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Myocardial plasticity: cardiac development, regeneration and disease

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The adult mammalian heart is unable to recover from myocardial cell loss due to cardiac ischemia and infarction because terminally differentiated cardiomyocytes proliferate at a low rate. However, cardiomyocytes in other vertebrate animal models such as zebrafish, axolotls, newts and mammalian mouse neonates are capable of de-differentiating in order to promote cardiomyocyte proliferation and subsequent cardiac regeneration after injury. Although de-differentiation may occur in adult mammalian cardiomyocytes, it is typically associated with diseased hearts and pathologic remodeling rather than repair and regeneration. Here, we review recent studies of cardiac development, regeneration and disease that highlight how changes in myocardial identity (plasticity) is regulated and impacts adaptive and maladaptive cardiac responses.

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Introduction: myocardial lineage and differentiation

Despite constituting only ~30% of all cardiac cells, myocardial cells are the primary source of cardiac contractile function which results in efficient pumping of blood throughout the body [1,2]. Myocardial cells can be broadly divided into working myocardium — responsible for blood flow (i.e. atrial, ventricular myocytes), and non-working myocardium — responsible for effectively guiding blood flow (i.e. outflow tract, inflow tract and conduction myocytes) [3,4]. During gastrulation, two waves of mesodermal-derived cells [i.e. first heart field (FHF) and second heart field (SHF)] constitute the majority of the myocardium within the left ventricle (FHF), right ventricle (SHF), right and left atria (FHF/SHF) and outflow/inflow tracts (SHF) [5–8]. These contributions occur sequentially with myocardial cells derived from the FHF contributing to the primitive heart tube, which is then further expanded by the addition of late differentiating SHF cells [9,10]. A third wave closely associated with the SHF forms the sino-atrial node (pacemaker) [11], while an additional set of neural crest derived cells contributes to the mesenchyme for the septation of the outflow tract [12]. Although each developmental lineage contributes to a specific anatomical set of myocardial cells (e.g. left/right ventricular myocardium — FHF/SHF), they also supply an overlapping variety of myocardial sub-types (e.g. working and non-working myocardium) [3,13].

Once established, myocardial cells must maintain appropriate contractile function throughout the entire development and morphogenesis of the heart. As the embryo develops and grows into an adult, the requirements on the heart change dramatically requiring alterations in the number, size and efficiency of the myocardial muscle. As a result, myocardial cells dynamically differentiate during embryonic and fetal development to meet these functional demands. Changes to myocardial cells during this time period include a metabolic switch from glycolysis to fatty acid metabolism, increases in cell size, diminished proliferative capacity, and changes in protein isoforms [14–22].

Many of these transformations, such as loss of proliferative capacity in the adult mammalian heart, become detrimental during acute heart disease when there is a large loss of myocardial cells. This is in contrast to other vertebrate animals such as the adult zebrafish, in which cardiomyocytes are able to respond to a similar injury by de-differentiating and proliferating to promote cardiac regeneration [23]. Interestingly, myocardial de-differentiation can also be observed in diseased adult mammalian hearts; however it is associated with the detrimental progression of disease but not cardiac proliferation and regeneration [24]. In this review, we bring together studies from cardiac development, regeneration and disease to summarize the role of myocardial plasticity in adaptive responses during regeneration as well as maladaptive responses during chronic adult mammalian cardiac disease.

