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Review

# The physiological role of cardiac cytoskeleton and its alterations in heart failure ☆

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ABSTRACT

Cardiac muscle cells are equipped with specialized biochemical machineries for the rapid generation of force and movement central to the work generated by the heart. During each heart beat cardiac muscle cells perceive and experience changes in length and load, which reflect one of the fundamental principles of physiology known as the Frank–Starling law of the heart. Cardiac muscle cells are unique mechanical stretch sensors that allow the heart to increase cardiac output, and adjust it to new physiological and pathological situations. In the present review we discuss the mechano-sensory role of the cytoskeletal proteins with respect to their tight interaction with the sarcolemma and extracellular matrix. The role of contractile thick and thin filament proteins, the elastic protein titin, and their anchorage at the Z-disc and M-band, with associated proteins are reviewed in physiologic and pathologic conditions leading to heart failure. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters.



**Contents**



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## 1. Introduction

### 1.1. Heart failure

Heart failure (HF) affects over 15 million people in Europe and continues to increase, representing a major cause of hospitalization and death [1]. HF is a condition that it is characterized and clinically defined by the inability of the heart to sufficiently supply normal blood perfusion to organs and tissues as the end-point of several physiological, genetic and environmental abnormalities. Coronary heart disease accounts for ~70% of total clinical HF manifestations [2]. Other main causes of HF are hypertension (~10%), cardiomyopathies (~10%) and factors such as drug abuse, toxins and endocrine abnormalities (~10%) [1]. About half of the patients show near normal contractile function and often hypertrophied heart (HF with preserved ejection fraction; HFpEF) with abnormal diastolic function, which contrasts with the other half that present contractile dysfunction and a dilated heart (HF with reduced ejection fraction, HFrEF) and impaired diastolic function [1,3].

### 1.2. Cardiac remodeling and contractile dysfunction

During each heart beat cardiac muscle cells (cardiomyocytes) undergo changes in length and load. Diastole reflects the ability of the heart muscle to relax and fill with blood (preload). During the diastolic phase, cardiomyocytes are elongated or stretched. During systole, contraction and ejection of blood is forced against the arterial resistance/pressure (afterload) as a result of shortening of cardiomyocytes. Sustained wall stress as occurs during pathological conditions such as volume- and/or pressure-overload, ultimately reshapes cardiomyocytes and the extracellular matrix (ECM) resulting in remodeling of the wall geometry of the heart [4]. Eccentric remodeling of the heart is associated with replication of sarcomeres in series and lengthening of cardiomyocytes in order to accommodate a large increase in end-diastolic volume (EDV; volume-overload) and maintain LVEF [4–6]. The cellular alterations decrease wall thickness and dilate the heart, and eventually impair systolic function and reduce LVEF [4,5]. Concentric remodeling of the heart is associated with replication of sarcomeres in parallel and cardiomyocyte thickening, and is the direct result of sustained pressure increase [6]. Concentric remodeling is associated with incomplete LV relaxation and increased filling pressures, i.e. increased LV end-diastolic pressure [4,5].

Cytoskeletal changes are both a cause and consequence of contractile dysfunction and cardiac remodeling in HF patients. In this review we will discuss the major changes in function and structure of cytoskeletal components of cardiomyocytes which occur during HF.

## 2. The ultrastructure of cardiac muscle

### 2.1. Contractile and cytoskeletal components

Cardiac muscle fibers are composed of myofibrils that contain the contractile components of striated muscle, responsible for the conversion of chemical energy into mechanical energy, in order to perform work and generate force. Running parallel along the axis of the cell, myofibrils are defined by a homogeneous succession of transverse stripes, containing repeating individual units called sarcomeres (Fig. 1, upper image). The sarcomeres can be subdivided in two main components based on their specific characteristics: 1) the contractile proteins that govern muscle contraction and relaxation and 2) the structural scaffolding or cytoskeletal proteins. Myofilament contraction is governed by the thin actin and thick myosin filament proteins that interact (cross-bridge) to generate force [7]. Force production and muscle shortening ensues as the collective sum of all "activated" tension-generating cross-bridges. Regulation of this interaction is dependent on the amount of available $Ca^{2+}$ and ATP as well as the thin filament regulatory troponin–tropomyosin complex that binds to actin and regulates cross-bridge interaction [8,9]. The cytoskeleton forms the scaffold of cardiomyocytes as it regulates cell shape, provides mechanical integrity and resistance, and stabilizes the sarcomeric proteins. Importantly this structural framework mediates biomechanical and biochemical signaling, both inwards and outwards the cell, that thereby alters gene expression, post-translational modulation and protein synthesis, directly remodeling the myocardium [10,11].

### 2.2. The role of contractile proteins in cardiac muscle function

Myofilament activation and contractility depends on the interaction between the thin actin and thick myosin filament. This interaction is initiated upon electrical activation of cardiomyocytes and the resulting increase in intracellular [$Ca^{2+}$]. It has been suggested that the myofilaments oscillate between three biochemical equilibrium transitions, reflecting different interactions of actin and myosin termed the blocked (B-state), closed (C-state) and open (M-state) states of thin filament regulation [8,9]. In the B-state $Ca^{2+}$ is not bound to cardiac troponin C (cTnC) and tropomyosin sterically blocks the myosin-binding sites on actin. The B-state equilibrium is associated to a weakly bound state of cross-bridges (i.e. weakly-bound cross-bridges). In the C-state $Ca^{2+}$

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