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Minireview

Gap junctional regulation of pressure, fluid force, and electrical fields in the epigenetics of cardiac morphogenesis and remodeling

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ABSTRACT

Epigenetic factors of pressure load, fluid force, and electrical fields that occur during cardiac contraction affect cardiac development, morphology, function, and pathogenesis. These factors are orchestrated by intercellular communication mediated by gap junctions, which synchronize action potentials and second messengers. Misregulation of the gap junction protein connexin (Cx) alters cardiogenesis, and can be a pathogenic factor causing cardiac conduction disturbance, fatal arrhythmia, and cardiac remodeling in disease states such as hypertension and ischemia. Changes in Cx expression can occur even when the DNA sequence of the *Cx* gene itself is unaltered. Posttranslational modifications might reduce arrhythmogenic substrates, improve cardiac function, and promote remodeling in a diseased heart. In this review, we discuss the epigenetic features of gap junctions that regulate cardiac morphology and remodeling. We further discuss potential clinical applications of current knowledge of the structure and function of gap junctions.

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Introduction

The heart keeps beating throughout our life. At every moment, coordinated cycles of systole and diastole are essential for proper blood delivery to tissues. The process resembles ballooning: after inflation, the air can be released from a balloon. The shape of the balloon, however, depends on how it is inflated; the thinner part expands first, but we can choose to expand other parts of the balloon, such as the tip or base, by grasping (adding pressure to) other parts. Similarly, the shape of the heart is determined by the equilibrium between tension in the cardiac walls and blood pressure. Because the heart is a dynamic organ, moment-to-moment changes of local force equilibrium constitute one of the principal epigenetic factors regulating heart morphology.

The gap junction apparatus is highly conserved in multicellular organisms, regulating coordinated contractions; i.e. the moment-to-moment changes of local force equilibrium in the heart. Mutations in

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gap junction-encoding *connexin* (*Cx*) genes influence cardiac differentiation, morphology, and function, although the mechanisms underlying these abnormalities are not fully understood [78]. Recent advancements in mouse and zebrafish genetic models suggest that electrical fields are as important as local force equilibria; both epigenetic factors are regulated by gap junctions. Moreover, there is growing evidence that epigenetic modulation of gap junctional regulation is critical for successful recovery from compromising heart events.

Effects of fluid and electrical forces on cardiac morphology

Spontaneous, rhythmic, and coordinated action potentials of cardiomyocytes periodically alter cardiac chamber morphology. The resultant tension and fluid forces within the heart have long been assumed to be essential epigenetic morphogenic factors underlying cardiac development [73,108–110]. There is a certain class of genes whose primary function is to affect cardiac contractility rather than regulate cardiovascular morphogenesis [29]. Mutations in these genes often cause secondary cardiovascular morphogenic defects (Fig. 1a). Null mutations of *TNNT2*, encoding the thin filament contractile protein cardiac troponin T (cTnT), lead to contractile inactivity and secondary endocardial cushion defects in the developing zebrafish heart [4,95]. *cTnT*-deficient mice show dilated cardiac chambers and an endocardial cushion defect, as well as defective sarcomere assembly, which leads to a lack of heartbeats [76]. Loss of the Na^{+}/Ca^{2+} exchanger also causes cardiac inactivity and morphogenic defects similar to those in *cTnT*-deficient mice [12,53,90,115]. In addition to the complete lack of heartbeat, and accordingly, no blood flow, an atrium-specific contractility defect in zebrafish and mice also has a profound impact on total cardiovascular development [7,40]. These genetic models clearly show that normal blood flow and intracardiac fluid forces are essential regulators of early cardiogenesis in mammalian embryos, whose nutrient and oxygen supplies completely depend on the placenta, and in the embryos of lower vertebrates, which can be fed partly by diffusion of the extra-embryonic fluid. When blood flow within the heart is directly eliminated by surgical placement of a bead at either the inflow or outflow tracts, zebrafish hearts show an abnormal third chamber, diminished looping, and impaired valve formation [39]. Fluid force is sensed by the endothelium [73,109,110]; monocilia in the endothelial lining of the developing heart may participate in the fluid force transduction cascade [105,114]. A recent study showed flow-dependent expression of *miR-21* within the atrioventricular canal endocardium, where it regulates valve formation in zebrafish [3]. In contrast, mice lacking *miR-21* show normal cardiovascular development [84]. The precise mechanisms by which fluid

