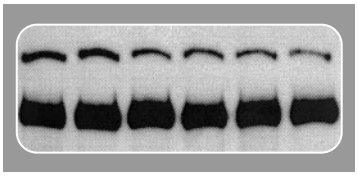
inside blood

GPIb, filamin, and platelet activation: a view from within

The platelet glycoprotein Ib (GPIb) receptor, once thought to have a straight-forward hemostatic function by mediating high-shear–dependent platelet adhesion to von Willebrand factor (VWF), is increasingly recognized as having a potentially diverse range of cellular functions. Over the last few years, an impressive number of potential ligands (VWF, thrombin, factors XI and XII), counter-receptors (Mac-1 [CD11b/CD18], P-selectin), and binding partners (filamin A, 14.3.3) for GPIb have emerged, and functional roles of this receptor now



extend to the regulation of the platelet cytoskeleton, coagulation, and potentially inflammation. GPIb also has the capability of transmitting signals linked to integrin $\alpha_{IIb}\beta_3$ activation, a fundamental step in the normal hemostatic and thrombotic processes. However, a clear understanding of how this receptor transduces signals has yet to emerge. One possibility, examined by Feng and colleagues in this issue (page 2122), is that the membrane skeletal anchorage of GPIb, as a consequence of its binding to filamin A, is necessary for cytoskeletal signaling events linked to integrin $\alpha_{IIb}\beta_3$ activation.

Feng and colleagues delve deeper into the molecular basis and functional importance of the interaction between the cytoplasmic tail of GPIbα and filamin A. In initial studies, they provide further definition to the specific region in the GPIbα tail that is required for filamin A binding, suggesting that the primary binding site may reside within residues 557-575, a finding consistent with previous observations.[1,2] To elucidate the functional consequences of disrupting the GPIb-filamin interaction in intact platelets, Feng et al employed a novel approach using a cell-penetrating peptide incorporating residues 557-575. The peptide specifically inhibited VWF-dependent aggregation and, under pathologic shear conditions, inhibited GPIb association with filamin. Moreover, the reduction in filamin binding to GPIb correlated with the inhibition of shear-dependent tyrosine phosphorylation suggests a role for this interaction in the regulation of GPIb signaling and, potentially, integrin $\alpha_{IIb}\beta_3$ activation.

These results are interesting and potentially important and, although they fall short of definitively establishing an essential role for the GPIb-filamin interaction for integrin $\alpha_{IIb}\beta_3$ activation, they nonetheless provide additional evidence that this interaction is likely to play a fundamental role in regulating the adhesive and signaling function of GPIb. These studies are timely as the recent development of transgenic mouse models expressing mutant forms of GPIb, combined with an improved understanding of the molecular basis for the GPIb-filamin interaction, sets the scene for more definitive studies on the importance of this interaction for normal platelet physiology. Perhaps some clarity to this long-standing vexing issue of platelet function will soon be realized.

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1. Englund GD, Bodnar RJ, Li Z, Ruggeri ZM, Du X. Regulation of von Willebrand factor binding to the platelet glycoprotein Ib-IX by a membrane skeleton-dependent inside-out signal. J Biol Chem. 2001;276:16952-16959.
2. Williamson D, Pikovski I, Cranmer SL, et al. Interaction between platelet glycoprotein Ibα and filamin-1 is essential for glycoprotein Ib/IX receptor anchorage at high shear. J Biol Chem. 2002;277:2151-2159.

Good-bye to GVHD

Bone marrow transplantation would be even more widely used if the complications of graft-versus-host disease (GVHD) could be routinely and simply avoided. GVHD is induced by T cells in the bone marrow (BM) graft recognizing and reacting against the host. The disease tends to be much more severe when host and donor differ at the major histocompatibility complex (MHC) but can also occur for MHC-identical transplants. The simple solution of removing all T cells from the graft prevents GVHD induction but then the graft, for reasons that are not totally clear, often fails. Residual T cells not only promote engraftment but also may provide some immune (particularly antitumor) protection. A solution to this problem might be a procedure that specifically removes only those T cells in the graft that can recognize and react against the host. Bachar-Lustig and colleagues (page 1943) describe such a protocol using "veto cells" for the successful transplantation of fully allogeneic BM containing large numbers of allogeneic T cells. They have worked with a mouse model but the design is such that the protocol should be readily transferable to the clinic. More important, they also show that when the immunosuppressive drug rapamycin is included in the protocol, it synergizes with rather than blocks the action of the veto cells.

Veto cells have been defined as cells that can delete T cells that recognize them.[1] As reviewed by Bachar-Lustig and colleagues, a number of different cells appear to have this ability, among them being $CD8^+$ cytotoxic T-lymphocyte (CTL) lines. Let A, B, C, and D represent 4 MHC-different inbred mouse strains. When an A anti-B mixed-lymphocyte reaction (MLR) is set up, strain-A origin CTLs reactive against strain B are generated. If $CD8^+$ CTLs syngeneic to the strain-B stimulator but not reactive against the A-strain responder (eg, from a B anti-D MLR) are included in the culture, they act as veto cells.[2] A anti-B CTL precursors in the culture that recognize strain-B antigens on the added CTLs are now known to undergo apoptosis in a process involving both CD8 and Fas-L on the veto cell (Figure 1 in Bachar-Lustig et al). When the same B anti-D CTLs are added to an A anti-C MLR they do