Effects of Disruption of Endothelial Cell Functions on Vascular Remodeling

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http://www.csm.ornl.gov/Internships/rams_06/abstracts/a_reedy.pdf

INTRODUCTION

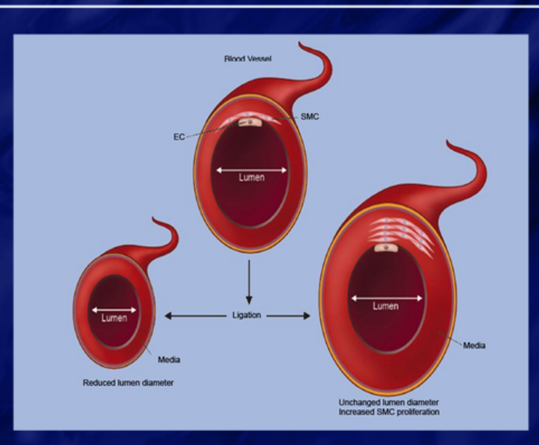
I. Vascular Remodeling Process

- Response of arterial wall to mechanical and/or biochemical injury
- Changes in arterial pressure and/or shear stress on the endothelial cell (EC) lining of arterial wall result from atherosclerotic lesions, balloon angioplasty, coronary atherectomy, intravascular stenting, and arterial grafting
- Alterations in arterial pressure or shear stress initiate signaling pathways in ECs, mainly the mitogen activated protein kinase (MAPK) pathway, leading to vascular remodeling
- ECs involved in dual components of vascular remodeling:
  - Geometrical remodeling – constrictive or expansive changes in arterial diameter
  - Intimal hyperplasia – deposition of smooth muscle cells (SMCs) and extracellular matrix (ECM) in inner layer of arterial wall (intima)

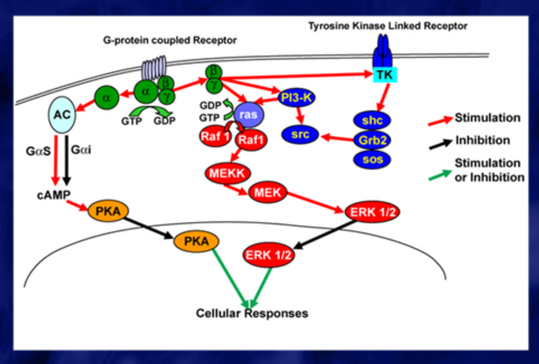
Different diagnostic methods for detection of vulnerable plaques: Magnetic Resonance Imaging (MRI), Computed Tomography (CT) Scan, Angiography, Intravascular Ultrasound (IVUS), Angioscopy, Optical Coherence Tomography (OCT), Thermography, Virtual Histology, Near Infrared (NIR)

II. Endothelial Cell Dysfunction in Vascular Remodeling

- Oxidizes low density lipoproteins (LDLs) to activate MAPK pathway for collagen degradation by upregulating matrix metalloproteinases (MMPs) 1 and 3 expression
- Decreases the nitric oxide synthase to increase smooth muscle cell (SMC) proliferation, reduce vasodilation controls, and intensify oxLDL synthesis
- Increases leukocyte migration and adhesion by upregulating cell adhesion molecules (CAMs) and chemokines (IL-8, MCP-1) via MAPK pathway
- Allows diffusion of lipids, monocytes, and leukocytes through sub-endothelial spaces from stress-induced conformational changes and reduced vasodilation controls
- Increases cytokines (TNF- alpha, IL1-Alpha) and growth factors (FGF, PDGF) to activate MAPK pathway for upregulation of EC expression of MMPs (1, 3, 8, 9, 11) to remodel ECM
- Results in intimal hyperplasia and/or positive or negative geometrical vascular remodeling of the artery