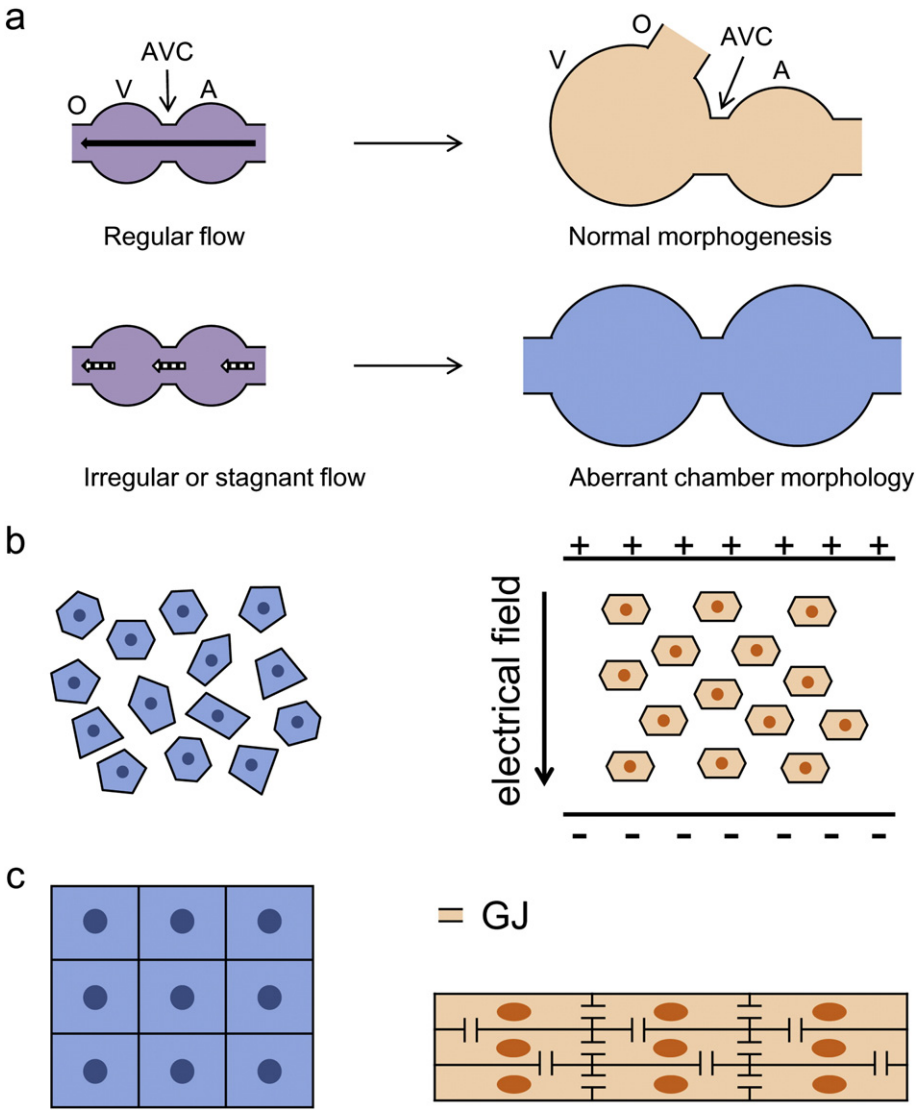

Fig. 1. Fluid force and electrical field control cardiogenesis. A, atrium; AVC, atrioventricular canal; V, ventricle; O, outflow tract.