Research uncovers target for safe and effective drugs to prevent heart attack-causing blood clots

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Researchers at the University of Birmingham have hit on a promising new molecule as a target for the development of better medicines to prevent blood clots, which could reduce lives lost from heart attacks and strokes.

Dr Yotis Senis – British Heart Foundation (BHF) Intermediate Research Fellow – and colleagues have discovered a vital new component of the trigger for blood clot formation, involving a protein called CD148.

CD148 has huge potential as a target for development of safer medicines than those currently used by thousands of people at risk of heart attack and stroke.

The research was published online last week in the journal Blood1.

Efficient blood clotting is vital to stop bleeding when we cut ourselves, but clot formation in diseased arteries feeding the heart or the brain can cause a heart attack or stroke. Together these conditions kill nearly 150,000 people in the UK every year2.

A blood clot – or 'thrombus' – builds up when small cells in the bloodstream, called platelets, sense injury.

Dr Senis explains: "When the inner wall of an artery is damaged because of fatty build-up, underlying cells and tissue are exposed. Like when a car's paintwork is bashed or scraped – you can see the underlying metalwork."

When protein 'sensors' on the surface of dormant platelets are exposed to these underlying tissues it acts as a wake-up call. The platelets immediately attach to the injured area and shoot out sticky arms to catch and clump together more cells. A fibrous mesh forms over the clot to stop it getting washed away with the force of the blood flow.

Dr Senis comments: "Our research is about identifying which of the proteins that stick out of the platelet surface are most important for the clotting process. This is no mean feat – we've used cutting-edge technology and ultra-sensitive equipment to uncover over 100 different surface proteins3, lots of which have a role in sensing injury and initiating thrombus formation."

Through careful analysis of human platelets' repertoire of surface molecules the researchers honed in on just a couple that looked like good candidates for further study.

One of these – CD148 – they've discovered is a really important player in the clotting process controlling the activity of other important platelet proteins that prime them for action. The team found that in mouse platelets in which CD148 was removed, the cells became sluggish and clots didn't form so well4. Importantly for the potential safety of any future medicines, getting rid of CD148 didn't cause dangerous bleeding.

Current anti-platelet medicines, such as aspirin are effective at protecting high risk people from heart attack or stroke. However, aspirin powerfully inhibits the activity of circulating platelets and as such carries risks of bleeding in the stomach5.

Medicines to block the action of CD148 have the potential to be less dangerous, because they target only one surface molecule leaving alternative activation proteins intact. CD148-blockers would potentially 'dampen' clotting activity without leaving the circulation unable to control bleeding.

Professor Jeremy Pearson, Associate Medical Director at the BHF – who funded the research – said: "Platelet research is vital to decipher the complex molecular processes underlying heart attack and stroke. What's particularly exciting about this discovery is that CD148 looks very promising as a realistic target for new drug development.

"It seems that blocking CD148 won't wipe out clotting ability, which is important for the safety of new anti-platelet drugs. Also, a large part of CD148 sticks out from the cell surface making it an ideal pharmaceutical target because medicines that circulate in the bloodstream would be able to find it easily. Target molecules that reside inside cells present an obstacle for drug-design, because the medicine would have to cross the cell surface in order to reach them.

"We look forward to supporting Dr Senis' as he advances with CD148 in the fight against heart disease."

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For further information contact Ben Hill, Press Officer, Tel 0121 4145134, Mob 07789 921163

Notes to editors

1 - The tyrosine phosphatase CD148 is an essential positive regulator of platelet activation and thrombosis by Yotis A. Senis et al. Blood First Edition Paper, prepublished online February 25, 2009; DOI 10.1182/blood-2008-08-174318. http://bloodjournal.hematologylibrary.org/papbyrecent.dtl

2 - BHF Coronary Heart Disease Statistics 2008. heartstats.org

3 - A comprehensive proteomics and genomics analysis reveals novel transmembrane proteins in human platelets and mouse megakaryocytes including G6b-B, a novel ITIM protein by Yotis A. Senis et. al. Molecular and Cellular Proteomics 2007;6:548-64

4 – Videos clearly showing the disturbed activation and clot-forming activity of CD148-'knocked out' platelets are available. Captions for the videos can be found below.

5 – For more information about current anti-platelet drugs and other medicines, download or order BHF's booklet 'Medicines for the Heart' at bhf.org.uk/publications

- Dr Yotis Senis is a BHF Intermediate Research Fellow. He works within the research team led by BHF Chair, Professor Steve Watson

- The British Heart Foundation (BHF) is the nation's heart charity, dedicated to saving lives through pioneering research, patient care, campaigning for change and by providing vital information. But we urgently need help. We rely on donations of time and money to continue our life-saving work. Because together we can beat heart disease. For more information visit bhf.org.uk

- The University of Birmingham has around 27,000 students and 6,000 members of staff and a turnover of £360 million. The School of Medicine has been delivering medical education for more than 180 years. It has doubled its intake of medical students over the last five years. Over 85% of students stay in the area in which they trained, once they have qualified. The School of Medicine teaching links with sixty-five general practices and sixteen teaching hospitals. All sixteen teaching hospitals and an increasing number of teaching General Practices are linked to the University by a broadband IT virtual campus.