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Editorial Focus

A radical explanation for the effect of the HPA-1b polymorphism in platelet αIIbβ3-integrin?

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Reactive oxygen species (ROS) have generally been considered as the "bad guys" of cell biology, and the focus on redox reactions has tended to be on the oxidative burst generated by the professional phagocytic cells, with high levels of free radical generation, and low levels of naturally occurring antioxidants associated with a variety of disease states including cardiovascular diseases. However, most if not all cells generate ROS as part of their normal cellular processes. Platelets are no exception, and evidence over the past few decades has clearly implicated ROS in various aspects of the platelet response. One area of emerging focus is the redox state of the platelet surface receptors. It has been known for more than 30 years that platelets have large numbers of free thiols on their surface, and these are found in many of the key glycoprotein receptors, including the agonist receptors for both collagen (GPVI) and ADP ($P2Y_{12}$), and adhesion receptors including GPIbα, α2β1-integrin and, relevant here, the αIIbβ3 fibrinogen receptor (1). The state of free thiols in these receptors appears to be an important regulator of function, through rearrangement of thiol/disulphide bonds involving endogenous, membrane associated protein disulphide isomerases (PDI), and the availability of the reduced form of glutathione (GSH).

However, redox regulation of the αIIbβ3-integrin is not the only factor affecting its function and many groups, including our own, have sought to understand the relationships between genetic sequence variation and αIIbβ3-integrin function. Since the report of Weiss et al. more than 10 years ago (2) one single nucleotide polymorphism (SNP) in αIIbβ3-integrin has dominated the literature: This is rs5918, the non-synonymous SNP in the β3-chain that results in a leucine to proline substitution at amino acid 33, resulting in the HPA1b (or Pl^{A2}) alloantigen. Recent data from Paul Bray's group suggests the main effect of this particular SNP is seen in outside-in signalling; in particular as a result of adhesion of the αIIbβ3 receptor to fibrinogen (3), rather than inside-out signalling. This helps to explain some of the conflicting data in the literature for this polymorphism, and reinforces our own findings as part of the Bloodomics study of the genetic regulation of platelet function (http://www.bloodomics.org/web/), in which fibrinogen binding to αIIbβ3-integrin was measured in platelets from a cohort of 500 healthy subjects (4), activated through the ADP and collagen signalling pathways (i.e. inside-out signalling). No association was found between this, or any other polymorphisms, in the αIIbβ3-integrin, despite an extensive strategy of resequencing and tagging to capture all potential sequence variation, resulting in genotypying of >100 tagSNPs for this receptor.

In the paper by Ball et al. (5) in this issue of *Thrombosis and Haemostasis*, three groups of researchers have combined forces to further clarify the importance of the redox state of the αIIbβ3-integrin in platelet adhesion, and to explore differences between the HPA-1a (leucine) and HPA-1b (proline) forms under conditions of flow. Adhesion of stably transfected Chinese hamster ovary (CHO) cells to fibrinogen was inhibited by physiologically relevant concentrations of glutathione (GSH), and at a ratio of GSH to its oxidized form (GSSH) that favours oxidation. The effect appeared to be independent of platelet activation as the αIIbβ3-integrin in the transfected cells was in a constitutively activated state. In the absence of GSH there was a significantly increased adhesion of the cells expressing the proline form of β3-chain, but this difference was abolished in the presence of GSH. As further evidence that these data may demonstrate a physiologically-relevant mechanism, platelets from HPA-1a and HPA-1b donors exhibited very similar responses to the transfected CHO cells.

This present study provides further evidence of the potential interaction of the redox state of αIIbβ3-integrin and of the proline-33 variant of β3-chain that appear to regulate this key platelet receptor. Much still remains to be explained. In particular, the specific effect of the leucine-proline substitution on the structure of the αIIbβ3 complex, and whether this alters the behaviour of the sulfhydril groups within the β3-chain of the receptor.

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