X-ray crystallography reveals structure of precursor to blood-clotting protein

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Using state-of-the-art robotic and x-ray crystallographic equipment, researchers at Saint Louis University have revealed for the first time the molecular structure of the zymogen, or inactive, form of a blood-clotting enzyme.

In an article published in Proceedings of the National Academy of Sciences, Enrico Di Cera, M.D., chair of the department of biochemistry and molecular biology at Saint Louis University School of Medicine and lead researcher of the study, said the NIH-funded research offers important information about the protein.

"This research is very basic and very important," said Di Cera. "It provides a missing link between the inactive zymogen form of thrombin and the mature enzyme generated upon vascular injury."

Before thrombin becomes active, it circulates throughout the blood in the inactive zymogen form. When the active enzyme is needed, for example after a vascular injury, the coagulation cascade is initiated and the zymogen is converted into an active enzyme that causes blood to clot.

Blood clotting performs the important function of stopping blood loss after an injury. However, when triggered in the wrong conditions, clotting can lead to debilitating or fatal conditions like heart attack, stroke and deep vein thrombosis.

In previous laboratory research, Di Cera re-engineered thrombin to act

as an anticoagulant, stopping blood from clotting and opening the door to the development of new therapeutic strategies for the treatment of thrombosis, the presence of blood clots in blood vessels, which is responsible for nearly a third of all deaths in the U.S.

While researchers have an understanding of the structure of active thrombin, very little was known about its zymogen form. In order to learn more, researchers used x-ray crystallography to gather data about the molecular structure of the protein.

The process involves growing a crystal of the protein, shooting x-ray beams through the crystal and analyzing the diffraction pattern generated on a detector plate in order to detail the three-dimensional structure of the protein.

The structure of the zymogen form of thrombin provides crucial details about the activation mechanism that sheds light on the way the mature enzyme works. Future research can capitalize on these new findings to define better strategies for therapeutic intervention.

"Until now, we've known nothing about the zymogen form of thrombin or any blood-clotting enzyme," said Di Cera. "All the structural information has been limited to the active form.

"We now know that the zymogen form of thrombin is very different from the mature enzyme, in ways that open new opportunities for therapeutic intervention."

Provided by Saint Louis University

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