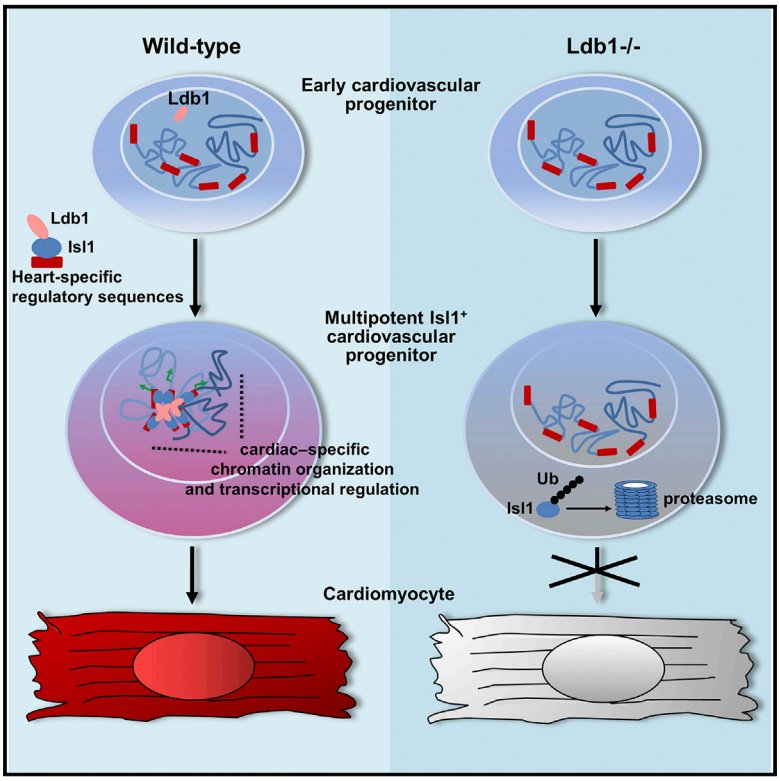
Article

Cell Stem Cell

The Isl1/Ldb1 Complex Orchestrates Genome-wide Chromatin Organization to Instruct Differentiation of Multipotent Cardiac Progenitors

Graphical Abstract



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In Brief

Caputo et al. identify Ldb1 as a crucial regulator of cardiogenesis. Ldb1 binds the key cardiac transcription factor Isl1 and protects it from degradation. The stabilized Isl1/Ldb1 complex orchestrates a network for transcriptional regulation and coordination in three-dimensional space, driving cardiac progenitor cell differentiation and heart development.

Highlights

- Ldb1 is required for differentiation of multipotent cardiac progenitor cells
- Ldb1 regulates second heart field development
- Ldb1 protects the key regulator of cardiac progenitors, Isl1, from degradation
- The Isl1/Ldb1 complex orchestrates cardiac-specific chromatin organization

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The Isl1/Ldb1 Complex Orchestrates Genome-wide Chromatin Organization to Instruct Differentiation of Multipotent Cardiac Progenitors

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SUMMARY

Cardiac stem/progenitor cells hold great potential for regenerative therapies; however, the mechanisms regulating their expansion and differentiation remain insufficiently defined. Here we show that Ldb1 is a central regulator of genome organization in cardiac progenitor cells, which is crucial for cardiac lineage differentiation and heart development. We demonstrate that Ldb1 binds to the key regulator of cardiac progenitors, Isl1, and protects it from degradation. Furthermore, the Isl1/Ldb1 complex promotes long-range enhancer-promoter interactions at the loci of the core cardiac transcription factors *Mef2c* and *Hand2*. Chromosome conformation capture followed by sequencing identified specific Ldb1-mediated interactions of the Isl1/Ldb1 responsive *Mef2c* anterior heart field enhancer with genes that play key roles in cardiac progenitor cell function and cardiovascular development. Importantly, the expression of these genes was downregulated upon Ldb1 depletion and *Isl1/Ldb1* haplodeficiency. In conclusion, the Isl1/Ldb1 complex orchestrates a network for heart-specific transcriptional regulation and coordination in three-dimensional space during cardiogenesis.

INTRODUCTION

Heart failure is the leading cause of morbidity and mortality worldwide. A number of cardiac regenerative strategies have been proposed, among which stem/progenitor cells hold great promise for heart repair (Aguirre et al., 2013; Hansson et al., 2009). Knowledge accumulated from developmental studies has significantly improved the methods for in vitro cardiac differentiation of embryonic stem cells (ESCs) and studies utilizing ESC differentiation have brought further insights into the regulatory networks that integrate multiple transcription factors and signaling molecules and strictly control the distinct steps of cardiogenesis. However, the current limitations for the use of stem/progenitor cells in regenerative medicine, e.g., those linked to their expansion, differentiation efficiency, and functional integration, call for a more complete understanding of the mechanisms driving cardiovascular lineage commitment and differentiation.

During embryogenesis the heart is generated by a common progenitor at gastrulation that segregates into two distinct populations, termed first and second heart fields. The first heart field (FHF) fuses at the midline and differentiates into the myocardium of the heart tube. After the initial heart tube formation, the heart tube grows by the addition of Isl1-positive second heart field (SHF) progenitor cells to its anterior and venous poles (Cai et al., 2003; Evans et al., 2010; Vincent and Buckingham, 2010). Studies in different model systems revealed the crucial function of the LIM-homeodomain (LIM-HD) transcription factor Isl1 in heart morphogenesis (Cai et al., 2003; de Pater et al., 2009; Witzel et al., 2012). Isl1-deficient mouse embryos lack the right ventricle and the outflow tract, both structures derived from the SHF, as Isl1 is required for the proliferation, survival, and migration of these cells into the forming heart (Cai et al., 2003). Importantly, the Isl1-positive cardiovascular progenitors are multipotent and can differentiate into all three cardiovascular lineages: cardiomyocytes, smooth muscle cells, and endothelial cells (Moretti et al., 2006). Moreover, Isl1 is required for the differentiation of these cells into the cardiomyocyte and smooth muscle lineage (Kwon et al., 2009), but the mechanisms underlying its function are poorly understood.

The acquisition of cellular identity involves genome reorganization and a coordinated series of large-scale transcriptional changes (Dixon et al., 2015; Gorkin et al., 2014; Peric-Hupkes et al., 2010). Studies using chromosome conformation capture (3C) assays and 3C-based technologies (de Wit and de Laat,