Msx1 and Msx2 regulate survival of secondary heart field precursors and post-migratory proliferation of cardiac neural crest in the outflow tract.

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Public Summary:
The heart is composed of several cell types with distinct origins. Understanding how these cell types come together to form the different parts of the heart remains a fundamental question. To address this question, we made use of mice with mutations in Msx1 and Msx2, genes encoding proteins that regulate the expression of specific genes. Such mice have defects in the formation of the septa (walls between different chambers) of the heart. The most important conclusion of the paper is that Msx1 or Msx2 is required for both the survival and proliferation of cells that form the septum between the aorta and pulmonary arteries. This finding has implications for understanding the mechanism of a class of birth defects that affect this septum.

Scientific Abstract:
Msx1 and Msx2 are highly conserved, Nk-related homeodomain transcription factors that are essential for a variety of tissue-tissue interactions during vertebrate organogenesis. Here we show that combined deficiencies of Msx1 and Msx2 cause conotruncal anomalies associated with malalignment of the cardiac outflow tract (OFT). Msx1 and Msx2 play dual roles in outflow tract morphogenesis by both protecting secondary heart field (SHF) precursors against apoptosis and inhibiting excessive proliferation of cardiac neural crest, endothelial and myocardial cells in the conotruncal cushions. During incorporation of SHF precursors into the OFT myocardium, ectopic apoptosis in the Msx1−/-; Msx2−/- mutant SHF is associated with reduced expression of Hand1 and Hand2, which from work on Hand1 and Hand2 mutants may be functionally important in the inhibition of apoptosis in Msx1/2 mutants. Later during aorticopulmonary septation, excessive proliferation in the OFT cushion mesenchyme and myocardium of Msx1−/-; Msx2−/- mutants is associated with premature down-regulation of p27(KIP1), an inhibitor of cyclin-dependent kinases. Diminished accretion of SHF precursors to the elongating OFT myocardium and excessive accumulation of mesenchymal cells in the conotruncal cushions may work together to perturb the rotation of the truncus arteriosus, leading to OFT malalignment defects including double-outlet right ventricle, overriding aorta and pulmonary stenosis.