

A Computational Model for Analyzing the Biochemical Pathways of Matrix Metalloproteinase (MMP) 2 & 9 in Collagen IV Proteolysis Type

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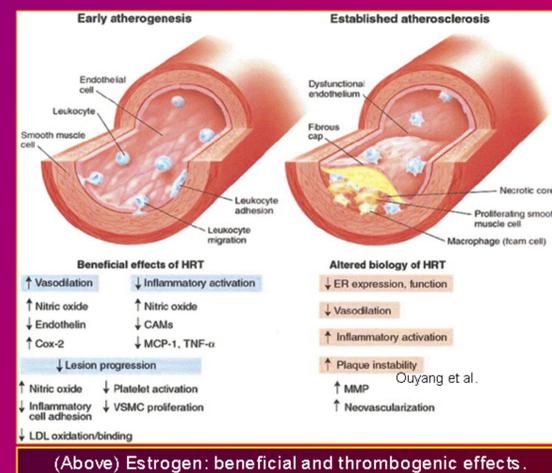
Computational Sciences and Engineering Division

http://www.csm.ornl.gov/Internships/rams_06/websites05/e_oquinn/

Matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase (MMP-9) belong to a family of enzymes responsible for the proteolysis of collagen and elastin that occur in the extracellular matrix (ECM) of arterial vessel walls. This process plays a vital role in various types of cardiovascular disease. While furthering investigation and implementation of a MMP-2 model from the literature, the research goal is to develop a similar model for MMP-9 and integrate the MMP-9 and MMP-2 models in association with estrogen studies. Pathways involving estrogen will be studied in correlation with the MMP theoretical model to better understand how hormone replacement therapy, in postmenopausal women, can have positive and/or negative effects on cardiovascular disease. Literature reports that estrogen is involved in the MMP mechanisms responsible for vascular remodeling and may have a direct or indirect affect on endothelial and smooth muscle cells. A computational model of the biochemical pathways involved in activation and inhibition of these proteases provides the user with a tool to determine the conditions under which these proteolytic processes are optimized.

Approach

- Complete implementation of MMP-2 model using JSim
- Implementation and analysis of MMP-9 proteolytic pathway
- Analysis of estrogen's link to MMP-2 and MMP-9 pathways
- Evaluate use of rate constants specific to MMP(s)
- Research references to evaluate input data
- Search for known substrates and reaction rates
- Analyze and develop specific experimental procedures with HPLC

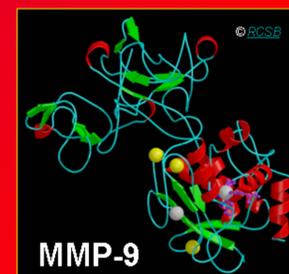
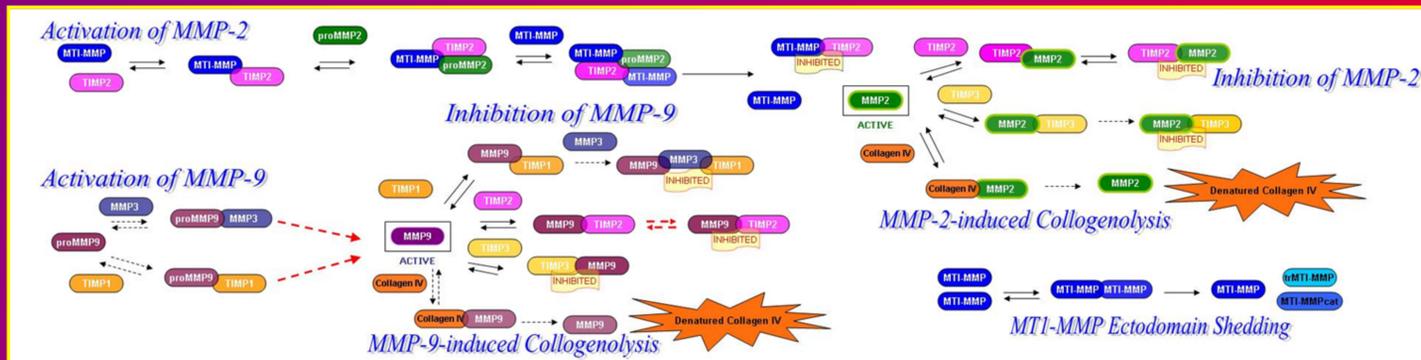


Implementation in JSim

- Developed by the University of Washington
- Mathematical modeling code
- Tool for modeling biochemical pathways
- Solved non-linear differential equation sets for modeling enzyme/substrate reactions

Experimental Analysis of Unknown Reaction Rates/Future Research

- Develop a protocol to measure rates of collagenolysis *in vitro* using high pressure liquid chromatography (HPLC)
- Measure reaction rates using HPLC
- Analyze individual and integrated models of MMP-2 & MMP-9 with measured rates
- Incorporate and analyze effects of estrogen on MMP-2 & MMP-9 models



Application

- ✓ This project also has important implications for other disease processes involving matrix metalloproteinases such as arteriosclerosis, angiogenesis in tumor formation, and some orthopedic diseases.
- ✓ This project is in collaboration with the Vascular Research Laboratory at the University of Tennessee Medical Center in Knoxville.