TABLE 50-2 PROCOAGULANT PROPERTIES OF PLATELETS

RECEPTOR-LIGAND INTERACTIONS PROMOTING ADHESION
*GPIb-IX-V-vWF †GPIIb/IIIa-fibrinogen and GPIIb/IIIa-vWF ‡GPIa/IIa-collagen §P-selectin–P-selectin glycoprotein ligand-1
RECEPTOR-LIGAND INTERACTIONS MEDIATING ACTIVATION
GPV-thrombin GPVI-collagen
SECRETED ALPHA-GRANULE PROTEINS
Ligands (fibrinogen, fibronectin, thrombospondin, vitronectin, von Willebrand factor) Enzymes (α_2-antiplasmin; factors V, VIII, and XI) Antiheparin (platelet factor 4)
SECRETED DENSE-GRANULE AGONISTS
Adenosine diphosphate, serotonin
COMPONENTS AND FUNCTIONS OF PLATELETS WHICH PROMOTE COAGULATION
Thromboxane A_2 formation, phosphatidylserine expression

GP, Glycoprotein.
*GPIb-IX-V complex is also known as CD42.
†GPIIb/IIIa (integrin $\alpha_{2b}\beta_3$) complex is also known as CD41.
‡GPIIa is also known as CD29.
§P-selectin is also known as CD62P and P-selectin glycoprotein ligand-1 as CD162.

transmembrane signaling produced by the GPIb-V-IX-vWF interaction results in loss of the normal platelet discoid shape and conformational change in another platelet receptor, GPIIb/IIIa (see Fig. 50-1A).

Ligands

The activated GPIIb/IIIa receptor then binds either to fibrinogen or to the larger vWF multimers at a site distinct from the GPIb-IX-V binding site. This secondary adhesion is a higher-affinity interaction, and it secures the platelets firmly to the subendothelium (see Fig 50-1B). At shear rates that approximate arterial occlusion, platelet adhesion to vWF multimers can be mediated entirely through GPIb-V-IX-vWF binding without platelet activation. One important regulator of this process of platelet binding and activation through vWF is the circulating vWF-cleaving protease in plasma; this is a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13). ADAMTS-13 modulates the activity of vWF by cleaving the ultralarge multimers into smaller fragments that have reduced overall affinity for platelet binding. Besides directly activating platelets, thrombin causes proteolysis of ADAMTS-13, thereby promoting the persistence of large vWF multimers and enhanced platelet recruitment into areas of vessel injury. Congenital or acquired pathologic loss of the ADAMTS-13 cleaving protease activity results in unchecked platelet adhesion to ultralarge vWF multimers and widespread microvascular thrombosis (see the discussion of *thrombotic thrombocytopenic purpura* in Chapter 52).

At more moderate shear rates, GPIb-V-IX-vWF adhesion is supplemented by platelet binding to subendothelial collagen, an adhesive moiety that is capable of arresting the platelet by binding to GPIa/IIa (see Table 50-2). Thus, subendothelial vWF and collagen act cooperatively to initiate platelet adhesion, with the former predominating at higher shear. Collagen is unique in that it can anchor platelets at one locus by binding to platelet GPIa/IIa and activate platelets at a second locus by binding to platelet GPVI; both platelet receptors are critical for physiologic platelet function. Indeed, the congenital absence of any of the critical platelet adhesion receptors—GPIIb/IIIa, GPIb/IX-V, GPVI, or GPIa/IIa—results in a significant hemostatic defect, correctable only by platelet transfusion. This finding is further reinforced by the fact that the α chain of GPIb normally serves as a cofactor for thrombin activation of platelets through both the GPV receptor and the protease-activated receptor (PAR). Like defects in platelet receptors, decreases in the vWF ligand, especially the larger multimeric forms, can lead to bleeding.

Once a layer of platelets is adherent to the site of injury, vWF bound to GPIb-IX-V on the luminal side of the adherent platelets serves to recruit additional platelets from the flowing blood into the growing platelet plug. Platelet recruitment is further enhanced by platelet activation and release of serotonin and ADP, which serve to activate and adhere platelets from the circulation to the growing platelet clot (see Fig. 50-1B and Table 50-1). Platelet activation is actually a series of interdependent processes with five major effects: (1) local release of ligands essential to stabilization of the platelet-platelet matrix, (2) continued recruitment of additional platelets, (3) vasoconstriction of smaller arteries to slow bleeding, (4) localization and acceleration of platelet-associated fibrin formation, and (5) protection of the clot from fibrinolysis.

The basis of the platelet plug is a platelet-ligand-platelet matrix with fibrinogen, fibronectin, and vWF serving as bridging ligands (Fig. 50-3). Both fibrinogen and vWF are endocytosed from plasma and stored in alpha granules inside the resting platelet, and both are released with activation. Fibrinogen plays the predominant role of binding to a GPIIb/IIIa receptor on each of two platelets, thereby linking them. Some data suggest that vWF is capable of a similar role. As mentioned earlier, platelet GPIIb/IIIa undergoes a calcium-dependent conformational change that allows it to bind to a locus containing the amino acid sequence arginine-glycine-aspartate (RGD) on fibrinogen, fibronectin, or vWF. Each fibrinogen molecule has two RGD sites on its polar ends, and the larger vWF multimers have several RGD sites, all capable of binding to conformationally altered GPIIb/IIIa and creating the platelet-ligand-platelet matrix. GPIIb/IIIa is the most abundant glycoprotein on the platelet surface, with about 50,000 copies on the *resting* platelet and additional GPIIb/IIIa receptors within the platelet cytosol that are mobilized to the surface after activation.

Activation

Platelets are also recruited into the platelet plug by local agonists (collagen, epinephrine, and thrombin) and by platelet release of agonists into the local microenvironment (see Fig. 50-1B). Both collagen (as noted previously) and thrombin interact with their specific platelet receptors to activate platelets strongly; although epinephrine alone is not a powerful platelet agonist, stimulation of the α-adrenergic receptor on platelets primes them for synergistic activation by even relatively weak agonists such as ADP. Activating compounds released directly from the platelet include thromboxane A_2 (TXA_2), which is formed in the platelet cytosol after cyclooxygenase 1 (COX1)–mediated