PPM1D inhibition will enable us to optimally choose the best combinatorial partners for PPM1D inhibition. On a final note, there is lack of a clinical-grade PPM1D inhibitor, which prohibits clinical translation of these important findings. It is therefore essential that novel PPM1D-targeting agents are developed so the potential of this approach can be further explored.

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THROMBOSIS AND HEMOSTASIS

Comment on Lafoux et al, page 2092

Hemostasis in arenavirus infection

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In this issue of *Blood*, Lafoux and colleagues[1] present a comprehensive study of mammarenavirus infection in cynomolgus macaques, a model for viral hemorrhagic fevers, analyzing the changes in hemostatic and platelet activation markers. Importantly, viral hemorrhagic fever infections are almost always associated with the activation of coagulation cascade and platelets, which can be due to the pathogen itself or can be a protective defensive host response to maintain hemostasis.[2,3] For instance, fibrin entrapment of bacteria is thought to be due to the host's response, but viral infections may also enhance fibrin depositions.[2] Although the virus itself might be too small to be entrapped in a fibrin network, viruses can interact with platelets. Platelets mediate viral clearance by engulfing them for destruction and thus limiting systemic viremia.[2,3]

Lafoux et al were able to identify hemostatic and platelet activation markers and correlate them with the hemorrhagic fever infection stages. The study compared the disease progression of the old-world arenavirus such as Lassa virus (LASV, using the arenavirus [AV] and Josiah strains), which is most prevalent in West Africa, with the new-world arenaviruses Machupo virus (MACV, the Carvallo strain) and Guanarito virus (GTOV, the INH-95551 strain), both endemic in South America.[1] Importantly, the cynomolgus macaque model recapitulates all reported hematologic features including thrombocytopenia, leukopenia, platelet dysfunction, clotting time prolongation, high plasminogen activator inhibitor-1 (reduced fibrinolysis), and hemorrhagic complications. Strain-specific features observed in human patients were confirmed in the presented study, showing distinct differences between the AV and Josiah LASV strains. Importantly, the study revealed that arenavirus infection can cause cerebral and cerebellar hemorrhages. These brain hemorrhages are severe and can lead to death by infarction and compression of the central nervous system. The authors found that the increased vascular permeability and lung edema can contribute to terminal shock syndrome by severely effecting fluid distribution and tissue hypoxia, with resultant multiorgan failure, as observed in severe human cases. Similar to human patients, the animals exhibited prolonged clotting times but limited signs of disseminated intravascular coagulopathy (DIC). Interestingly, the authors measured a downregulation of fibrinolysis, potentially suggesting that the host body tries to accommodate fluid loss during bleeding by stabilizing hemostatic plugs. This could point to a role of coagulation activation as protective wound healing response. In addition, the authors reported the occurrence of a soluble factor in plasma directed against procoagulant proteins in animals infected with the LASV Josiah strain. They also found that the observed thrombocytopenia was not a result of DIC or inflammation-dependent reduced platelet production but suggested that there is a so-far unknown factor induced by the virus. Identification of this unknown infection-associated factor has the potential to be of great therapeutic benefit.

Animals fatally infected with LASV Josiah, MACV, and GTOV had hemorrhages in the lungs, gastrointestinal tract, and intercranial space. The authors observed that tissue factor (TF) expression was elevated in monocytes and the vessel wall, which correlated with fibrin deposition.[1] Lafoux et al concluded that vascular leakage is not connected to viral infection of endothelial cells (ECs).[1] Overall, the authors suggested that all signs including the expression of TF on monocytes suggest a sepsislike phenotype.

In general, viral infections are detected by innate immune receptors like toll-like receptors (TLRs). TLR7 is activated directly by the viral single-stranded RNA (ssRNA) genome.[2,3] During replication, ssRNA viruses, like arenaviruses, have a double-stranded RNA (dsRNA) genomic phase. TLR3 is activated by dsRNA.[2] Viral dsRNA can be released by infected cells or recognized by phagocytotic cells. This suggests that in ssRNA virus infections, TF expression is induced by TLR7 or other ssRNA sensors in the primary host cell of the viral life cycle like lung epithelial cells (EpCs) during respiratory virus infection or by similar mechanisms in phagocytotic cells like monocytes and macrophages. Indeed, TLR7 stimulation can induce TF in macrophages.[4] Arenaviruses prefer myeloid cells for replication.[5] The reported monocyte TF expression in arenavirus infection[1] could be an intentional danger signal to warn about an increased systemic viremia. Moreover, these findings also suggest that dsRNA sensors, including TLR3, may be involved in increased TF expression during wound healing and tissue repair processes in noninfected, bystander cells. These bystander cells are essential in limiting blood or fluid loss and include cells of the vessel wall or EpCs like lung EpCs. In line with this, increased TF expression was observed by Lafoux et al in the vessel wall of infected animals. We and others have reported that dsRNA can induce TF in ECs but not macrophages in vitro and in vivo.[6,7] In other severe virus infections like influenza A virus (IAV) or severe coronavirus infections, increased lung TF expression was observed.[8] In a murine model of IAV infection, lung EpCs are responsible for the increased lung TF after infection.[9] Importantly, lack of TF in lung EpCs leads to severe hemorrhages into the airspace during IAV infection in mice.[9] The increased lung TF expression could be due to TLR7-mediated TF expression in virus-infected EpCs as immune response or due to TLR3-mediated TF expression in noninfected EpCs. This TLR3-mediated induction could be a compensatory mechanism to account for the loss of virus-infected EpCs. In line with this, there is increased TF expression in lung EpCs in vitro and lung EpCs in vivo when stimulated with a dsRNA mimetic (S. Sharma and S. Antoniak, unpublished data, 2023). Similar responses may occur in the vessel wall

during arenavirus infection as found by Lafoux et al. Moreover, the thrombocytopenia observed in arenavirus infection could be caused by interaction of arenaviruses with TLR7 expressed by platelets. TLR7-dependent platelet activation leads to thrombocytopenia, which was thought to be a protective mechanism in systemic viral infections.[3,10]

In summary, the study comprehensively summarizes the hemostatic changes in arenavirus infection. The authors concluded that the observed imbalance was not due to DIC since signs of a consumptive coagulopathy were missing. It is not clear if the changes in the hemostatic parameters were directly due to the virus, or were a result of the host's innate antiviral response, or were due to both. More mechanistic studies are needed to resolve the mystery of the effects of viral infection on coagulation.

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TRANSPLANTATION

Comment on Leiding et al, page 2105

HCT alleviates disease burden in CGD

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In this issue of *Blood*, Leiding et al[1] describe outcomes after allogeneic hematopoietic cell transplant (allo-HCT) for patients with chronic granulomatous disease (CGD). This multicenter study confirms that allo-HCT can significantly reduce the disease burden, independent of age, genotype, oxidase status, and history of preceding infections/autoinflammation.[1] Increased rates of graft failure (GF) and chronic graft-versus-host disease (GVHD) were seen in patients with reduced performance status, exuberant inflammation before allo-HCT, and human leukocyte antigen (HLA)–mismatched donors.

In 1997, when I was a freshly minted HCT physician, one of my first patients was a 14-year-old boy with X-linked

CGD experiencing pulmonary aspergillosis. He underwent myeloablative allo-HCT from his HLA-identical sister after