Molecular mechanisms underlying cardiac muscle contraction and novel therapeutic approaches

Our lab aims to dissect the molecular mechanisms underlying cardiac diseases, to increase our knowledge about the function of the physiologic vs pathologic heart, and to develop novel and more effective therapeutic approaches for the treatment of the failing heart. To achieve this goal, we use multidisciplinary methodologies encompassing molecular and cellular biology, biochemistry, single- and multiple-cell functional assay, microscopy, nano- and aptamer technology, and experimental models of cardiac disease.

Molecular mechanisms for the regulation of cardiac muscle contraction: remodeling of calcium handling, signal transduction, and identification of new therapeutic drugs.

Maintenance of calcium (Ca\(^{2+}\)) homeostasis is critical for preserving the physiology of the heart. Complex mechanisms intervene in the regulation of intracellular levels of Ca\(^{2+}\) and of its compartmentalization between the cytosol and the sarcoplasmic reticulum (SR). Ca\(^{2+}\) release from the SR, the major intracellular Ca\(^{2+}\) store, to the cytosol is regulated through the so-called Calcium Induced Calcium Release (CICR) mechanism in cardiac cells, which triggers the release of Ca\(^{2+}\) from the SR to the cytoplasm through the ryanodine receptor (RyR). A close association between the L-Type Calcium Channel (LTCC) complex and RyRs is required for efficient CICR and is dependent on the density of LTCCs within the T-tubular invagination of the plasma membrane. The increase in free intracellular Ca\(^{2+}\) allows Ca\(^{2+}\) to bind to troponin C, initiating muscle contraction. This process is a major regulator of cardiac excitation-contraction coupling, and a major determinant for intrinsic properties of the heart for physiological roles. The LTCC, and thus Ca\(^{2+}\) handling, has also been associated with the modulation of cell structural integrity and gene expression, critical processes during heart development and physiology, which are deregulated in cardiovascular pathologies. As such, factors influencing the expression, half-life, subcellular trafficking, dynamics, and gating of LTCCs are key determinants for the function and structural integrity of cardiac cells both in physiology and disease. Several acquired and genetic based conditions of cardiac pathologies are causally associated to alterations of the LTCC protein density and function. A central focus of the lab is the in-depth understanding of the mechanisms underlying LTCC life cycle and function and to address fundamental questions related to translational applications of regulation of the LTCC and its molecular chaperone, Cavβ2, in cardiac physiology, development, and disease. Peptide- and aptamer-based tools for the in vitro and in vivo modulation of LTCC have been generated.

Biomimetic nanoparticle formulations for cardiac-specific drug delivery.

The difficulties associated with the use of conventional pharmacological therapies (i.e. drug instability, insufficient efficacy, collateral side effects due to unspecific tissue targeting, and invasive drug administration in end-stage disease) drastically challenge the therapeutic management of cardiac diseases. In fact, despite improvements in care, 1-year mortality rates for heart failure (HF) patients remain high, and up to 1 in 4 of HF patients die within 1 year, dependent on the stage of the disease at the time point of diagnosis. In addition, mortality rates in HF are high even for patients compliant with the best available treatments. As such, new approaches for safe, efficient, and cardiac-specific delivery of therapeutic drugs are strongly required. The lab is working for the development of innovative bioinspired and self-assembling nanoparticle formulations for drug delivery, which are i) biocompatible and biodegradable, ii) designed for crossing biological barriers, iii) specifically guidable to the target site, and iv) properly designed for a non-invasive therapeutic approach, which is “patient-friendly” (easy to administer) and thus facilitates the patient compliance (adherence to the treatment plan).
References:


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