

# Two blood-clotting disorders with different causes interact synergistically

September 4 2019, by Jeff Hansen

---

Two rare but potentially deadly blood-clotting diseases, namely thrombotic thrombocytopenic purpura, or TTP, and hemolytic uremic syndrome, or HUS, show similar pathologies—a multitude of painful blockages in small blood vessels that cause varying degrees of organ injury throughout the body. However, the two disorders have distinct biological mechanisms.

Now, in a preclinical study published in the journal *Blood*, researchers have found a synergistic connection, or crosstalk, between the two disorders. Such a linkage between the two thrombotic microangiopathic disorders "may provide a rationale for a more targeted therapeutic intervention in patients with refractory thrombotic microangiopathy," said X. Long Zheng, M.D., Ph.D., who led a team of researchers at the University of Alabama at Birmingham.

At UAB, Zheng is the Robert B. Adams Professor of Pathology and Division Director of Laboratory Medicine in the Department of Pathology, UAB School of Medicine.

TTP is mostly caused by autoimmune antibodies that attack one of the body's own enzymes, ADAMTS13, first identified and cloned by Zheng in 2001. HUS, particularly the atypical form, is caused mostly by improper activation of complement through the alternative complement pathway, a part of the immune system that helps, or "complements," the clearance of infecting microbes or damaged cells from the body.

Some clinical evidence from patients with TTP led Zheng and colleagues at UAB and the University of Pennsylvania to test the hypothesis that there may be a synergy between ADAMTS13 deficiency and complement activation in pathogenesis of thrombotic microangiopathy.

They used two existing mouse lines—one that completely lacks ADAMTS13 and one that has a heterozygous mutation in complement factor H gene, or *cfh*, where the mouse has one gene with unmutated *cfh* and one with the mutated *cfh*. Mammals like humans and mice have two copies of each chromosome, so there are two copies of the gene *cfh*.

These two lines are known as *Adamts13*<sup>-/-</sup>, which completely lacks the enzyme ADAMTS13, and *cfh*<sup>W/R</sup>, where the W indicates the amino acid tryptophan in the normal CFH protein from the unmutated gene, and R indicates that the tryptophan has been replaced by an arginine in the mutant CFH protein. Those two mouse lines remain completely asymptomatic for thrombotic microangiopathy despite the presence of occasional microvascular thrombi in various organ tissues on histology analysis.

To look for interactions between the pathogenic pathways for TTP and atypical HUS, the researchers generated a third strain, which showed the signs and symptoms, and laboratory evidence, of thrombotic microangiopathy.

They found that mice carrying both *Adamts13*<sup>-/-</sup> and *cfh*<sup>W/R</sup> showed thrombocytopenia, which is low counts of blood platelets because the platelets have left circulating blood to form blood clots. The mice also had low plasma haptoglobin and increased fragmentation of erythrocytes in peripheral blood smears, the signs of red blood cells that were broken trying to squeeze past blood clots. The mice also had increased plasma levels of lactate dehydrogenase activity, [blood](#) urea nitrogen and creatinine, signs of general organ damage and [kidney damage](#) from clots,

and these mice also had an increased mortality rate.

Strains of mice that had the cfh mutation in both genes, known as the homozygous mutation cfhR/R, with or without Adamts13-/-, developed an even more severe thrombotic microangiopathy. The mortality rate in mice with both Adamts13-/-and cfhR/R was significantly higher than that in [mice](#) with cfhR/R alone.

All three affected mouse strains had microscopically visible disseminated platelet-rich thrombi in terminal arterioles and capillaries of major organ tissues, including brain, heart, lungs, kidney, liver and intestine.

"Altogether," Zheng said, "our results support the synergistic effects of ADAMTS13 deficiency and complement activation in the pathogenesis of thrombotic microangiopathy. The results may help design a potentially novel strategy to treat the refractory thrombotic microangiopathy in the future."

**More information:** Liang Zheng et al. Synergistic effects of ADAMTS13 deficiency and complement activation in pathogenesis of thrombotic microangiopathy, *Blood* (2019). [DOI: 10.1182/blood.2019001040](https://doi.org/10.1182/blood.2019001040)

Provided by University of Alabama at Birmingham

Citation: Two blood-clotting disorders with different causes interact synergistically (2019, September 4) retrieved 24 April 2024 from <https://medicalxpress.com/news/2019-09-blood-clotting-disorders-interact-synergistically.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private

study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.