Linking gene dynamics to intimal hyperplasia – toward a predictive model of vein graft adaptation

Stefano Casarin[1,2], Scott A. Berceli[3,4], and Marc Garbey[1,2]

[1]Houston Methodist Research Institute, Houston, TX [2]LASIE UMR CNRS, University of La Rochelle, La Rochelle, France

[3]Malcom Randall VAMC, Gainesville, FL [4]Department of Surgery, University of Florida, Gainesville, FL

Introduction

Coronary Artery Bypass Graft (CABG) surgery is the most performed treatment in case of coronary artery occlusion [1].

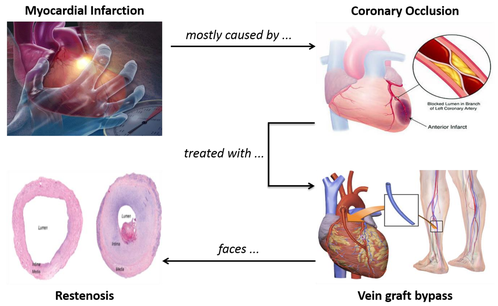

Fig. 1 – Vein graft for CABG surgery undergoes restenosis as result of unbalanced arterialization

Statistics show how a re-occlusion of the graft is experienced in 10-12% of the cases within just few months [2].

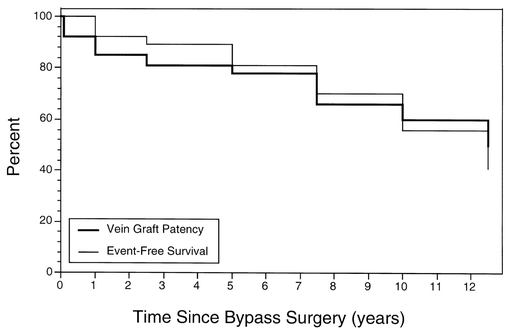

Fig. 2 – Long-term graft patency and event-free survival after saphenous vein bypass surgery [2]

An efficient therapy must be found at the genetic level. Accordingly, we propose a multiscale model that replicates both the arterialization of the graft and the impact employed by targeted group of genes on it.

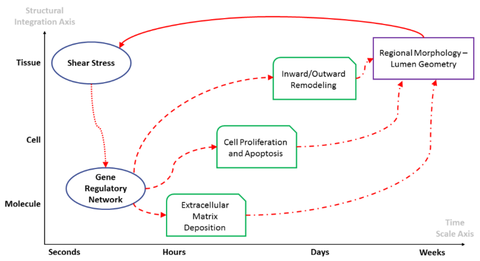

Fig. 3 – The dynamic interplay between events at different scales that regulates the arterialization of the graft described with a multiscale model

Our model links the genetic, cellular and tissue levels with feedback bridges. A variation on a single element is reflected on all the other components creating a highly organized loop.

Methods

Graft Arterialization

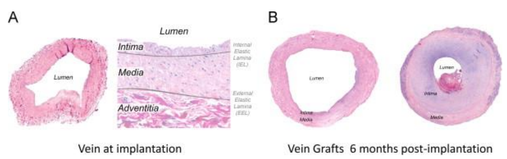

Fig. 4 – Structure and cross section of a healthy graft (A), that undergoes arterialization with different outcome after a 6 months follow up (B) [3].

Genes dataset

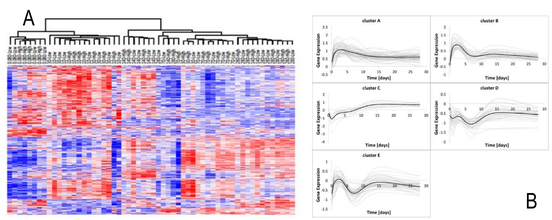

Fig. 5 – 34'990 genes microarray probe from rabbit model (A) collapsed in 5 significant clusters of expressions (B).

- The expression of over 34'000 genes is retrieved with microarray probe from rabbit model.
- 5 significant clusters are identified and their temporal dynamic recorded for a month of follow-up.

1. Dynamical System (DS)

$$\begin{cases} \dot{A}^I_{SMC} = -\alpha_1 \Delta\tau^- A^I_{SMC} \\ \dot{A}^I_{ECM} = -\alpha_2 \Delta\tau^- A^I_{SMC} \; if \; A^I_{ECM} > 0, and \; 0 \; otherwise \end{cases}$$

- The arterialization of the vein is replicated with a Dynamical System (DS) [3].
- The variation of intimal area due to SMC and ECM dynamics ($\dot{A}^I_{SMC}$ and $\dot{A}^I_{ECM}$) is triggered by perturbation in shear forces ($\Delta\tau^-$).
- The DS is driven by constant parameters (α_1 and α_2), originally heuristically evaluated from experimental observation.

