Plasmin has a central role in the regulation of the inflammatory response via MMP9 activation. Administration of CpG/DG activates TLR-9 in different cell populations, which stimulates the secretion of urokinase-type plasminogen activator that will modify plasminogen into its active form, plasmin. The activation of TLR-9 in monocyte/macrophages will activate production of a cytokine storm, which involves the production of transmembrane TNFα, chemokine ligand 2 (CCL2), and interleukin-1 (IL-1) and IL-6. Notably, the generation of plasmin promotes the activation of MMP9, which will cleave mTNFα into its soluble form (sTNFα), increasing the inflammatory response. The transient inhibition of plasmin with YO-2 decreases the inflammatory response, increasing the viability of treated mice; however, it did not affect the increase in blood coagulation markers, suggesting that CpG/DG activates the coagulation cascade in a plasmin-independent manner. This response might be mediated by the activation in endothelial cells of the NFκB pathway, which has been described as being activated by CpG and being involved in the inflammatory and coagulation responses mediated by endothelial cells. mTNFα, membrane TNF-α; uPA, urokinase-type plasminogen activator. Professional illustration by Somersault18:24.
determine its contribution to chronic inflammatory conditions.

Although pharmacological inhibition of plasmin controlled acute inflammation and liver damage, it did not diminish the activation of the coagulation pathway. Although these results could be due to a different pathway involving fibrin deposition and fibrin-associated inflammatory response as suggested by the authors, the administration of CpG/DG also activates a TLR-9 response in endothelial cells that triggers the activation of the NFκB pathway. This latter pathway has been related to the activation of the coagulation cascade (see figure). Furthermore, the genetic deletion of plasmin in mice generates spontaneous thrombosis, thereby limiting the opportunity for therapeutic intervention. Nonetheless, despite these limitations, the global decrease in survival were significant achievements.

The authors noted that TLR-9-driven TNFα activation was mediated through a plasmin/matrix metalloproteinase 9 (MMP9) axis (see figure). They show how in MMP9-deficient mice, the activation with CpD/DG was significantly diminished, resulting in improved survival. Importantly, these data are supported by previous reports, demonstrating that MMP9 deficiency has a protective effect in response to lipopolysaccharide challenge by reducing the inflammatory response. Moreover, similar results have been recently described using a blocking antibody against TLR-9 after the administration of CpG/DG, confirming the importance of the TLR-9/plasmin/MMP9 axis in the control of the cytokine storm response.

In summary, the article by Shimazu et al describes a relevant model of MAS in which TLR-9 stimulation contributes to the activation of plasmin, augmenting the inflammatory response through the control of MMP9. This study reveals the importance of plasmin in the control of acute inflammatory cytokine production and opens the door for the development of alternative therapeutic approaches for treating syndromes associated with an acute cytokine storm, such as MAS or HLI.

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Comment on Wang et al, page 73

Hemochromatosis, iron-loading anemia, and SMAD

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In this issue of Blood, Wang et al show that SMAD1 and SMAD5 act cooperatively to increase hepatic hepcidin expression in response to iron-mediated bone morphogenetic protein (BMP) signaling, and they provide evidence that erythroferrone produced by bone marrow progenitors may suppress hepatic hepcidin expression by inhibiting these same factors (see figure).1

Hepatic iron accumulation is a significant cause of morbidity and mortality. Iron overload results in a variety of organ dysfunction, with the liver affected initially.2 In the body, iron is delivered to the liver by transferrin-bound iron and is stored in the form of ferritin, which is a protective mechanism against iron-induced oxidative stress.3 Iron accumulation results in the gradual depletion of ferritin, and eventually, it becomes iron overload.4 Iron overload is associated with a variety of conditions, such as hemochromatosis, anemias characterized by ineffective erythropoiesis, and systemic iron overload or hemochromatosis.5 Hemochromatosis is an iron-storage disease characterized by iron deposits in multiple organs, including the liver, pancreas, and heart. It is inherited as an autosomal recessive trait and is caused by mutations in the HEMACHROMATOSIS (HFE) gene.6 HFE encodes the HFE protein, which regulates iron absorption from the diet.7 Mutations in HFE lead to increased iron absorption and accumulation in the body, resulting in a risk of iron overload.8

