

Targeting the molecular 'grip' of thrombosis

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(PhysOrg.com) -- New research at The University of Nottingham could help prevent the harmful blood clots associated with heart disease and stroke, the single greatest cause of disease-related death worldwide.

Scientists have gained new insights into the coagulation of <u>blood</u> in a study which could pave the way for new treatments aimed at preventing thrombosis — clots in the blood that obstruct the flow of blood through the <u>circulatory system</u> — as well as treatment of the inherited bleeding disorder thrombotic thrombocytopenic purpura.

These conditions arise from defects in the process of blood coagulation in the heart or brain. Now, for the first time, in a study funded by the Wellcome Trust, University of Nottingham scientists have revealed the 'hand-like' molecular structure of a receptor from the surface of platelets that can trigger blood clots.

Platelets are small cellular fragments which can trigger the development of harmful blood clots, known as thrombi, by aggregating and



obstructing blood flow. The strong grip of the platelet receptor glycoprotein Ib on its ligand plasma protein von Willebrand factor has been shown to be a key contributor to this process.

A team led by Dr Jonas Emsley at The University of Nottingham Centre for Biomolecular Sciences, in collaboration with Dr Robert Andrews from the Australian Centre for Blood Diseases at Monash University, have determined this new inhibitor complex structure. It marks a major step forward on the way to new drugs and treatments to tackle thrombotic disease.

This data reveals that the receptor structure forms the shape of a 'hand' which normally interacts with the extended finger tips and the thumb clasping the ligand von Willebrand factor. This is a firm hold required by the platelet to stick and utilises what is termed a large protein-protein interaction.

What is particularly interesting and unique about these new findings is the mode of action of the inhibitor to block this large protein-protein interaction. Instead of acting as a competitive inhibitor the structure shows the inhibitor acts allosterically — a process involving a change in the shape and activity of a protein that results from molecular binding with a regulatory substance at a site other than the active or ligand binding site.

It binds to a separate site to von Willebrand factor interaction on the palm of the 'hand'. This affects the receptor structure bending the 'thumb' region back and thereby very effectively preventing von Willebrand factor binding and thus platelet aggregation.

Dr Jonas Emsley, Associate Professor and Reader in Crystallography at The University of Nottingham, said: "Current anti-coagulants for treating thrombosis in heart attacks and strokes, such as heparin, target



multiple proteins. These often also play a central role in healthy blood clotting and hence are more prone to side effects, such as bleeding.

"Studies suggest that targeting glycoprotein Ib as anti-platelet agents could avoid these side effects, so this will be of great interest in the drive to discover novel anticoagulant therapies."

Targeting protein-protein interactions and using allosteric inhibitors is considered one of the great contemporary challenges in drug discovery, according to Scientific American, August 2009, page 64.

Platelet glycoprotein Ib is part of an extended family of proteins mediating protein-protein interactions involved in a variety of disease processes such as sepsis, asthma, immunodeficiencies, atherosclerosis, bacterial infection, Alzheimer's and leukaemia. This new structure has great potential to provide a template for targeting these other diseases.

"Although the complex structure represents a big step forward in understanding this important protein," Dr Emsley added, "it will require many more years of work to design and synthesise inhibitors that dock into the structure and can be translated into successful clinical drugs."

More information: The new study has just been published online in the journal <u>BLOOD</u>.

Provided by University of Nottingham (<u>news</u> : <u>web</u>)

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