CORRESPONDENCE

ABSENCE OF THE γ-Leu 427 (γ′) VARIANT IN THE PLATELET α-GRANULAR FIBRINOGEN POOL SUPPORTS THE ROLE OF GLYCOPROTEIN IIB/IIIA IN MEDIATING FIBRINOGEN UPTAKE INTO PLATELETS/MEGAKARYOCYTES

To the Editor:

There is increasing evidence for the plasmatic origin of platelet α-granular fibrinogen (FG).[1-6] Furthermore, it has been proposed that glycoprotein (GP) IIb/IIIa and/or other FG binding integrins may mediate FG endocytosis within megakaryocytes (MKs) and platelets. Recently, Coller et al[7] related the relative contributions of the platelet GPIIb/IIIa and $\alpha_v\beta_3$ (vitronectin) receptors to the intracellular levels of FG and vitronectin in platelets from two groups of Glanzmann's thrombasthenic patients: Iraqi-Jewish patients lacking both receptors and Arab patients deficient only in GPIIb/IIIa. They concluded that GPIIb/IIIa is probably the major receptor mediating FG uptake and that $\alpha_v\beta_3$ probably plays little or no role in this process. They also suggested a novel role of $\alpha_v\beta_3$ in the exocytosis of vitronectin from MKs and platelets.

Two further pieces of evidence also support the exclusive role of GPIIb/IIIa in mediating FG endocytosis: (1) the complete absence within platelets of the γ-Leu 427 (γ′ variant) lacking the γ chain GPIIb/IIIa binding sequence in both normals[8] and patients with certain forms of dysfibrinogenemia[9]; and (2) the inability of the normal γ-chain to bind to the $\alpha_v\beta_3$ receptor.[10] The apparent dependence of FG uptake on the presence of the normal FG γ-chain site (residues 400-411) would therefore suggest that the $\alpha_v\beta_3$ is not important in FG uptake. However, it is still possible, that FG could bind simultaneously to $\alpha_v\beta_3$ and GPIIb/IIIa via the α- and γ-chains, respectively, and that cooperation between the two receptors may mediate FG binding and ultimate uptake. Coller et al's data would suggest that $\alpha_v\beta_3$ is unlikely to be relevant in this process.[7] Further studies may delineate this novel function of GPIIb/IIIa and the role of the γ-chain in this process.

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RESPONSE

Harrison et al discuss some subtle, but important implications of our study of platelet fibrinogen and vitronectin in patients with Glanzmann thrombasthenia, and we welcome their support for our conclusion that glycoprotein (GP) IIb/IIIa is the major receptor mediating fibrinogen uptake. We would caution, however, against interpreting our data as indicating an "exclusive" role of GPIIb/IIIa in this process, because although total platelet fibrinogen was markedly reduced in both groups, there was a consistent suggestion that the platelets of the Iraqi-Jewish patients (who lack both GPIIb/IIIa and $\alpha_v\beta_3$) had a slightly more severe fibrinogen deficiency than did the platelets from the Arab patients (who lack only GPIIb/IIIa). It is also important to interpret our data in the light of the marked difference in quantitative expression of GPIIb/IIIa (~40,000 to 50,000 receptors per platelet) and $\alpha_v\beta_3$ (50 to 200 receptors per platelet). Thus, even if $\alpha_v\beta_3$ is as efficient as GPIIb/IIIa in mediating endocytosis of fibrinogen, the $\alpha_v\beta_3$ receptor would be expected to contribute less than 0.5% of the total platelet fibrinogen. Such a contribution could be consistent with the small differences in platelet fibrinogen we observed while still producing a γ′ concentration below the 1% of total platelet

fibrinogen estimated to be required for its detection even with sensitive techniques.[1] We would also caution against interpreting the study cited by Harrison et al[2] as indicating that platelet $\alpha_v\beta_3$ receptors cannot bind fibrinogen γ-chains because the $\alpha_v\beta_3$ receptors in that study were on endothelial cells, not platelets; precedent exists for apparently identical integrin receptors having different ligand specificities when expressed in different cells.[3,4] We therefore believe that more data will be required to establish the ligand specificity of platelet $\alpha_v\beta_3$ receptors and whether they can mediate uptake of plasma fibrinogen into α-granules.

Although it was not the subject of our study, we certainly agree with Harrison et al that the nearly complete or complete absence of fibrinogen containing the γ′ chain in platelets is a very important observation.[1,5,6] This would seem to exclude a major uptake mechanism mediated by either of the two RGD sequences in the Aα-chains, even though an antibody to the RGD sequence near the carboxy-terminus of the Aα-chain can inhibit platelet adhesion to immobilized fibrinogen by ~40%.[2] Moreover, because even the heterodimeric γ, γ′-fibrinogen molecules appear to be excluded, it leads to the intriguing possibility that both γ-chain dodecapeptides are required, suggesting a requirement for bivalent binding to two different GPIIb/IIIa receptors to trigger endocytosis. Further studies of these phenomena are likely to lead to important new insights into the requirements for both ligand binding and endocytosis.

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