studies suggest, and the spleen participates in the clearance of PS-positive vesicles after their release, then the prothrombotic effects of extruded vesicles may be greater than predicted based on the percentage of PS-positive erythrocytes alone. Further evidence and characterization of such free vesicles in vitro and in vivo is now crucial. Second, if it is determined that PS-positive vesicles, in isolation or tethered to erythrocytes, contribute to thrombosis in SCD, then strategies aimed at removing these vesicles or cells from the circulation could be therapeutically useful. Some of the uniquely exposed inside-out epitopes might, for example, provide a means to overcome the desensitization of hyposplenism; the “don’t eat me” signal conferred by CD47 should be inside-out and make targeted clearance effective for nano-vesicles.11 The study of developmental processes can thus improve our understanding of disease pathogenesis and also suggest novel therapeutic strategies.

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Platelets mediate acetaminophen hepatotoxicity

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In this issue of Blood, Miyakawa et al show that platelets and protease-activated receptor (PAR)-4 contribute to acetaminophen (APAP)-induced liver damage. Using various strategies in a mouse model of APAP overdose, the authors demonstrate that platelets participate in the progression of liver damage, and that the direct thrombin inhibitor lepirudin and PAR-4 deficiency attenuate hepatotoxicity. These findings have the potential to help identify future therapeutic targets for APAP-induced hepatotoxicity.1

APAP is one of the most widely used medications in the United States; although its safety and efficacy at therapeutic doses have been established for >50 years, overdose of APAP is a leading cause of poisoning-related deaths.2 APAP overdose represents the most frequent cause of acute liver failure in many developed countries,3 resulting in death or liver transplantation in over one-third of patients.4 The mainstay of treatment to prevent hepatotoxicity following APAP overdose is N-acetylcysteine (NAC); however, this agent has limitations including decreased efficacy when initiated more than a few hours after ingestion.5 Thus, there is active research interest in broadening our understanding of the mechanisms involved in APAP-induced toxicity and identifying new therapeutic targets.

Prior data based on decades of studies in rodent models of APAP overdose reveal that its reactive metabolite, N-acetyl-p-benzoquinonimine (NAPQI), is a critical early contributor to hepatotoxicity.6 Detoxification of NAPQI involves its binding to glutathione; following APAP overdose, glutathione stores are depleted, resulting in binding of NAPQI to cellular proteins initiating hepatotoxicity. A wide variety of downstream molecular and cellular mechanisms have been proposed to amplify the injury responses resulting in hepatotoxicity. These include mitochondrial dysfunction, oxidant stress, reactive nitrogen species, cytokines, and cells of the innate immune system, among others.6 The clinical efficacy of NAC in APAP overdose is believed to be due largely to its effects in restoration of glutathione stores.5

The article by Miyakawa et al1 broadens our understanding of the mechanisms responsible for hepatotoxicity following APAP overdose. Prior studies from both human and animal models revealed an association between activation of coagulation and APAP hepatotoxicity. The same group showed in an earlier study that APAP toxicity was attenuated in mice pretreated with heparin and in mice deficient in either tissue factor (TF) or PAR-1.7 That earlier study suggested that TF-dependent thrombin generation contributes to APAP-induced liver injury via PAR-1. However, because PAR-1 does not mediate activation of mouse platelets by thrombin, as opposed to human platelets,8 it was unclear whether platelets mediated liver injury in this model. In the current study,1 the authors show that APAP overdose results in thrombocytopenia as well as hepatic accumulation of platelets prior to the onset of
liver damage. Accumulation of platelets and liver injury were attenuated in mice pretreated with the direct thrombin inhibitor lepirudin and in mice lacking PAR-4. Furthermore, antibody–induced platelet depletion attenuated liver injury and neutrophil recruitment in this model. These findings provide evidence that platelets contribute to APAP-induced liver injury in mice. Surprisingly, although PAR-4 contributed to the responses, PAR-4 on platelets was not involved because bone marrow transplant experiments showed that PAR-4 on hematopoietic cells was not required for APAP-induced liver damage. The cells responsible for PAR-4–mediated contribution of APAP-induced toxicity remain to be determined; whether liver sinusoidal endothelial cells account for PAR-4–dependent effects in this model, as speculated by the authors, is a plausible possibility in need of future investigation.

The mechanisms by which platelets contribute to liver injury in APAP overdose remain to be defined. Increasing evidence supports the notion that platelets represent immune cells, mediating a variety of inflammatory and immune responses. One possible mechanism by which platelets may contribute to APAP-induced liver injury is via their interactions with leukocytes in promoting inflammation, as occurs in various other models of sterile inflammation. Alternatively, platelets contain a host of proinflammatory mediators, which conceivably may mediate their role in APAP–induced liver injury. Furthermore, as suggested by the authors, platelets may serve to amplify thrombin activity, possibly contributing to injury via microthrombus formation. Finally, the findings by Miyakawa et al, in light of a recent report that NAC reduces the size of von Willebrand factor (VWF) multimers and platelet-VWF string formation on endothelial cells, lead to the interesting speculation that the therapeutic effect of NAC in APAP overdose might be due in part to inhibition of platelet accumulation and subsequent platelet-mediated liver injury.

Overall, the article by Miyakawa et al provides intriguing observations on the role of platelets and activation of coagulation in APAP–induced hepatotoxicity. Future studies aimed at defining the mechanisms by which platelets and PAR–mediated responses contribute to hepatotoxicity have the potential to provide new therapeutic strategies for patients with APAP overdose.

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Comment on Arumugam et al, page 1844

It’s “PT” for SCD!

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In this issue of Blood, Arumugam et al report that long-term reduction of prothrombin (PT) expression results in diminished vascular inflammation, attenuation of multiple organ damage, and survival advantage in a mouse model of sickle cell disease (SCD).1

SCD is a hematologic disorder caused by a single nucleotide mutation in the β-globin gene, with hemolytic anemia and vaso-occlusive crises being the primary pathologies of the disease. Furthermore, SCD is also associated with chronic vascular inflammation and activation of coagulation.2 Increased expression of tissue factor (TF), the primary initiator of the extrinsic coagulation pathway, has been demonstrated in leukocytes and endothelial cells in sickle cell patients and in mouse models of SCD.2,3 Despite the well-documented hypercoagulable state of SCD, the question remains whether the activation of coagulation significantly contributes to the pathology of this disease or if it is merely a secondary event.

This question was partially addressed by a recent study demonstrating that inhibition of TF not only attenuated activation of coagulation but also reduced several markers of vascular inflammation in 2 mouse models of SCD.4 Interestingly, monocyte and endothelial cell TF contributed to the vascular inflammation via a thrombin-dependent and...
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