units found in sarcoplasmatic reticulum. Recently, we developed targeted versions of a highly sensitive cytosolic cAMP Förster resonance energy transfer (FRET)-based biosensor Epac1-camps and expressed them in transgenic mice to study the regulation of local cAMP dynamics and their alterations in cardiac disease. Using these new tools and live cell imaging, we could uncover that cardiac hypertrophy and early heart failure are associated with relocation of the cGMP-regulated phosphodiesterases (PDEs) 2 and 3 between beta-adrenoceptor (beta-AR)-associated submembrane microdomains and between plasma membrane and sarcoplasmic reticulum. In addition, some cAMP-specific PDE4 isoforms were found to relocate between calcium release channels and the cytosol. This newly identified molecular mechanism allows some functional compensation, such as augmentation of catecholamine-stimulated cardiac contractility in early disease, or may even lead to arrhythmias originating from high cAMP levels at certain subcellular locations. Together with previously established beta-AR redistribution and changes in AKAP-PKA/PDE interactions, these alterations make up a series of microdomain-associated pathological changes. Those may be therapeutically addressed in the future to more specifically combat cardiovascular diseases.

Host: Prof. Fabio Mammano