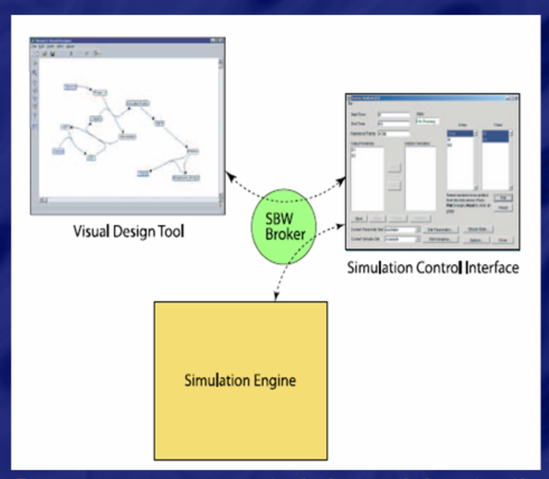
Geometrical Vascular Remodeling



Magnetic resonance imaging
MAPK Pathway

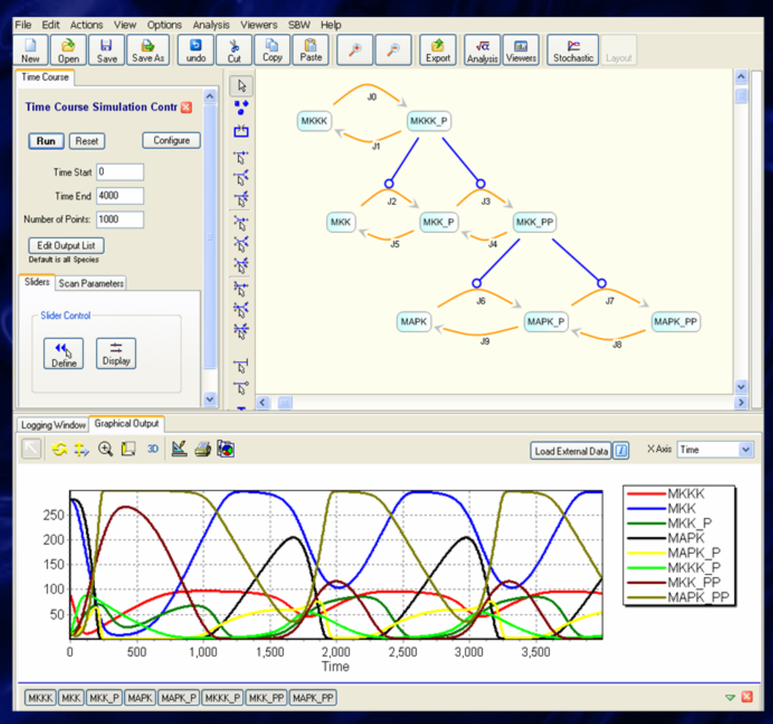
METHODS / PROCESSES

- Vascular remodeling process examined through analysis of critical MAPK cell signaling pathway
- Simulations of MAPK pathway performed utilizing California Institute of Technology's Systems Biology Workbench (SBW)
- SBW designed to share models and resources through libraries, messaging passing systems, and proxies
- SBW includes:
  - User interface for developing simplistic or detailed models
  - Two levels of Application Programming Interfaces (APIs) for integrating software components into SBW



Programmers connect their modules to the SBW system using interface libraries. The libraries implement the necessary APIs to communicate from one module to another via SBW framework. Data stream message passing back and forth through the infrastructure gives the appearance of direct communication.

RESULTS



MAPK Cascade Model (Simple Version)

CONCLUSIONS

- Primary goal is to understand vascular remodeling to produce patient-specific predictions and treatments
- Solutions for reducing vascular remodeling hypothetically lie in variation of treatment depending on biochemistry of patient:
  - Enhancing progenitor endothelial proliferation
  - Increasing NO production with estrogen
  - Auto-implanting progenitor endothelial cells
  - Inhibiting MMPs before collagen is converted to gelatin
  - Reducing MMP-proliferation of SMCs
- Detailed understanding of MAPK signaling biomechanisms may be crucial, as it affects most reactions of vascular remodeling
- SBW used to theoretically analyze future MAPK pathway models in simple or complex versions, although currently lacking reaction-diffusion modeling needed to research signaling pathways

FUTURE RESEARCH

- Integrate into complex computational models of vascular remodeling
- Incorporate an enhanced understanding of biomechanisms of vascular diseases
- Provide predictive models to optimize treatments for atherosclerosis and to reduce of intimal hyperplasia

The Research Alliance in Math and Science program is sponsored by the Mathematical, Information, and Computational Sciences Division, Office of Advanced Scientific Computing Research, U.S. Department of Energy. The work was performed at the Oak Ridge National Laboratory, which is managed by UT-Battelle, LLC under Contract No. De-AC05-00OR22725. This work has been authored by a contractor of the U.S. Government, accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes.

A special thanks to Kara Kruse and Richard Ward for this opportunity to research and learn while working on this project. Thank you to the excellent Vascular Research Team at the University of Tennessee Medical Center in Knoxville for all of their direction and experimental data in this on-going working project. Also, thank you California Institute of Technology for SBW information. Thanks to the Biology and Chemistry departments at Alabama Agricultural and Mechanical University for scholastic strengthening and a well-defined expectation bar. Additionally, thank you, Debbie McCoy for making the provisions for this research experience. Most importantly, thank God for navigating me.

Office of Science U.S. DEPARTMENT OF ENERGY

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