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Review

The molecular and functional identities of atrial cardiomyocytes in health and disease☆,☆☆

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ABSTRACT

Atrial cardiomyocytes are essential for fluid homeostasis, ventricular filling, and survival, yet their cell biology and physiology are incompletely understood. It has become clear that the cell fate of atrial cardiomyocytes depends significantly on transcription programs that might control thousands of differentially expressed genes. Atrial muscle membranes propagate action potentials and activate myofilament force generation, producing overall faster contractions than ventricular muscles. While atria-specific excitation and contractility depend critically on intracellular Ca^{2+} signalling, voltage-dependent L-type Ca^{2+} channels and ryanodine receptor Ca^{2+} release channels are each expressed at high levels similar to ventricles. However, intracellular Ca^{2+} transients in atrial cardiomyocytes are markedly heterogeneous and fundamentally different from ventricular cardiomyocytes. In addition, differential atria-specific K^+ channel expression and trafficking confer unique electrophysiological and metabolic properties. Because diseased atria have the propensity to perpetuate fast arrhythmias, we discuss our understanding about the cell-specific mechanisms that lead to metabolic and/or mitochondrial dysfunction in atrial fibrillation. Interestingly, recent work identified potential atria-specific mechanisms that lead to early contractile dysfunction and metabolic remodelling, suggesting highly interdependent metabolic, electrical, and contractile pathomechanisms. Hence, the objective of this review is to provide an integrated model of atrial cardiomyocytes, from tissue-specific cell properties, intracellular metabolism, and excitation–contraction (EC) coupling to early pathological changes, in particular metabolic dysfunction and tissue remodelling due to atrial fibrillation and aging. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Integration of Developmental and Environmental Cues in the Heart edited by Marcus Schaub and Hughes Abriel.

1. Introduction

Atrial and ventricular cardiomyocytes each develop their unique, cell-specific identities at an early embryonic stage by regulated gene expression. For instance, the transcription factor *Tbx5*, which plays an important role in the development of both the atria and the left ventricle during cardiogenesis, regulates the expression of the gap junction channel α-subunit connexin-40 (*Gja5*) and the prohormone natriuretic peptide precursor A (*Nppa*), which are both essential components of the atrial cell system [1,2]. Furthermore, atrial myocyte specific in vivo ablation of the nuclear receptor *COUP-TFII* is sufficient to switch cell size, transverse (T-)tubule density, and the action potential shape to ventricle-like fates [3]. Based on ~2500 differentially regulated gene transcripts, adult atria and ventricles maintain significantly different molecular profiles, which underlie their cell-specific cardiomyocyte structure and function [3]. In contrast, voltage-dependent L-type Ca^{2+} channels (LTCC/Cav1.2) and ryanodine receptor (RyR2) Ca^{2+} release channels, each individually known to be essential for heart development and excitation–contraction (EC) coupling, are expressed at similar levels in atria and ventricles [4]. However, intracellular Ca^{2+} transients in atrial myocytes are profoundly heterogeneous, i.e. characterized by centripetal Ca^{2+} concentration gradients [5]. Yet, atrial compared to ventricular muscle contracts faster, explained by significantly higher expression levels both of the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase SERCA2 [6] and the high-velocity α-MHC myosin-ATPase [7]. Ultimately, atrial cardiomyocytes contribute to distinct electrical, contractile, stretch-sensing, and hormonal functions within the complex-trabeculated and thin atrial muscle chambers. The highly compliant atrial chambers allow for flexible biomechanical coupling and blood

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cycling between the atrial and ventricular chambers at relatively low venous blood pressures. Ventricular function, in turn, depends directly on atrial refilling in order to eject the right proportion of blood volume during each heartbeat to meet metabolic organ demands.

Indeed, in the human heart, cardiac output (volume ejected) correlates with ventricular filling (diastolic volume) as described by the Frank–Starling law [8]. In other words, during diastolic filling of the ventricles, the atria have an essential role to acutely adjust the blood volume loaded into each ventricular chamber, and to precondition each systolic contraction. Hemodynamic studies in animals [9–13] and humans [14–18] established that atrial systole augments left ventricular filling and performance. At rest, the quantitative contribution of atrial systole to filling of the ventricles is relatively low: atrial contraction contributes ~10–20% to the left ventricular end diastolic pressure and stroke volume [16]. In contrast, if the heart rate increases 2–3 times during physiological exercise or stress, atrial contraction accounts for ~20–30% of the effective ventricular stroke volume [12]. To describe the specific atrial hemodynamic contribution the term atrial 'kick' was coined. Importantly, cardiac aging and common comorbidities like hypertension and diastolic dysfunction cause profound pathological remodelling in atrial tissue including hypertrophy and loss of contractile function [19]. This also means that the ventricular dependence on atrial filling can be pathologically increased, and sudden onset of atrial rhythm disorders can severely impair ventricular filling with deleterious effects in patients [19].

