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

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[1], my project is 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. JSim[2], developed by the University of Washington, is the software application used for this research. Mathematical modeling code within JSim is used to model the biochemical pathways and the reaction rates at which the ECM is degraded by MMP-9 & MMP-2. Active MMP-2 (66-kDa Gelatinase) and active MMP-9 (82-kDa Gelatinase) each form a complex with collagen type IV to denature this ECM protein. Collagenolysis by MMP-2 and MMP-9 can be measured using gel electrophoresis, gel transfer to NCP paper and immunoblotting to further understand unknown reaction rates. This project is in collaboration with the Vascular Research Laboratory at the University of Tennessee Medical Center in Knoxville. Kinetic modeling of proteolytic behavior is an approach to 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.

[1] Karagiannis, E. D. and Popel, A. S., "A Theoretical Model of Type I Collagen Proteolysis by Matrix Metalloproteinase (MMP) 2 and Membrane Type 1 MMP in the Presence of Tissue Inhibitor of Metalloproteinase 2", *Journal of Biological Chemistry*, Vol. 279, No. 37, pp.39105-39114, 2004.
[2] http://nsr.bioeng.washington.edu/PLN/

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