2. Cluster Network (CN)

$$\begin{cases} \frac{d}{dt} G_1 = \lambda(t) \sum_{i=1}^{5} A_{i1}(G_i - B_i) \\ \dots \\ \frac{d}{dt} G_5 = \lambda(t) \sum_{i=1}^{5} A_{i5}(G_i - B_i) \end{cases}$$

- The expression of the targeted clusters (G_i) is replicated with an Ordinary Differential Equation (ODE) system.
- A third order polynomial function ($\lambda(t)$) drives the outcome toward the trend described by experimental data by simulating both the transient inflammatory state and the final relaxation.
- The constant B_i replicates the asymptotic trend of the experimental data

Hybrid Model

$$\begin{cases} \dot{A}^I_{SMC} = -\left[\frac{\sum_{i=1}^{5} \beta_{1i} * w_{1i} * G_{i_{Mit}}(t)}{5} - \frac{\sum_{i=1}^{5} \beta_{2i} * w_{2i} * G_{i_{Apop}}(t)}{5}\right] * \Delta\tau^- A^I_{SMC} \\ \dot{A}^I_{ECM} = -\left[\frac{\sum_{i=1}^{5} \beta_{3i} * w_{3i} * G_{i_{ECM}}(t)}{5}\right] * \Delta\tau^- A^I_{SMC} \; if \; A^I_{ECM} > 0, and \; 0 \; otherwise \end{cases}$$

- A hybrid model is obtained by replacing the constant parameters α_1 and α_2 with the time-dependent gene expression dynamic associated to cell proliferation and ExtraCellular Matrix (ECM) dynamic respectively.
- $\beta_{1i}, \beta_{2i}, \beta_{3i}$ scale the gene expression unit of measure into the hybrid model, while w_{1i}, w_{2i}, w_{3i} represent the weights that each cluster employs on the different cellular events. All of the are calibrated on a base of experimental data from rabbit model.
- The model is calibrated on experimental data, taking as reference the one-month follow up of intimal thickness within the rabbit model.

Intimal Thickness → **Genetic Algorithm (GA)**

- A gene therapy is simulated by acting on the gene network to directly minimize intimal thickness with a GA
- Effect of therapy on lumen radius and wall thickness is checked *a posteriori*

Results

From Fig. 6, the hybrid model gets closer to experimental data than the original DS. The model is validate is validated with a percentile error less than 1%

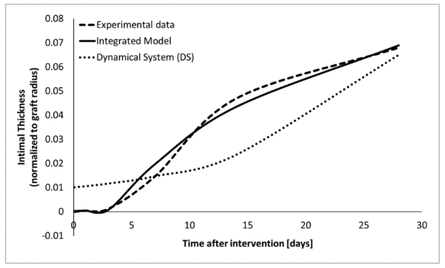

Fig. 6 – Intimal thickness temporal dynamic from rabbit model (dashed line) retrieved as output of the DS (dotted line) and the hybrid model (solid line)

From Fig. 7, by halving the expression of cluster C, a 98% reduction of intimal thickness is recorded. This doubles the lumen radius, but without affecting the thickening of the wall, which is a necessary condition for structural reasons.

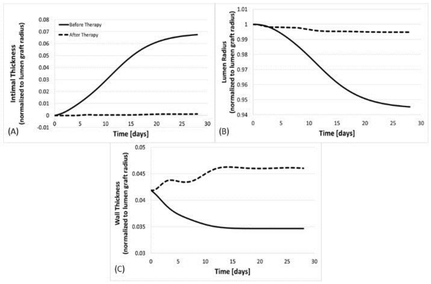

Fig. 7 – Graft arterialization in absence (solid line) and in presence (dashed line) of targeted gene therapy. Temporal dynamic of (A) intimal thickness, (B) lumen radius, and (C) wall thickness.

Conclusions

- The model is accurate and predictive.
- It is able to test in advance the outcome of targeted gene therapies.
- It can potentially reduced the number of potential therapies from million to just few hundreds, speeding up the research aimed to improve CABG surgery long-term outcome

Acnowledgments

The NIH grant U01HL119178-01 supported and currently supports this research

References

[1] Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. The Annals of Thoracic Surgery 1968; 5(4):334-339

[2] Motwani JG, Topol EJ. Aortocoronary Saphenous Vein Graft Disease: Pathogenesis, Predisposition, and Prevention. Circulation 1998; 97(9):916-931

[3] Garbey M, Berceli SA. A dynamical system that describes vein graft adaptation and failure. Journal of Theoretical Biology 2013; 336:209-220