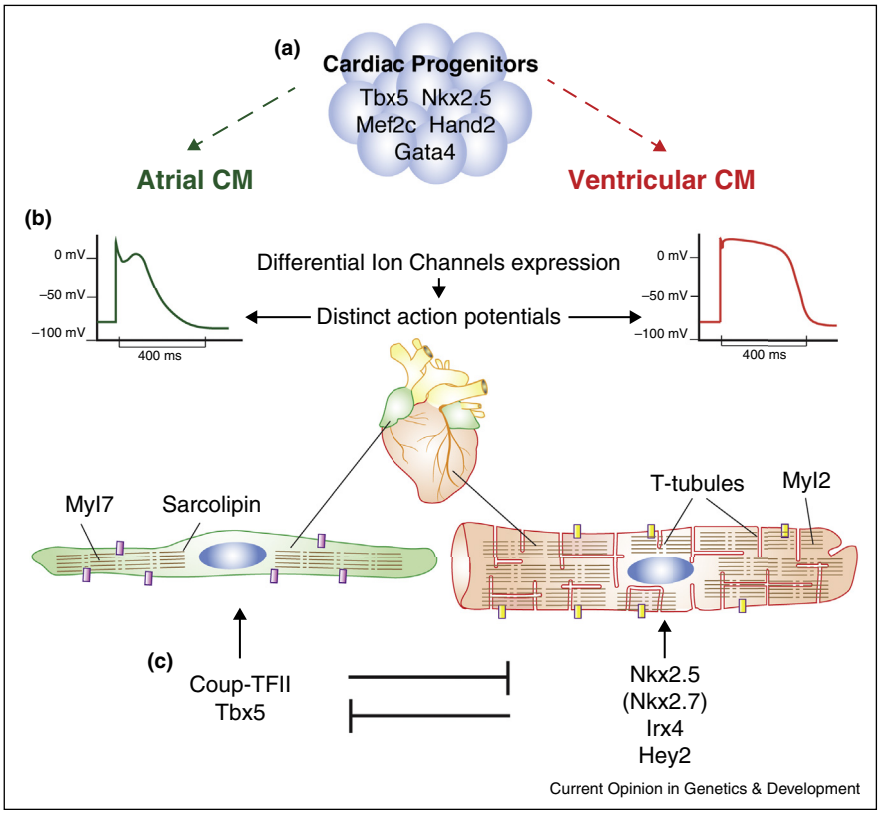
Each of these fields is extensive, thus we apologize in advance to our colleagues whose valuable work has been omitted due to space constraints. Furthermore, readers are directed to more extensive reviews focused on each individual topic [3,24–28].

Restriction of atrial and ventricular myocardial identity during development

Differentiated atrial and ventricular myocytes display specialized structural, physiological and molecular differences (Figure 1). For example, ventricular myocytes exhibit a rod-like morphology, specialized T-tubule sub-structures and a flat action potential plateau. In contrast, atrial myocytes are more squamous, and display a triangular shaped action potential with a shorter contraction and relaxation period [29–36].

Despite these distinct differences, recent genetic studies reveal that differentiated cardiomyocytes are able to exchange their identities during development. These studies show that after the specification and differentiation of atrial and ventricular myocytes, a set of complementary transcription factors continue to maintain the identity of differentiated chamber myocytes by repressing the gene program of the opposing chamber (atrial or ventricular) and promoting their own chamber-specific gene regulatory network. For example, *COUP-TFII* is an orphaned nuclear hormone receptor restricted to atrial myocytes, where it maintains atrial identity [37]. Conditional removal of *COUP-TFII* in the heart, after the formation and differentiation of atrial myocytes, results in atria containing cardiomyocytes with ventricular identity; conversely, forced ventricular expression of *COUP-TFII*, leads to ectopic atrial myocytes [38••]. Microarray and ChiP-seq studies further revealed that *COUP-TFII* controls a large range of genes crucial for both atrial and ventricular identity including *Tbx5* (important for atrial identity [39–41]) and *Hey2* (important for ventricular identity [42]). Thus, *COUP-TFII* likely acts by repressing the ventricular transcriptional network while promoting the atrial expression program. Intriguingly, *COUP-TFII* restricts atrial plasticity until mouse embryonic day 15.5, after which the *COUP-TFII* gene program is no longer needed to maintain chamber identity [38••].

Figure 1



Restriction of atrial and ventricular identity. **(a)** Atrial (green) and ventricular (red) cardiomyocytes arise from distinct yet overlapping sets of cardiac progenitors, characterized by the expression of transcription factors such as *Tbx5*, *Nkx2.5*, *Mef2c*, *Hand2* and *Gata4*. **(b)** Atrial and ventricular cardiomyocytes display distinct physiological, structural and molecular differences. For example, ventricular cardiomyocytes display a flatter action potential plateau, have specialized T-tubule structures and express different sarcomeric genes for example, *Myl2*/*Mlc2v* (ventricle), *Myl7*/*Mlc2a* (atrial). **(c)** Atrial and ventricular cardiomyocytes each express a mutually exclusive transcriptional program that enforces their own identity and suppresses the other. CM: cardiomyocyte, purple/yellow squares: differential ion channels expression, segmented lines: sarcomeres.