Mechanistic examination of sarcoplasmic reticulum and mitochondrial interactions in cardiomyocytes during development and disease

Summary

In heart muscle cells, calcium plays a crucial role in regulating contraction and energy production by mitochondria, which are essential for mechanical work and maintaining ion balance. In adult mammalian cells, the primary source of calcium is the sarcoplasmic reticulum (SR). Recent research has indicated that the SR and mitochondria are physically connected and work together to regulate mitochondrial respiration. The precise interaction between these two components is vital for maintaining the heart's energy balance; however, many aspects of this regulatory pathway are still not well understood. This project aims to explore the mechanistic details of the SR-mitochondria interaction by examining the structural and functional changes in heart muscle cells that occur during development and disease. The primary focus of the candidate will be to conduct experiments in conjunction with mathematical modeling to describe the magnitude of calcium uptake by mitochondria in different age groups and diseases, as well as the role of SR in this process. The insights gained from this research will also be relevant to understanding heart diseases, as failing hearts often exhibit characteristics similar to those observed in the early stages of heart development.

Research field:	Applied physics and mathematics
Supervisor:	Dr. Martin Laasmaa
Availability:	This position is available.
Offered by:	School of Science Department of Cybernetics
Application deadline:	Applications are accepted between June 01, 2025 00:00 and June 30, 2025 23:59 (Europe/Zurich)

Description

Background

Cardiomyocytes undergo significant structural and functional changes during development, including a metabolic shift from glycolytic to oxidative phosphorylation and reorganization of calcium handling systems. In neonatal hearts, the sarcoplasmic reticulum (SR) network is sparse and primarily subsarcolemmal, while mitochondria are centrally located. This contrasts sharply with adult cardiomyocytes, where SR forms a continuous network closely associated with highly organized, crystal-like mitochondrial arrangements. In contrast to neonatal, in adults, the SR-mitochondria interaction enables local high calcium concentrations necessary for mitochondrial calcium uptake via the mitochondrial calcium uniporter (MCU), which has relatively low calcium affinity compared to typical cytosolic calcium levels. Therefore, the high local calcium concentrations generated near calcium release sites require close spatial proximity between SR and mitochondria. This physical coupling between SR and mitochondria is crucial for cardiac energy homeostasis. However, the functional consequences of this developmental reorganization on mitochondrial calcium handling remain poorly understood.

Research Objectives

There are three main research objectives:

- Examine how structural changes in SR-mitochondria organization during cardiac development affect mitochondrial calcium dynamics.
- Investigate whether close physical proximity between SR and mitochondria is required for effective calcium regulation of ATP production.
- Compare SR-mitochondria interactions in healthy versus failing cardiomyocytes to identify potential maladaptive mechanisms.

Approach

The study will utilize the natural structural and functional changes occurring during cardiac development as a model system. We will correlate structural organization with functional outcomes, examining both developing hearts (where SR-mitochondria connections are initially sparse) and failing hearts (which show similar disorganization to developmental stages).

Since the candidate will be working in an interdisciplinary laboratory, the candidate will have access to the experimental data measured on-site and will be given the opportunity to design and participate in the experimental work to support your research. We have an extensive range of equipment and well-established experimental protocols available in the laboratory, including biochemical and single-cell microscopy approaches.

Expected Impact

This research will advance our understanding of cardiac physiology and potentially identify new therapeutic targets for heart failure treatment by elucidating the mechanisms underlying SR-mitochondria communication and its role in cardiac energy homeostasis.

Responsibilities and (foreseen) tasks

- Development of experimental protocols to:
  - simultaneously measure calcium release from SR and uptake by mitochondria in cardiomyocyte;
  - determine effect of calcium on ATP synthesis in mitochondria.
- Develop mathematical models to gain insight of calcium fluxes between SR-mitochondria and its role in ATP synthesis.
- Data analysis and fitting by the models
- Design of new experiments required to distinguish between possible alternative hypotheses
- Writing academic papers
- Presenting the results in international meetings
- Supervision of junior students
- Participation in the teaching of the courses given by the laboratory

Applicants should fulfill the following requirements:

- a master’s degree in relevant field
- a clear interest in the topic of the position
- programming in Python or C++
- excellent command of English
- strong writing skills (English) that are compatible with doctoral-level requirements
- capacity to work both as an independent researcher and as part of an international team
- capacity and willingness to provide assistance in organizational tasks relevant to the project

The following experience is beneficial:

- Experience with development of mathematical models
- Experience with solving numerically ODEs and/or PDEs
- Working knowledge of SQL
- Working knowledge of statistics and statistical software
- Working with cells

We offer:

- Fully funded 4-year PhD position in one of the largest universities in Estonia
- The chance to do high-level interdisciplinary research in a supporting environment
- Great opportunities for self-development
- Opportunities for conference visits, research stays and networking with globally leading research centers in the field

About the department

The Laboratory of Systems Biology is a part of the Department of Cybernetics, School of Science, Tallinn University of Technology.

The main aim of the laboratory is to study regulation of intracellular processes and understand functional influences of intracellular interactions.

We use interdisciplinary approaches to tackle questions in cardiac physiology. For that, we have formed a team of researchers with backgrounds in biophysics, biology, and applied mathematics/physics. As a result, we are able to approach scientific questions on different scales, from organ to molecular level, using combinations of different experimental and theoretical techniques. When needed, we find new ways to characterize the data, develop new mathematical models, build new hardware, and program it to carry out novel experimental protocols.

(Additional information)

For further information, please contact Assistant Prof Martin Laasmaa<martin@sysbio.ioc.ee> or visit https://sysbio.ioc.ee.

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