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Cell diversity and signalling in the cardiovascular system

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The special issue of *The Journal of Physiology* entitled **"Cell diversity and signalling in the cardiovascular system"** is the outcome of the 7th UC Davis Cardiovascular Symposium, which was held on 25 and 26 March, 2022 and brought together leading experts from around the world to share their insights on this important and rapidly evolving area of research. The symposium highlighted the critical role of cellular diversity in maintaining cardiovascular health, and the need to understand the complex interplay between cells and their signaling pathways in both health and disease. The special issue includes a white paper, a review, and six original research papers, as well as corresponding perspectives providing expert commentary and analysis of the latest exciting findings in this important field.

The white paper in this special issue provides a comprehensive overview of the state of the art in cell diversity research, highlighting key findings and identifying areas where more work is needed (Grandi *et al.*). The article examines the role of myocytes and non-myocyte cells in the heart and in the vasculature and how they interact with other cell types to maintain normal heart function. A perspective article (Kass) highlights the significance of the white paper in surveying the key cell types and signaling pathways involved in cardiovascular function, the complexity that exists at the subcellular, cellular, and system levels, and the importance of technological advancements that enable the exploration of this diversity, which ultimately enhances our understanding of integrated cardiovascular function and dysfunction. As such, the white paper serves as a resource not only for investigators in the field of cardiovascular physiology but also for those seeking relevant references for reviewing the state of the art in this field, regardless of their area of specialization (Kass).

The topical review by Salameh *et al.* delves into the developmental progression of the human heart, with a specific emphasis on its structure, electrophysiology, metabolic profile, and contractile function (Salameh *et al.*). While making helpful comparisons with animal models of cardiac development, the article primarily focuses on human tissue samples, and thus offers a unique perspective and a detailed exploration of the field. The authors identify the limited number of publications from human tissue samples as a major limitation, highlighting the need for more comprehensive studies to better understand pediatric cardiomyocyte physiology. These studies are essential to expand our knowledge of normal cardiac physiology and pathophysiology and will help to improve clinical care by guiding the development of age-appropriate treatment strategies for cardiac disease (Salameh *et al.*).

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The six original research papers in this special issue tackle a wide range of topics related to cell diversity in the cardiovascular system, from the identification and characterization of novel interactions of signaling pathways and cell types in cardiovascular disease and arrhythmia to the role of subcellular and ionic processes in modulating cardiovascular responses to stressors. These papers provide insights into the complex and multiscale landscape of the heart and blood vessels, shedding light on the mechanisms underlying both physiological and pathological processes.

Chowkwale *et al.* introduce a computational framework that enables the modeling of cellular dynamics and immune-fibroblast interactions in the context of myocardial infarction (Chowkwale *et al.*). Through calibration and validation against existing datasets from mice, the model successfully predicts several critical biological parameters related to cardiac wound healing, such as cytokine secretion, phagocytosis, and cell content. Moreover, the framework is utilized to investigate the factors that contribute to inflammation onset and resolution. Model predictions establish a novel concept of inflammation-fibrosis coupling: the study's key findings highlight intriguing connections between cardiac infarct size, neutrophil content, and collagen deposition, with an IL-1beta-mediated mechanism implicated in these interactions. These mechanisms can be further explored experimentally and provide rationale for designing new therapeutics to improve the response after myocardial infarction. Indeed, the proposed modeling framework offer promising prospects for a range of future experimental and joint modeling-experimental investigations.

Zhang *et al.* developed a rigorously validated multi-scale model that simulated the electrical activity and calcium signaling in human atrial myocytes. The work provided quantitative insights into the crucial role of cardiac cell architecture (i.e., the transverse-axial tubular system) in regulating cardiac function and its potential impact on atrial arrhythmogenesis (Zhang *et al. a*). The computational framework further allowed for the investigation of various concomitant disease-associated factors, such as changes in ion channel distribution and remodeling, and their interaction with transverse-axial tubular remodeling (Zhang *et al. b*). This is an area of active investigation in the field, as the cardiac cell ultrastructure has been shown to play a critical role in the propagation of electrical signals in the heart and in the regulation of calcium handling and contraction during cardiac development (Manfra *et al.*, 2023), normal function, and pathophysiology. An accompanying editorial highlights quantitative and modeling approaches as essential to address several unresolved questions about the relative importance of various mechanisms involved in cardiac disease arrhythmia and their suitability as antiarrhythmic targets (Heijman & Dobrev).The notion that structural and electrophysiological remodeling are intricately linked is also nicely demonstrated in a recent paper in the *Journal* elucidating the role of cardiac fibrotic remodeling in repolarization heterogeneity and ventricular arrhythmia risk in aged spontaneously hypertensive rats (Khwaounjoo *et al.*, 2022). As suggested in the accompanying translational perspective, arrhythmia is likely to reflect the balance between macro-structure and functional control, whereby neural remodeling might play a key regulatory role of arrhythmogenesis in the setting of scars (Shivkumar *et al.*, 2023). In a computational study included in the special issue, Gibbs *et al.* explore the impact of graft-host connectivity and conductivity on graft-initiated arrhythmias in human pluripotent stem cell-derived cardiomyocyte grafts within the infarcted ventricle (Gibbs *et*

al.). The results suggest spatiotemporally heterogeneous graft–host coupling can create an electrophysiological milieu that favours graft-initiated host excitation. The findings of the study hold significance in the clinical domain as they shed light on regions with a greater risk of arrhythmia. The computational framework created for this study could serve as a guide for targeted graft implantation to avoid these high-risk areas.