To perform throughout a normal lifespan, atrial muscles rely on oxidative metabolism to sustain billions of contractions, heart rate and beat-to-beat adaptations, underlining the central importance of atrial energy metabolism. Excessively rapid heart rates, sustained during atrial rhythm disorders in patients, expose atrial cardiomyocytes to sharply increased metabolic burdens and can impair energy metabolism (ATP depletion with ADP accumulation) leading to adverse protein modifications through e.g. excessive production of reactive oxygen species (ROS) [20]. Indeed, atrial fibrillation (AF) is not only the most common sustained cardiac arrhythmia, but patient numbers increase exponentially due to population aging [21,22]. On the other hand, existing anti-arrhythmic therapies have only limited efficacy and significant adverse effects. Antiarrhythmic drug treatment in general relies on unphysiological block of ion channel permeability. Not surprisingly, the efficacy of antiarrhythmic ion channel blocking drugs is significantly limited by their adverse side effects including life-threatening off-target ventricular activity [23]. However, some voltage-gated K^+ channels are expressed at physiologically relevant levels only in atrial myocytes, which renders these candidates particularly attractive as targets for atria-specific antiarrhythmic drug development. In addition, remodelling of atrial myocytes during rapid atrial arrhythmias through metabolic mechanisms is an important area of research and motivates preclinical drug development. This review highlights the current understanding of metabolic disease mechanisms and introduces recent strategies for rational interventions based on cell-specific protein function, modulation of allosteric ion channel gating, and redox signalling.

2. Striated muscle cell attributes of atrial cardiomyocytes

2.1. EM ultrastructure of atrial membranes and organelles

The first quantitative data from EM studies of atrial tissue sections, from the adult cat heart, revealed typical morphological features different from ventricles, which are generally considered to be specific for atrial cardiomyocytes: 1) transverse tubules (TTs) are rare; 2) prominent perinuclear Golgi complexes associate with atria specific granules; 3) numerous peripheral sarcoplasmic reticulum (SR) cisterns form discontinuous membrane contacts with the surface membrane; and 4) there is a high density of mitochondria [24]. Different from ventricular cardiomyocytes, atrial myocytes typically feature only one central elongated nucleus (Fig. 1A). Each of the two nuclear pole regions associates with a voluminous Golgi complex, numerous granules, vesicles, and mitochondria [24,25]. Apart from the perinuclear core, the cytoplasm contains a high number of axially aligned mitochondria of variable length that intercalate between the myofilaments every 0.2–0.5 μm [24]. This suggests a potentially denser transversal packing of mitochondria between myofilaments in atrial compared to ventricular cardiomyocytes.

Atrial myocytes are ~100 μm long brick-shaped polar cells with distinct surface membrane regions, each with inherent physiological functions (Fig. 1A). The longer atrial myocyte sidelong regions are delimited by the lateral surface membrane or sarcolemma. The smaller end regions evolve highly interdigitated membrane foldings (Fig. 1A), visualized as thick intercalated disks between neighbouring myocytes in tissue sections. In addition, muscle-specific stationary membrane invaginations including caveolae and transverse tubules (TTs) are continuous with the lateral surface membrane. Under physiological conditions omega-shaped caveolar invaginations with ~34 nm wide necks occur at an estimated surface density of 10 necks/μm^2 or higher [26]. Furthermore, EM sections showed many necks that connect laterally to 1–5 caveolar vesicles, forming pinwheel arrangements of local submembrane caveolae networks [26]. Finally, immunogold labelling identified the muscle-specific membrane-integral protein caveolin-3 (Cav3) in atrial caveolae [27].

Interestingly, Cav3-positive membrane structures were also identified during TT development in skeletal muscle cells, suggesting further roles of caveolae in the biogenesis of TT invaginations [27]. TTs are by definition membrane invaginations continuous with the lateral surface membrane that traverse the cytosol approximately perpendicular to the main cell axis, usually near sarcomere Z-disks. A model of TT biogenesis based on extracellular space tracking in ventricular myocytes suggests that TTs grow deeper into the cytosolic space through progressive accrual of membrane lipids and proteins through caveolae fusions [28]. However, in the adult guinea pig atria, OsFeCN-stained membranes in EM sections show few short TT structures extending only to the peripheral myofibrils compared to far more extensive TTs in ventricular myocytes [25], but see also Section 2.3.

Furthermore, dense secretory granules not found in ventricular myocytes are interspersed between the Golgi complexes at the nuclear poles (Fig. 1A)[29]. Up to 600 distinct granules per atrial myocyte were counted mainly concentrated at the cytoplasmic core around the perinuclear axis, scattered between the myofilaments, and locally accumulated near the sarcolemma (Fig. 1B)[29]. At the sarcolemma, large atrial granules lie right between but spatially separate from caveolae [26]. Interestingly, atria specific secretory granules and the Golgi complex are bounded by similar membrane structures, described as unit membrane [29]. Furthermore, atria specific granules and peripheral Golgi stacks co-occur near the plasma membrane (Fig. 1A)[29]. Using tannic acid to arrest secretory granule fusion with the sarcolemma, electron-dense clathrin-coats were found associated with 12% of atrial secretory granules, suggesting a role in post-fusion retrieval [25]. Clathrin-coated pits and vesicles are frequently observed in atrial sections [30]. Taken together, atrial cardiomyocytes exhibit a high density of organelles including mitochondria and scattered Golgi complexes, a secretory pathway for atria specific vesicles, and both clathrin- and Cav3-associated membrane invaginations and trafficking mechanisms (Fig. 2A).

Finally, endocrine secretory functions of the atria are essential for physiological fluid homeostasis and survival. In particular, atrial myocyte secretory granules are the major source of atrial natriuretic peptide (ANP) exocytosis in vertebrates (Figs. 1B and 2A) [31]. Secretory ANP granules are released during hemodynamic stress, leading to increased atrial cell stretch within the highly compliant atrial tissues [28]. Following secretion from atrial myocytes, circulating ANP acts as a potent peptide hormone that activates renal salt and water excretion, and regulates smooth muscle tone in vessels and blood pressure, fluid homeostasis, and even complex interactions with the brain (for comprehensive reviews see [32,33]).

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