ROLE OF VASCULAR SMOOTH MUSCLE CELL PHENOTYPE SWITCHING IN THE ROSS PROCEDURE: A COMPUTATIONAL STUDY

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Introduction

The Ross procedure is an excellent surgical solution to repair a diseased aortic valve. However, autograft failure is often observed due to excessive dilatation. We hypothesize that vascular smooth muscle cells (vSMCs) in the autograft adopt a degradative phenotype [1] and investigate whether the long-term outcomes of the Ross procedure would benefit from pharmacological treatment that reverts this phenotype switch.

Methods

The Ross procedure was performed on three sheep, who were euthanized after six months of autograft remodeling. Bulk RNA sequencing on the three extracted autograft samples was followed by differential analysis compared to four sheep pulmonary artery control samples. With this data, Gene Set Enrichment Analysis (GSEA, Bioconductor package fgsea) [2] was performed on selected curated gene sets from the GO Molecular Function and Biological Process ontologies [3], as well as from the Reactome pathway database [4], that are relevant to tissue growth and remodeling.

Our computational model for growth and remodeling of pulmonary autograft tissue [5] was adapted to account for the gene signature of vSMCs after phenotype switching obtained from GSEA. The simulation is also repeated assuming healthy vSMC behavior.

Results

GO/Reactome term	NES	p	BH p
(1) GO:1904707	1.49	0.04	0.10
(2) GO:0030020	1.36	0.11	0.18
(3) R-HSA-1474228	1.65	<0.01	<0.01
(4) R-HSA-216083	2.01	<<0.01	<<0.01

Table 1: Results of GSEA, indicating normalized enrichment score (NES) and (BH adjusted) p-value (p, BH p).

Results of GSEA given in Tab. 1 show the gene expression profile of autograft vSMCs including upregulated cell proliferation (1), production of collagens (2), production of ECM degrading proteases (3), and integrin to cell surface interactions (4). No significant change in apoptosis, vSMC contraction and production of elastic matrix was observed.

Fig. 1 shows the outcomes of the model, either accounting for this vSMC behavior observed through GSEA or assuming a healthy phenotype, where in the latter case, the radius increases more slowly over time.

Tab. 2 gives an overview of mechanical and geometrical properties estimated by the model of native pulmonary artery, and autograft after the two types of remodeling. Results show that the cross sectional wall area was preserved better when vSMCs stay in their initial phenotype, while the distensibility increases less.

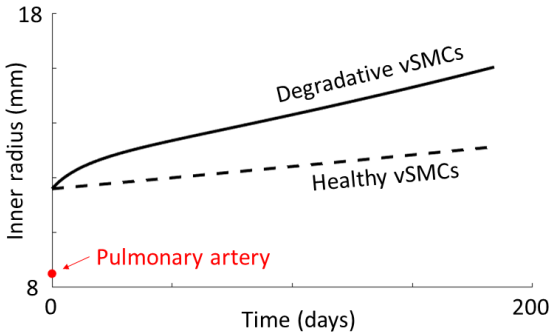

Figure 1: Increase of predicted autograft radius with degradative (full line) and healthy (dashed line) vSMCs over time. The red dot indicates the radius of a native pulmonary artery.

	PP	PAd	PAh
Distensibility (MPa^{-1})	1.7e2	8.3	15
Cross section (mm^2)	87	66	86

Table 2: Distensibility between diastole and systole and cross sectional wall area for native pulmonary artery (PP) and autograft with degradative and healthy vSMCs (PAd, PAh).

Discussion

A clear reduction of dilatation rate can be observed when vSMCs keep their healthy phenotype, proving the relevance of finding pharmacological solutions to avoid phenotype switching. However, due to the continuous turnover of collagen, gradual dilatation cannot be fully avoided, such that also (temporary) mechanical support of the autograft is recommended.

References

1. Li et al, J Clin Invest. 130(3) :1233-1251, 2020.
2. Korotkevich et al, bioRxiv.
3. geneontology.org, 26/01/2023.
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