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

MMP-2

MMP-9

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http://www.csm.ornl.gov/Internships/rams_05/abstracts/e_oquinn.pdf

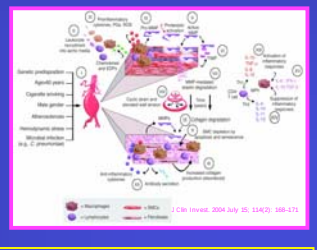
What ?

Matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) belong to a well documented family of enzymes responsible for the proteolytic processes that occur in the extracellular matrix (ECM) of arterial vessel walls. In arterial aneurysm formation, the biochemical reactions of MMP-2 and MMP-9 are known to play a vital role in the process of collagen, gelatin and elastin breakdown which lead to the ballooning of the artery and eventual rupture. 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. After investigation and implementation of a MMP-2 model for proteolysis of collagen type I published in the literature, my project was to develop a similar model for MMP-2 and MMP-9 for the proteolysis of collagen type IV, the predominant protein involved in the ECM of vascular tissue.

How ?

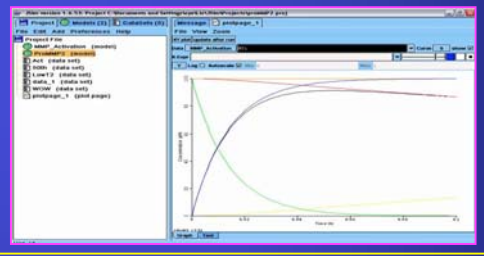
Approach

- Implementation of MMP-2 model using JSim
- Evaluate use of rate constants specific to MMP(s)
- Research references to evaluate input data
- Analysis of MMP-9 proteolytic pathway
- Search for known substrates and reaction rates
- Analyze previous experimental procedures
- Develop specific experimental procedures

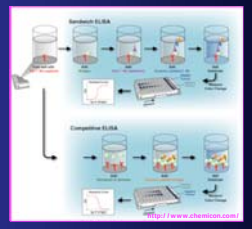


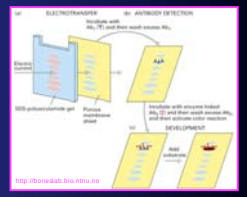
Left: Pathophysiology of abdominal aortic aneurysms (AAA). Schematic diagram illustrating events thought to contribute to the development and progression of AAA's.

Below: This is an example of data output from JSim model showing enzymatic behavior.



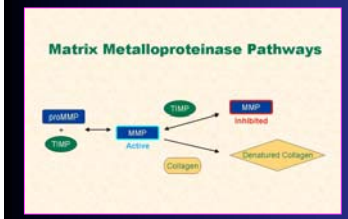
Enzyme-Linked Immunosorbent Assay (ELISA) vs. Western Blot





Implementation

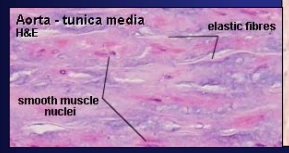
JSim
- Developed by the University of Washington
- Mathematical modeling code
- Tool to model biochemical pathways
- ✓ Important to check validity of reaction rates using experimental data

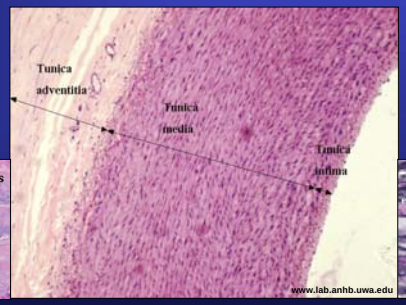


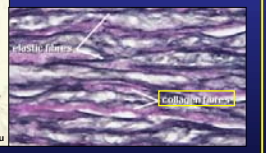
Experimental Analysis of Unknown Reaction Rates

- Analyze complex formation of MMP-2 & MMP-9 with collagen type IV
- Measure rates of collagenolysis in vitro using gel electrophoresis, gel transfer to nitrocellulose membrane and immunoblotting techniques
- Western blot used to differentiate between molecular weights
- This project is in collaboration with the Vascular Research Laboratory at the University of Tennessee Medical Center in Knoxville.

Histology of the Aorta







Why ?

Future Research / Application

✓ Kinetic modeling of proteolytic behavior is an approach for understanding complex systems which describe the enzyme's mechanism and behavior quantitatively.

✓ This project also has important implications for other diseases processes involving matrix metalloproteinases such as arteriosclerosis, angiogenesis in tumor formation, and some orthopedic diseases.

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