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 myocardialisation 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 myocardialisation and EMT.