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Challenges in cardiac muscle physiology

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The beating heart muscle is an ever-intriguing sight. Be it an observation *in situ* during open-chest surgery, in the lab as a Langendorff perfusion experiment, or under the microscope as a twitching muscle or single cell, its dynamic nature demands attention of the observer. As such, it is not surprising that it was the subject of intense investigation since the dawn of physiology. Over the centuries, tools and techniques have undergone developments that now allow the investigation of not only the primary physiological output of cardiac muscle, i.e. the ability to contract and relax rhythmically, but also investigate the molecular and cellular events that lead up to force development. We can investigate electrical activity of tissues, cells, and single channels, we can investigate the mechanical activity at the ventricular, cellular, and even molecular level, and follow various biochemical events and ion movements during contractile cycles. Where we have made the greatest strides in the past centuries is to better understand the structure and function of the various proteins involved in bringing about this intriguing organ's function. We have developed the tools to make single amino-acid modifications, and study the resulting altered biochemical, mechanical, and electrical function. The new tools developed have however come at a price; while the more reduced approach allows for a better control of experimental conditions needed to carefully and unambiguously carry out the experiments, it also strips the reduced preparation of many of its interactors and governors, and as such the result of the molecular intervention of the organ system as a whole becomes hard, if not impossible, to assess. Herein thus lies our future challenge; how can we integrate the molecular intervention to change the components of the system with the assessment of change that is a specific result of the intervention in physiological function of the intact system. Clearly, transgenic mice or knock-out mice have fulfilled this role to a certain extend, and with much insight gained. However, significant differences between function and protein composition in mice versus human and the compensatory changes that occur during as a result of the genetic manipulation impose 2 important limitations on this tool. In the decades to come, we are expecting to see significant improvements in gene-delivery techniques that may overcome many of our current limitations to link an altered molecular composition directly to the resulting altered physiological function. Virus-mediated gene delivery, using a growing number of vectors and vector systems is emerging as a powerful tool to help us tackle the challenge. Multiple protein expression strategies, including overexpression, specific knock-down, and mutagenesis, in combination with emerging molecular tools such as siRNA's and organ-specific delivery vectors, are increasingly being used and further developed. The other side of the challenge is the assessment of altered function. Here too new techniques and methods are emerging to help us meet the overall challenge. Novel microscopy techniques are emerging, allowing us to observe functional processes in live cells and live tissue with greater spacial and temporal resolution. Other assessment techniques too are being increasingly employed, such as the ability to study *in vitro* processes under near-physiological conditions, whereas in the past these may have been performed under conditions remote from the normal *in vivo* condition. These techniques better allow the extrapolation of functional data to the *in vivo* situation, and facilitate the translational aspect of the findings.

In summary, the challenge of the field lies in how we are going to find better ways to link the molecular intervention tools that can change the components of the system to the assessment of physiological significance that is a specific result of such an intervention. Only if we can unambiguously link a molecular perturbation of the system to a change in function that is assessed under conditions functionally relevant to the system as a whole can we further make strides in understanding cardiac muscle function. The tools on both sides of the challenge, molecular intervention and assessment of function, are rapidly emerging, leading me to conclude that there are exciting times ahead in the area of cardiac muscle physiology.

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