MedicalXpress

Clot-busting enzyme plays 'peek-a-boo' with blood clots

March 8 2012

By discovering how a blood clot-busting enzyme is switched on, researchers have unlocked a century-old atomic riddle that could lead to new treatments for clotting and bleeding disorders, and some cancers.

In findings published today in *Cell Reports*, Monash University researchers, led by Professor James Whisstock and Associate Professor Paul Coughlin, together with colleagues at the Australian Synchrotron have shown how the protein plasminogen is converted into plasmin, an enzyme that removes disease-causing clots and clears up damaged tissue.

Clinicians currently use drugs called plasminogen activators to generate plasmin in treating heart attack and stroke patients. Further, as plasmin is responsible for breaking down tissue barriers in cancer, a large number of researchers worldwide are developing plasmin inhibitors as anti-cancer therapeutics.

Professor Whisstock, from the Department of Biochemistry and Molecular Biology at Monash, said scientists had been trying for nearly a century to understand how plasminogen is activated to plasmin.

"Now we can see the atomic details of the plasminogen we can finally get a detailed picture of how the whole system works and how plasmin is produced," Professor Whisstock said.

Co-lead author, Dr Ruby Law, also of the Department of Biochemistry and Molecular Biology, said plasminogen displayed unexpected

behaviour.

"A casual look at the structure would suggest that plasminogen seems to completely guard its activation site. However, we found that one part of plasminogen seems to be very unstable and can transiently pop open a fraction – a little like a child playing a game of 'Peek-a-boo'," Dr Law said.

"Proteins in the blood clot bind to this part of the molecule when it is exposed, with the result that plasminogen is trapped in a form that can be converted to plasmin."

Dr Tom Caradoc-Davies, from the Australian Synchrotron, said the extremely intense X-ray crystallography beamline at the Synchrotron made it possible to determine the atomic structure of plasminogen.

"Plasminogen only yielded its secrets when exposed to the most focused and powerful X-rays the synchrotron can currently produce - technology which has only become available in the past few years," said Dr Caradoc-Davies.

Associate Professor Coughlin, of the Australian Centre for Blood Diseases at Monash said that until now, the molecular details of current plasminogen-activating drugs to treat stroke had not been understood.

"There are a large number of drugs in current clinical use, or in late stages of development, that function to convert plasminogen to plasmin. Now, we can use our current discoveries to improve the efficacy of these therapeutics," Professor Coughlin said.

Provided by Monash University