Breakthrough in understanding of important blood protein

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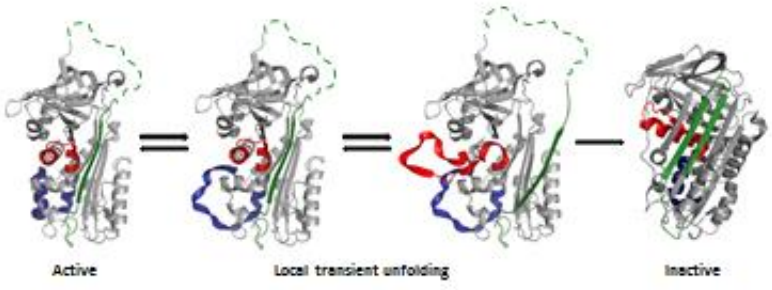

The red and blue ribbons show how the protein PAI-1 unfolds right before it destroys itself. On the last picture the protein's active site (green dotted line) has been inactivated (turned into a wide green line), indicating that now the protein is off. It cannot be activated again, but will be removed from the blood as garbage, and new PAI-1 proteins will be produced. Credit: University of Southern Denmark

The human body contains a unique protein that has the unusual property

of destroying itself after a few hours of existence - it must therefore be continually recreated and is no stable protein. The protein, called PAI-1, affects many physiological functions, including the dissolving of coagulated blood. If you get a blood clot, it is due to the fact that the a clot has accumulated in a blood vessel, and therefore PAI-1 is extremely important – for the human body's survival in general and for helping people with a blood clot or other blood diseases in which coagulation plays a role.

Now researchers from the University of Southern Denmark and Aarhus University in Denmark describe exactly how PAI-1 protein behaves in its short life. With this new detailed knowledge, researchers will now have a better understanding of how the protein is regulated, and that allows for a way to better control when it causes more or less coagulation.

"The shape change of PAI-1, we study, is one of the largest shape changes known in the world of proteins. Our findings provide insight into the mechanism of this shape change, and it gives us a fundamental new knowledge about the workings of nature", says Thomas J. D. Jørgensen, associate professor and research group leader at the Department of Biochemistry and Molecular Biology, University of Southern Denmark.

Along with postdoctoral researcher Morten Beck Trelle and their colleagues, postdoctoral researcher Jeppe B. Madsen and Professor Peter A. Andreasen, Department of Molecular Biology and Genetics, Aarhus University, he has published the findings in the prestigious journal *Angewandte Chemie*. The article is selected by the journal to be particularly important and has therefore been termed "Hot Paper". Morten Beck Trelle is first author.

Researchers now know that if you lack PAI-1 proteins, you will be at

increased risk of bleeding. Conversely, you have an increased risk of blood clots if you have too many PAI-1 proteins. The big challenge is to find a way to regulate PAI-1 proteins so precisely that you can use the regulation pharmaceutically.

PAI-1 has also been shown to be present in the blood at high levels in people who age faster than average, and it also appears to play a role in the development of tumors.

The University of Southern Denmark and Aarhus University researchers have revealed what specifically goes on in PAI-1's short life. This became possible, when Morten Beck Trelle and Thomas J. D. Jørgensen studied the protein using a highly refined technique (see below) which is used only a few places in the world - including the University of Southern Denmark.

"When PAI-1 gets ready to destroy itself it makes a special unfolding of itself. That is unique to this protein. We discovered that if we prevent this unfolding, the protein will not destroy itself - then it will remain active. One can thus regulate the protein - and thus provide more or less of it - by slowing or accelerating the unfolding of it, "explains Thomas J. D. Jørgensen.

Caption: The red and blue ribbons shows how the protein PAI-1 unfolds right before it destroys itself. On the last picture the protein's active site (green dotted line) has been inactivated (turned into a wide green line), indicating that now the protein is off. It cannot be activated again, but will be removed from the blood as garbage, and new PAI-1 proteins will be produced.

How did the researchers do:

The researchers studied the protein using hydrogen / deuterium exchange

and mass spectrometry (HDX-MS). This is an advanced technique where you weigh protein molecules when they are in heavy water (D2 O). Here the proteins will gradually replace some of their light hydrogen atoms (H) with heavy hydrogen atoms (D) according to their internal motions. The proteins thus become heavier, and this can be directly measured with a "weight" for molecules, namely a mass spectrometer.

Thomas J. D. Jorgensen and Morten Beck Trelle are specialists in this technique and by using a special technique they also managed to get a very detailed picture of the protein's molecular movement pattern. This particular technique is developed by Thomas J. D. Jørgensen and his research group, and it is now used by scientists worldwide.

Provided by University of Southern Denmark