Iron absorption is tightly regulated by a complex signaling pathway involving BMPs and SMADs. BMPs are a family of ligands that act through the BMP receptor complex to activate the SMAD signaling pathway. SMADs are a family of proteins that mediate the intracellular effects of BMPs. SMAD1, SMAD5, and SMAD8 are three SMADs that are known to be involved in the regulation of iron metabolism.9 In the liver, BMP signaling leads to the phosphorylation of SMAD1, SMAD5, and SMAD8, which leads to the transcription of hepcidin, a protein that regulates iron absorption.10 Hepcidin binds to the ferroportin protein on the enterocytes, leading to the internalization of iron, which is then stored in the body.11 In the absence of hepcidin, iron is absorbed from the diet and stored in the body, leading to iron overload.12

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Hepcidin is a protein that regulates iron absorption and is produced by hepatocytes. Hepcidin is produced in response to iron overload and prevents the release of excess iron into the bloodstream.13 Hepcidin binds to the ferroportin protein on the enterocytes, leading to the internalization of iron, which is then stored in the body.14 In the absence of hepcidin, iron is absorbed from the diet and stored in the body, leading to iron overload.15 In this issue of Blood, Wang et al show that SMAD1 and SMAD5 act cooperatively to increase hepatic hepcidin expression in response to iron-mediated bone morphogenetic protein (BMP) signaling, and they provide evidence that erythroferrone produced by bone marrow progenitors may suppress hepatic hepcidin expression by inhibiting these same factors (see figure).1

In particular, previous research indicated that iron-related BMP signals lead to the phosphorylation of SMAD proteins in hepatocytes, and the phosphorylation of SMAD proteins is a central event in the regulation of iron metabolism. In this issue of Blood, Wang et al show that SMAD1 and SMAD5 act cooperatively to increase hepatic hepcidin expression in response to iron-mediated bone morphogenetic protein (BMP) signaling, and they provide evidence that erythroferrone produced by bone marrow progenitors may suppress hepatic hepcidin expression by inhibiting these same factors (see figure).1

How patients with anemias characterized by ineffective erythropoiesis develop systemic iron overload in the absence of blood transfusions is a fascinating question that hematologists have pondered for many years. Thalassemia major and intermedia syndromes are important examples of the association of the increased erythropoietic activity of intramedullary hemolysis with enhanced intestinal iron absorption. The magnitude of iron overload that may occur in conditions marked by ineffective erythropoiesis is independent of the degree of anemia,1 and the predominantly parenchymal iron loading in ineffective erythropoiesis is similar to hereditary hemochromatosis. These observations raised the possibility that the 2 conditions share in common a final pathophysiologic pathway. Indeed, this proved to be the case; it emerged over the past 15 years that hepcidin produced by hepatocytes has a central role in iron homeostasis and that deficiency of hepcidin with respect to the body’s iron burden underlies the iron loading seen in both hereditary hemochromatosis and anemias characterized by ineffective erythropoiesis.5

HFE, HJV encoding hemojuvelin, HAMP encoding hepcidin, and TFR2 encoding transferrin receptor 2 are genes of the hepcidin-activating pathway in hepatocytes; autosomal-recessive inactivation of any 1 of these genes leads to deficiency of hepcidin and systemic iron overload or hemochromatosis.5 Investigation of the function of these genes showed that BMP signaling through phosphorylation of SMAD proteins is a central pathway to regulate hepcidin transcription.6 In particular, previous research indicated that iron-related BMP signals lead to the phosphorylation of SMAD1, SMAD5, and SMAD8 and to the promotion of hepcidin transcription through the common mediator SMAD4.7 In this issue, Wang et al explored the individual contributions of SMAD1,
Plasmin regulation of acute cytokine storm

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