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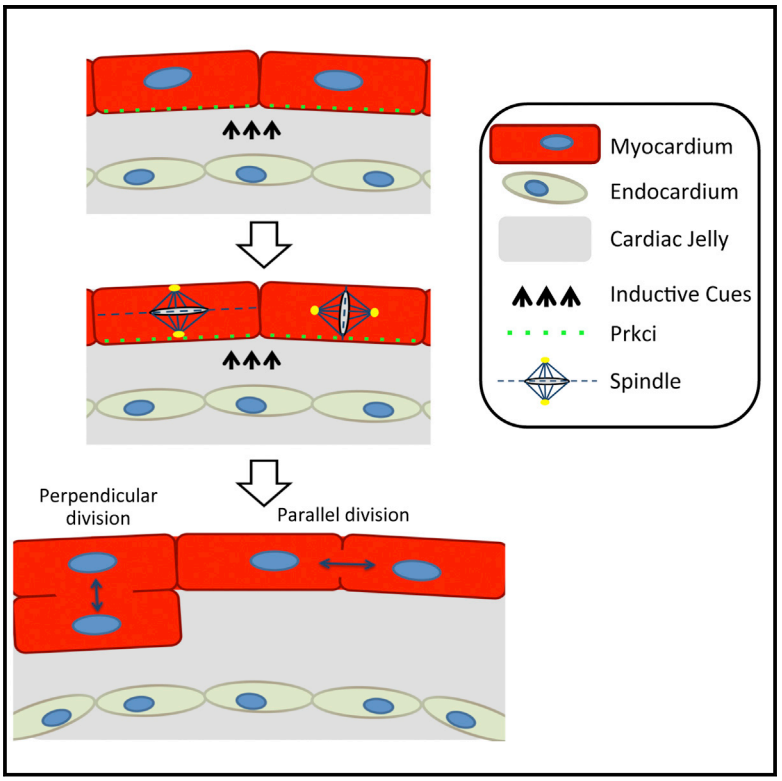
Atypical Protein Kinase C-Dependent Polarized Cell Division Is Required for Myocardial Trabeculation

Graphical Abstract



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In Brief

Prkci-dependent cell polarization is required for the ventricular trabeculation of the mammalian heart. Passer et al. find that Prkci and its interacting partners polarize luminal myocardial cells and is required for cardiac trabeculation in the nascent heart.

Highlights

- Prkci localizes primarily to luminal side of cardiomyocytes in the early embryonic hearts
- A subset of these cells undergoes polarized cell division perpendicular to the lumen
- Cell polarization requires a normal composition of the cardiac jelly
- Deletion of Par complex components results in loss of myocardial trabeculation

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Atypical Protein Kinase C-Dependent Polarized Cell Division Is Required for Myocardial Trabeculation

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SUMMARY

A hallmark of cardiac development is the formation of myocardial trabeculations exclusively from the luminal surface of the primitive heart tube. Although a number of genetic defects in the endocardium and cardiac jelly disrupt myocardial trabeculation, the role of cell polarization remains unclear. Here, we demonstrate that atypical protein kinase C iota (Prkci) and its interacting partners are localized primarily to the luminal side of myocardial cells of early murine embryonic hearts. A subset of these cells undergoes polarized cell division with the cell division plane perpendicular to the heart's lumen. Disruption of the cell polarity complex by targeted gene mutations results in aberrant mitotic spindle alignment, loss of polarized cardiomyocyte division, and loss of normal myocardial trabeculation. Collectively, these results suggest that, in response to inductive signals, Prkci and its downstream partners direct polarized cell division of luminal myocardial cells to drive trabeculation in the nascent heart.

INTRODUCTION

During early mammalian cardiogenesis, progenitors of the cardiac crescent coalesce at the ventral midline to form the linear heart tube. At that point, the nascent heart is constituted of an inner endocardial cell layer separated from an outer myocardial layer by a complex of extracellular matrix (ECM) proteins termed the cardiac jelly (Moorman and Christoffels, 2003). By the end of cardiac looping on embryonic day (E) 9.0–9.5 in mouse, myocardial trabeculations orient toward the cardiac jelly and endocardial cells in the cardiac lumen (Manasek, 1968; von Gise and Pu, 2012). A number of genetic defects in the endocardium (Grego-Bessa et al., 2007; Liu et al., 2010) and cardiac jelly (Camenisch et al., 2000) have resulted in abnormal trabeculation of the early heart. Mutations in hyaluronan synthase-2 (Has2), for example, cause a loss of hyaluronic acid (HA) in the cardiac jelly, embryonic lethality at midgestation, and a lack of myocardial trabeculation (Camenisch et al., 2000). Likewise an increasing body of evidence suggests that oriented cell division is essential for establishing proper tissue architecture of the developing heart (Meilhac et al., 2004). Additionally late in heart development, oriented division of epicardial cells also controls epicardial cell migration and contribution to the myocardium (Wu et al., 2010). However, the underlining molecular mechanisms that regulate proper spindle positioning in early cardiac development and trabecular formation remain poorly understood.

Cell polarity is an essential and highly conserved component of all eukaryotic cells during tissue development and refers to the polarized organization of cell membrane-associated proteins as well as the asymmetric organization of organelles and cytoskeleton. (Bryant and Mostov, 2008). Recent studies in mammalian tissue culture cells suggest that polarized cell divisions rely on the unequal distribution and segregation of key polarity proteins during mitosis. These proteins govern the generation and proper axis alignment of differentiated cell types during organogenesis. During embryogenesis, polarity proteins regulate normal cellular physiology as well as tissue homeostasis and morphogenesis (Gonzalez, 2007; Knoblich, 2010; Martin-Belmonte and Perez-Moreno, 2012).

Cell polarity and spindle orientation are coupled through the Par polarity complex. The Par complex is composed of three proteins, Par3, Par6, and protein kinase C iota (Prkci), and controls the cell polarity necessary for normal tissue generation and morphogenesis. First discovered during embryogenesis of *Caenorhabditis elegans* where polarity gene mutants caused loss of normal blastomore asymmetry and subsequent division cleavage planes (Watts et al., 1996). After establishment of the Par complex to one cell pole, Par3 interacts with the adaptor protein Inscuteable (Insc in mammals) that binds directly to Pins (partner of Insc, homolog of vertebrate LGN/Gpsm2 and AGS3/Gpsm1). Pins then associates with the heterotrimeric G proteins ($G\alpha_i$) and NuMA. Critically, NuMA interacts directly with the cell spindle to control the orientation and of the spindle and the division plane of mitotic cells (Siller and Doe, 2009). Loss of function of any one of these genes results in an abnormal spindle orientation during