Cardiovascular Mechanobiology - a Special Issue to look at the state of the art and the newest insights into the role of mechanical forces in cardiovascular development, physiology and disease

Editorial

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There has been much progress recently in the area of cardiovascular mechanobiology and this Special Issue aims at taking stock. This editorial gives context of the main motivation for this special issue as well a brief summary of its content.

Cardiovascular diseases (CVD) are the primary cause of mortality, and the disease burden is projected to grow because of sedentary lifestyles and an ageing society. Vascular diseases and especially atherosclerosis, if untreated, are the dominant underlying cause of CVD. Moreover, cardiac disease progressing to heart failure is the leading cause of death among cardiovascular diseases. Underlying genetic causes and mechanisms are progressively being uncovered, e.g. through Genome-Wide Association Studies (GWAS)(Lahm et al., 2021; Shah et al., 2020), metabolomics (Albert and Tang, 2018; Wang et al., 2019), proteomics (Lam et al., 2016; Mokou et al., 2017), (single cell) genomics (Samad and Wu, 2021) or multi-omics studies (Joshi et al., 2021; Li et al., 2020). However, there is still a gap in understanding that cannot be filled without considering the mechanical/physical signals and mechanisms in addition to genetic and chemical factors (Iskratsch et al., 2014; Ward and Iskratsch, 2020). Consequentially, there has been a surge in studies investigating the role of mechanical signals in the formation of the heart, or the onset and development of cardiovascular disease. The growing number of research groups dedicated to studying mechanical forces and mechanosensing mechanisms in the cardiovascular system suggests a further expansion in this area and gives hope for novel therapeutic approaches based on the research outcomes.

This Special Issue contains a series of review articles that discuss matters from engineering approaches, over computational methods, to clinical implications, to cover all important aspects of cardiovascular mechanobiology. It aims to update on the state of the art and the newest insights of this topic, especially since over the past decades it has become ever clearer that tissue mechanics regulate cardiac function and at the same time contribute to cardiac disease (also outlined in the introductory commentary by Michael Sheetz (Sheetz, 2021). Emig et al., discuss in their review the important parameters and methods to assess especially passive tissue mechanics *in vitro* or *in vivo* (Emig et al., 2021), while Swiatlowska et al. provide an up to date overview of techniques used to study *and* modulate the cardiovascular mechanobiology across the different scales, from single molecule to whole tissue scale (Swiatlowska and Iskratsch, 2021). Tissue mechanics is determined by both the extracellular matrix as well as intracellular components. The former is discussed in the review from Singh and Young, in which the authors focus on the cardiac nanoenvironment, interacting cardiomyocytes and platforms to study the nanoscale interactions (Singh and Young, 2021). On the other hand, Crocini and Gotthardt comprehensively review the intracellular side: especially the role of the sarcomere in active and passive tissue mechanics as well as its

potential as a target for therapeutic approaches for cardiac disease (Crocini and Gotthardt, 2021). The article from van der Pijl et al., further explores the N2B and N2A regions of the giant protein titin as major biomechanical and metabolic signalling hubs, in health and disease (van der Pijl et al., 2021). Solis and Russell expand to discuss how deformation of striated muscle proteins due to physical forces, as well as structural changes downstream of chemical signals are both integrated in muscle adaptation (Solis and Russell, 2021).
Sarcomere-generated forces are transmitted to neighbouring cells through highly organized intercalated discs (ID) located at the cell ends, which are also mechanosignalling hubs. Desmosomes that constitute an integral part of the IDs are further discussed by Zhang et al., bringing our attention to its non-canonical functions, such as the desmosomal cross-talk with electrical channels, link to protein degradation and inflammation (Zhang et al., 2021).
On the whole organ level, MacDonald and Quinn look at how cardiac pacemaking is regulated through sinoatrial node mechanosensitivity, 'membrane' and 'calcium-clocks' (MacDonald and Quinn, 2021).
Not only the scale, but also study models have been of great interest among the cardiac mechanobiology field. Induced pluripotent stem cells (iPSC) cardiomyocytes are routinely used in the lab environment and are a promising model system for drug testing, especially in the form of microtissues. However, obtaining mature iPSC cardiomyocytes still constitutes a major problem, which can be improved by precisely controlling the mechanical signals the cells are exposed to. An up to date overview of the different strategies is put together here by Carlos-Oliveira et al (Carlos-Oliveira et al., 2021).
With current progress in cardiac computational modelling techniques and future developments, this approach has been applied more broadly along with biological experimental data sets. Sharifi and colleagues elegantly outline computational models that simulate cardiac growth and myofiber remodelling, complementing the article with limitations and future perspectives (Sharifi et al., 2021).

Mechanoregulation is also a widely studied topic in the circulatory system. Wang and Valdez-Jasso take a closer look at the mechanical regulation in pulmonary arterial hypertension, thoroughly discussing recent studies of endothelial cells, smooth muscle cells and fibroblasts *in vitro, in vivo and in silico* (Wang and Valdez-Jasso, 2021). The review from Johnson et al, on the other hand discusses how mechanical forces affect the arterial smooth muscle cell cytoskeleton, which eventually projects on cellular phenotype and contractility (Johnson et al., 2021). From a bioengineering perspective, Nquyen et al., provide a detailed review of microfluidic platforms for studying the mechanobiology of human circulatory system (Nguyen et al., 2021), while Herault et al look at the role of miRNAs and their regulation into clusters and families in vascular mechanobiology (Herault et al., 2021).

Fitting to the topic of cardiovascular biology, this issue further includes a self-portrait of the journal Editor, Elisabeth Ehler, as part of the “meet the editor” series, in which she discusses her scientific upbringing, source of interest in (cardiac) muscle biology and her thoughts on mentoring and equality(Ehler, 2021).

We would like to thank all the authors of this Special Issue for their commitment, efforts and promptness in writing these exciting and timely reviews. We hope that together these will be helpful to everyone working in this area and further enhance the appreciation of the importance of cardiovascular mechanobiology in general.

Conflict of Interest Statement
The authors report no conflict of interest.

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