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Cells in focus

Cardiomyocytes structure, function and associated pathologies

Elizabeth A. Woodcock [a,*], Scot J. Matkovich [b]

[a] *Cellular Biochemistry Laboratory, Baker Heart Research Institute, PO Box 6492, St. Kilda Road Central, Melbourne, 8008 Vic., Australia*
[b] *Department of Physiology and Cellular Biophysics, Center for Molecular Cardiology, Columbia University College of Physicians and Surgeons, 630 W 168th Street, New York, NY 10032, USA*

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Abstract

The heart is the first formed organ in the developing fetus. During fetal and postnatal development cardiomyocytes become terminally differentiated muscular cells that are connected end to end by gap junctions, allowing concerted contractile activity. The contraction–relaxation cycle of cardiomyocytes is orchestrated by cyclic increases and decreases in intracellular Ca^{2+} initiated by depolarization of the sarcolemma and sustained by Ca^{2+} release and re-uptake by the sarcoplasmic reticulum. When stressed, cardiomyocytes undergo hypertrophic growth and apoptotic responses in vivo as well as in cell culture models. Such changes predispose to heart failure in the longer term.

Keywords: Cell culture; Contraction; Hypertrophy; Heart Failure

Cell facts

- Cardiomyocytes are the cells responsible for generating contractile force in the intact heart.
- Specialized cardiomyocytes form the cardiac conduction system, responsible for control of rhythmic beating of the heart.
- Cardiomyocytes undergo enlargement (hypertrophy) in response to chronic demand for increased contractile force, but an inability to meet these needs leads to insufficient cardiac output for the demands of the whole organism (heart failure), one of the most common causes of death in the Western world.

1. Introduction

Cardiomyocytes within the heart are required to contract in unison in order to provide effective pump action that can ensure adequate blood perfusion of the various organs and tissues. This review will

* Corresponding author. Tel.: +61 3 8532 1255; fax: +61 3 8532 1100.
E-mail address: liz.woodcock@baker.edu.au (E.A. Woodcock).

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outline the properties of these cells that allow them to function under physiological conditions and how these responses are compromised under pathological conditions.

2. Cell origin and plasticity

The heart is the first organ to be formed in the developing embryo and for this reason cardiac abnormalities are major contributors to fetal death. Heart progenitor cells are observed soon after gastrulation in a region of the anterior mesoderm adjacent to the endoderm. Embryonic cardiomyocytes develop into a linear heart tube that subsequently undergoes rightward looping to initiate a primitive heart structure. Subsequent growth of the looped heart, together with septal development and the formation of the valves, yields the multichambered heart required for separation of the pulmonary and systemic circulations. Development of the two ventricular chambers is regulated at least in part by different combinations of transcription factors. Effective functioning of the heart requires that all parts of the separate chambers contract in unison and that the atria, which collect blood from the venous circulation, empty before the ventricles contract. This is achieved by an efficient conduction system that transmits electrical signals from the sino-atrial pacemaker node in the right atrium. Recent evidence points to development of this conduction network from precursor ventricular myocytes in response to neuregulins and endothelin-1 (Olson & Schneider, 2003).

A distinctive feature of adult cardiomyocytes is that two separate nuclei are present. At or around birth cardiomyocytes lose their ability to divide. Cardiomyocyte DNA synthesis is associated with cell proliferation (cytokinesis) during fetal life, and a second DNA synthesis phase occurring after birth (up to approximately neonatal day 3) is associated only with binucleation (karyokinesis without cytokinesis) (Soonpaa, Kim, Pajak, Franklin, & Field, 1996). After birth, cardiac growth involves increasing the size of the myocytes without substantial increases in cell number. Regulation of this process of physiological hypertrophy is currently not well understood, although some of the intracellular signalling pathways involved have been identified (Dorn & Force, 2005). Importantly, the low proliferative capacity of adult cardiomyocytes means that loss of working myocytes in the adult heart must be compensated by increased workload of the remaining myocytes, which will be discussed below. Despite these considerations there is now evidence that the heart retains some ability to regenerate. Adult hearts from human and mouse have been shown to contain a population of cells that appear to be cardiac stem cells. These can be stimulated to form all of the major cell types present in the functional heart, working myocytes, conducting myocytes, endothelial cells and vascular smooth muscle cells (Messina et al., 2004). It is conceivable that these resident stem cells allow some degree of cardiac regeneration throughout the aging process and after pathological insult.

Recently there have been attempts to regenerate cardiomyocytes from externally introduced stem cells, mostly derived from the bone marrow. Many different laboratories have shown functional improvements after infarct elicited by delivery of such cells. Nevertheless, it is not absolutely clear that such cells actually form functional myocytes and the possibility remains that the major functional benefit derives from stimulation of the endogenous stem cells resulting in angiogenesis and possibly myocardial regeneration, or perhaps beneficial paracrine stimulation of surviving myocytes (Dimmeler, Zeiher, & Schneider, 2005).

3. Functions

The primary function of the heart is to pump blood efficiently by virtue of an orchestrated contraction–relaxation cycle of the working myocytes. Regulation of contractility of the individual cardiomyocytes is achieved by a spatially defined program of ion channels and exchangers that accurately control Ca^{2+} entry into and out of the cell and the sarcoplasmic reticulum. The control of Ca^{2+} release, and therefore the regulation of contractility, is predominantly achieved via the electrical activity of the sarcolemma. The cardiac action potential is initiated by depolarization of the sarcolemma and sustained in the plateau phase by the activation of voltage-gated L-type Ca^{2+} channels ($I_{Ca,L}$) (Fig. 1). Ca^{2+} entry via these channels causes Ca^{2+} release from the sarcoplasmic reticulum (SR) mediated by intracellular calcium receptors generally known as ryanodine