Contribution ID : **82** Type : **Oral**

Structure and function studies on human plasminogen glycoforms

Thursday, 20 November 2014 12:10 (20)

Plasminogen is a 7-domain protein (with an N-terminal Pan-apple domain, five kringle domains and a C-terminal serine protease domain) that adopts a closed, activation-resistant conformation in the circulatory system. The recruitment of plasminogen to its target sites is dependant on the lysine binding sites of the kringle domains. Binding to lysine residues on cell receptors and fibrin clots simultaneously triggers a conformational re-arrangement of the molecule to adopt an open conformation. The open form is readily converted to plasmin by tissue- and urokinase-type Plasminogen Activators. Plasmin plays a key role in number of physiological and pathological processes including degradation of extracellular matrices, cell migration, tissue remodeling, wound healing, angiogenesis, inflammation, pathogen invasion and cancer migration.

We have solved the X-ray crystal structure of human plasminogen in the closed conformation. Our results revealed that the N-terminal Pan-apple domain and the serine protease domain maintain the closed conformation via interactions made throughout the kringle array, in particular, Kringles 2, 4 and 5. Our data suggests that Kringle 1 governs proenzyme recruitment to target sites and binding to external lysine of Kringle 5 in the closed conformation may trigger the formation of the open conformation.

Glycosylation affects the overall conformation of the protein and therefore its functions. There are two plasminogen glycoforms in the plasma; our structural data suggests that these glycoforms have distinct structural characteristics. Here we discuss our studies on the activation and inhibition of these two glycoforms.

Keywords or phrases (comma separated)

Glycosylation, fibrinolysis, conformation, crystallography, SAXS

Summary

Primary author(s) : Dr LAW, Ruby (Monash University)

Co-author(s) : Mr QUEK, Adam (Monash University); Ms ABU-SSAYDEH, Diana (Monash University); Prof. CASTELLINO, Francis (University of Notre Dame); Prof. WHISSTOCK, James (Monash University); Dr SANDERSON-SMITH, Martina (University of Wollongong); Dr COWIESON, Nathan (Australian Synchrotron); Prof. COUGHLIN, Paul (Monash University); CARADOC-DAVIES, Tom (Australian Synchrotron.)

Presenter(s) : Dr LAW, Ruby (Monash University)

Session Classification : Structural Biology I

Track Classification : Structural Biology