Platelets are normally responsible for the arrest of bleeding but this function, for example, their ability to aggregate can contribute to pathological states, such as atherosclerosis and heart disease. In addition to their obvious role in hemostasis/thrombosis, platelets also seem to be firmly rooted with a great deal of other tasks primarily related to inflammatory/immune mechanisms. In particular, platelets express many important immune molecules such as T- and B-lymphocyte costimulatory CD154/CD40 molecules, bacterial proteins, and most of the members of the Toll-like receptor family. It is becoming increasingly recognized that these types of molecules empower platelets with the ability to play critical proinflammatory immune-like roles in infectious states such as sepsis. Toll-like receptors are germ-line pattern recognition receptors and probably the most important immune sentinels of infectious attack, and all 13 members contain a common structural motif in the form of leucine-rich repeat units. Similarly, the GPIb-IX complex on the platelet also contains leucine-rich repeat; however, whether this shared sequence with Toll-like receptors confers anti-infectious properties to GPIb-IX is not clear. In this issue, Corken et al have attempted to define some of the physiological (Figure) functions of platelet GPIb-IX in a murine model of sepsis.

See accompanying article on p 996

The authors used von Willebrand factor (vWF) knockout mice and mice devoid of GPIb-IX and exposed them to a well-characterized cecal ligation and puncture (CLP) procedure to assess the role of the GPIb-IX/vWF axis during sepsis. The murine GPIb-IX-deficient mice (hIL-4R/Ib) express a chimeric α-subunit of GPIb-IX, which consists of the human interleukin-4 receptor extracellular fragment fused to the transmembrane and cytoplasmic domains of human GPIb rendering the mice deficient in the endogenous murine GP Ib gene. The results demonstrate that in contrast to the well-known proinflammatory aspects of platelets, GPIb-IX contributes to an anti-inflammatory property measured by changes in platelet/neutrophil and platelet/monocyte interactions, Mac-1 expression and proinflammatory chemokine/cytokine secretion. This not only identifies GPIb-IX as an important player in modulating the host’s anti-infectious innate immune system but also unveils another piece of the puzzle of the inflammatory and coagulation interface. During sepsis the majority of patients (and animals) become thrombocytopenic although one of the deleterious effects of sepsis is platelet activation and likely thrombosis. Why this occurs is still unknown; however, it may relate to how infectious agents interact with platelets perhaps via the GPIb-IX/vWF axis. Surprisingly, one of the key observations of the article was that compared with wild-type mice, vWF knockout mice exhibited reduced mortality in the CLP model. This was not observed in mice devoid of GPIb-IX. This suggests that the GPIb-IX complex is somehow protective by reducing inflammation but alternatively may be pathological via increasing platelet aggregation; loss of the GPIb-IX phenotype transforms the animal to a wild-type response against CLP. Thus, eliminating the ligand portion of the GPIb-IX/vWF axis improves survival, whereas eliminating the receptor portion of the axis was not beneficial. It was also found that in contrast to the WT and vWF knockout mice, there was a significant reduction in both platelet monocyte and platelet neutrophil associations in the GPIb-IX–deficient mice. To determine whether these reduced platelet/leukocyte associations correlated with altered proinflammatory cytokine production, serum tumor necrosis factor levels were measured. Compared with prebleed samples, by 24 hours after CLP, tumor necrosis factor levels in GPIb-IX–deficient mouse serum were significantly higher compared with serum levels in wild-type or vWF knockout mice. This was also observed for other primarily monocyte-derived proinflammatory chemokines and cytokines. In sharp contrast, interleukin-15 levels seemed to be dependent on the expression of GPIb-IX. Taken together, the results demonstrate that the expression of GPIb-IX attenuates several proinflammatory processes related to platelet–monocyte/neutrophil interactions, cytokine secretion, and adhesion molecule expression. Although we tend to think of platelets as proinflammatory in nature, these experiments identify a novel anti-inflammatory role for GPIb-IX where abrogation of the molecule acts to suppress platelet interactions with monocytes and neutrophils, and this somehow leads to enhanced chemokine/cytokine levels and increased Mac-1 expression by neutrophils.

The authors show us yet another unidentified piece of the platelet/immune axis, but their results also raise several questions related to how the lack of GPIb-IX reduces platelet–leukocyte aggregate formation and dampens chemokine/cytokine responses. For example, as the authors discuss, does this reflect the activation status of the platelets in the CLP mice? However, is it possible that like Toll-like receptor, GPIb-IX interacts with and binds infectious agents and does this affect...
monocytes and neutrophils? And from an immunologist’s perspective, the only cytokine that seemed to be dependent on intact GPIb-IX was interleukin-15, a predominantly monocyte-derived cytokine that essentially supports the generation of T-lymphocyte responses; do GPIb-IX-dependent lymphocyte responses, for example, T-regulatory cells aid in the observed anti-inflammatory effect? It is only a matter of time before the fine details of how GPIb-IX dampens proinflammatory responses in sepsis are revealed.

Disclosures
The author declares no financial conflicts.

References

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