Coronary patterning
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Magali Theveniau-Ruissy[1], Pauline Parisot[1], Fanny Bajolle[2], Lucile Houyel[2], Stephane Zaffran[3], Robert G. Kelly[1] and Damien Bonnet[2]

[1] **Developmental Biology Institute of Marseille-Luminy, UMR6216 CNRS Universite de la Mediterranee, Marseille**
[2] **Centre de Référence Malformations Cardiaques Congénitales Complexes, Hôpital Necker-Enfants Malades, Paris**
[3] **U910 Inserm, Faculté de Médecine de Marseille, Universite de la Mediterranee, Marseille**

Introduction

Efficient delivery of oxygenated blood to the myocardium is critical for cardiac function. Defects in the development and patterning of coronary arteries are of major medical impact and coronary artery patterning anomalies are frequently associated with congenital heart defects affecting the arterial pole of the heart, including common arterial trunk, tetralogy of Fallot and double outlet right ventricle. The objectives of our project were to define the molecular and cellular basis of coronary artery patterning and correlate findings in mouse models with coronary anomalies in specific congenital heart defects in man.

Coronary anomalies in *Tbx1* null mice

Mice lacking the DiGeorge sydnrome candidate gene *TBX1* display coronary patterning anomalies associated with common arterial trunk and failure of addition of a subpopulation of progenitor cells to the heart, normally giving rise to subpulmonary myocardium (Figure 1).

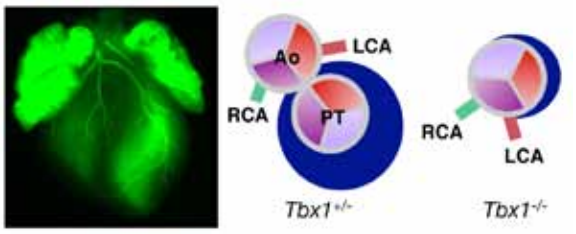

Figure 1. The *Tbx1* null coronary artery phenotype is associated with loss of subpulmonary myocardium (blue).

Defining the subpulmonary myocardial transcriptiome

We have identified a number of genes differentially expressed in future subpulmonary myocardium by microarray, candidate gene evaluation and position effect transgene integration site analysis. These include genes encoding the signaling molecules Semaphorin3C, Neuropilin2, the extracellular matrix molecule TenascinC and the transcription factors Barx1 and Dlx2 (Figure 2).

Mouse genetics has been used to identify an interaction between *Tbx1* and the retinoic acid sythesis enzyme Raldh2 during great artery development. Furthermore we have found that the subpulmonary lineage is retinoic acid dependent and derived from *Hoxb1* and *Hoxa1* expressing progenitor cells (Figure 2). The functional importance of novel subpulmonary markers in maintaining a coronary free zone at the base of the pulmonary trunk is under analysis in explant and transgenic systems.

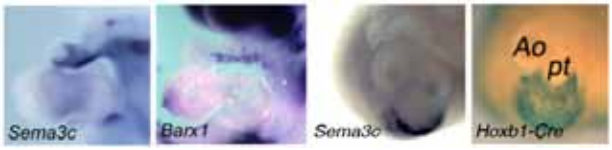

Figure 2. Gene expression in future subpulmonary myocardium at days 10.5 and 13.5 of development.

Coronary patterning in conotruncal defects

Investigation of coronary artery patterning in conotruncal congenital heart defect patients and anatomical specimens from the national reference centre for congenital malformations has revealed specific defects in cases of common arterial trunk, in particular a posteriorally positioned left coronary artery and a larger intercoronary artery angle relative to other malformations.

Conclusions

Our study i) implicates failure of subpulmonary myocardium in anomalous coronary artery patterning, ii) has begun to define a subpulmonary genetic program and iii) furthers understanding of the association of coronary anomalies with human congenital heart defects.

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CONTACT :
damien.bonnet@nck.ap-hop-paris.fr
stephane.zaffran@univmed.fr
robert.kelly@ibdml.univmed.fr
magali.theveniau-ruissy@ibdml.univmed.fr