A novel transgenic mouse model reveals an essential role for Bcar1/p130Cas in embryonic heart development and outflow tract septation

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Background/Introduction

The adapter protein p130Cas, encoded by the Bcar1 gene, is a key regulator of cell movement, adhesion, and cell cycle control in diverse cell types. Bcar1 constitutive knockout mice are embryonic lethal by embryonic days (E) 11.5-12.5, exhibiting marked systemic congestion, growth retardation and gross defects in the development of the heart, suggesting an important role for Bcar1 in normal embryonic development.

Purpose

We aimed to investigate the role of Bcar1 specifically in cardiovascular development and define the underlying cellular and molecular mechanisms disrupted following targeted Bcar1 deletion.

Methods

We crossed Bcar1 floxed mice with SM22-Cre transgenic lines allowing for cell-specific knockout either in cardiomyocytes (SM22-Cre), smooth muscle cells (smMHC-Cre) or endothelial cells (Tie2-Cre), and characterised these conditional knock outs using a combination of histological and molecular biology techniques.

Results

Conditional knockout of Bcar1 in SM22-expressing smooth muscle cells and cardiomyocytes (Bcar1SM22KO) was embryonically lethal from E14.5 due to severe cardiovascular defects, including abnormal right ventricular development and failure of outflow tract (OFT) septation. Septation of the entire length of the OFT failed in the Bcar1SM22KO mutants leading to a single outflow vessel reminiscent of persistent truncus arteriosus (PTA). Defective myocardisation of the OFT was apparent, together with a failure of OFT cushion cells to undergo differentiation to septal mesenchymal cells positive for SMC-specific α-actin (SMA), and disrupted expression of proteins involved in epithelial-to-mesenchymal transformation (EMT). In contrast, conditional knockouts of Bcar1 in differentiated smooth muscle cells (smMHC positive smooth muscle cells), endothelial cells (Tie2 positive), survived to term and appeared phenotypically normal at birth and in early post-natal life.

Conclusion(s)

Our work reveals a cell-specific requirement for Bcar1 in early myogenic lineages and cardiac progenitors and indicates an important role for Bcar1 in OFT myocardisation and EMT.