Meier *et al.* present a novel approach to the computational modeling of cardiac electrophysiology by introducing a framework that integrates ion-channel trafficking, which is currently not accounted for in existing models (Meier *et al.*). The framework includes temperature- and drug-dependent effects on Kv11.1 (hERG) channel kinetics and trafficking, allowing for a more sophisticated modeling of channel behavior. This comprehensive approach reveals complex regulation of ventricular cardiomyocyte repolarization by mutations, temperature, and various medications affecting KV11.1 channel trafficking and gating across different time scales. The novel *in silico* trafficking framework marks a significant advance in modeling the physiology of ion channel function on the cardiac action potential, as highlighted in the accompanying editorial (Burgess & Delisle, 2023). This pioneering effort represents a crucial initial step that can serve as a potential framework for future studies on channel trafficking modulation and its role in arrhythmogenesis, extending beyond electrogenic proteins.

The study by Raph *et al.* describes a metabolic mechanism of mesenteric vasculature tone regulation, by specifically investigating the contribution of voltage-gated K^+ channel (Kv) to vasodilation of mesenteric resistance arteries induced by lactate and hydrogen peroxide (Raph *et al.*). The authors propose that lactate dehydrogenase-mediated synthesis of NADH in response to lactate cause increasing open probability of Kv1 channel. They further propose that both NADH and H_2O_2 increase Kv1 channel activity, with a synergetic effect that can be blocked by increasing the Kv1.5-subunit Kvβ1:β2 ratio. These results enrich the knowledge of intestine blood flow, local tissue adaptation, and general mechanisms regulating vessel contractility. In a broader context, this study brings critical new insights into how Kv1 channels can act as a hub integrating multiple redox signals to regulate mesenteric arteries diameter and blood flow.

Together, these articles offer a rich and diverse collection of approaches and a range of topics, including the role of cellular dynamics of immune-fibroblast interactions, the influence of ion-channel trafficking and expression on arrhythmia and vascular reactivity, the arrhythmogenic interplay between cellular ultrastructural and ionic remodeling, and the effect of graft-host interaction on arrhythmias. The articles emphasize the significance of cellular diversity in coordinating cardiovascular function and the importance of understanding the interplay between cells and crosstalk of various signaling pathways in health and disease. This is further highlighted in several recent articles in the *The Journal of Physiology*. For example, Dokshokova *et al.* showed that cardiomyocytes and sympathetic neurons participate in bidirectional cellular communication (Dokshokova *et al.*, 2022), whereby cardiomyocyte are directly involved in maintaining cardiac innervation and may participate in pathophysiologic denervation processes. In another article, proinflammatory T cell accumulation around both the aorta and mesenteric arteries has been shown to contribute to age-induced endothelial dysfunction and arterial stiffening (Trott *et al.*, 2021).

Several articles in the special issue demonstrate the power of computational modeling approaches to integrate experimental data at various spatial and temporal scales to quantitatively understand the mechanistic underpinnings of cardiac physiology and pathophysiology. Other recent examples in the *Journal* include the study of Gharahi *et al*, who developed mathematical models of *in vivo* myocardial hemodynamics to probe the mechanisms underlying vascular metabolic regulation (Gharahi *et al.*, 2022). In another recent article, theoretical models of optogenetic control cardiac myocytes were used for design optimization and technological enhancement (Pyari *et al.*, 2022). Along these lines, a recent review discusses how recent developments in computer vision algorithms and ratiometric techniques might be employed to overcome the limitations of conventional optical mapping with non-contracting hearts (Kappadan *et al.*, 2023). These novel approaches have the potential to provide valuable insight into the intricate mechanisms involved in mechano-electrical coupling. Further, advancements in *in vivo* measurements, such as new non-invasive optical coherence tomography-based approach to visualize and quantify microvascular structure and function (Sciarrone *et al.*, 2022), hold significance in that they provide powerful tools to better understand the intricate dynamics and characteristics of cardiovascular structure and function in living organisms.

The studies included in the special issue contribute to the growing body of literature on **“Cell diversity and signalling in the cardiovascular system”**. The articles shed light on new avenues for research and potential therapeutic targets for cardiovascular disease, and will help to advance our understanding of the fundamental mechanisms that govern cardiovascular health and disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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