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Akt1 signaling coordinates BMP signaling and β-catenin activity to regulate second heart field progenitor development.

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Abstract

Second heart field (SHF) progenitors exhibit continued proliferation and delayed differentiation, which are modulated by FGF4/8/10, BMP and canonical Wnt/β-catenin signaling. PTEN-Akt signaling regulates the stem cell/progenitor cell homeostasis in several systems, such as hematopoietic stem cells, intestinal stem cells and neural progenitor cells. To address whether PTEN-Akt signaling is involved in regulating cardiac progenitors, we deleted Pten in SHF progenitors. Deletion of Pten caused SHF expansion and increased the size of the SHF derivatives, the right ventricle and the outflow tract. Cell proliferation of cardiac progenitors was enhanced, whereas cardiac differentiation was unaffected by Pten deletion. Removal of **Akt1** rescued the phenotype and early lethality of Pten deletion mice, suggesting that **Akt1** was the key downstream target that was negatively regulated by PTEN in cardiac progenitors. Furthermore, we found that inhibition of FOXO by **Akt1** suppressed the expression of the gene encoding the BMP ligand (BMP7), leading to dampened BMP signaling in the hearts of Pten deletion mice. Cardiac activation of Akt also increased the Ser552 phosphorylation of β-catenin, thus enhancing its activity. Reducing β-catenin levels could partially rescue heart defects of Pten deletion mice. We conclude that Akt signaling regulates the cell proliferation of SHF progenitors through coordination of BMP signaling and β-catenin activity.

KEYWORDS: Akt; BMP; Mouse; Second heart field; β-catenin

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