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Myocardial-specific R-spondin3 drives proliferation of the coronary stems primarily through the Leucine Rich Repeat G Protein coupled receptor LGR4

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ABSTRACT

Coronary artery anomalies are common congenital disorders with serious consequences in adult life. Coronary circulation begins when the coronary stems form connections between the aorta and the developing vascular plexus. We recently identified the WNT signaling modulator R-spondin 3 (*Rspo3*), as a crucial regulator of coronary stem proliferation. Using expression analysis and tissue-specific deletion we now demonstrate that *Rspo3* is primarily produced by cardiomyocytes. Moreover, we have employed CRISPR/Cas9 technology to generate novel Lgr4-null alleles that showed a significant decrease in coronary stem proliferation and thus phenocopied the coronary artery defects seen in Rspo3 mutants. Interestingly, Lgr4 mutants displayed slightly hypomorphic right ventricles, an observation also made after myocardial specific deletion of Rspo3. These results shed new light on the role of Rspo3 in heart development and demonstrate that LGR4 is the principal R-spondin 3 receptor in the heart.

Key Words: Coronary artery, Secondary heart field, endothelial proliferation, R-spondin3 (*Rspo3*), Wnt signaling, Leucine Rich Repeat G Protein Coupled Receptor (*Lgr4*)

INTRODUCTION

Coronary arteries are essential for supplying blood to the heart and coronary artery anomalies can lead to serious consequences such as sudden cardiac death (Riley and Smart, 2011). Furthermore, coronary heart disease, resulting from obstruction of the coronary arteries, is one of the leading causes of death worldwide (Aisagbhoni et al., 2014). Hence, understanding the molecular mechanisms guiding coronary artery formation is crucial for developing novel treatments for heart disease.

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