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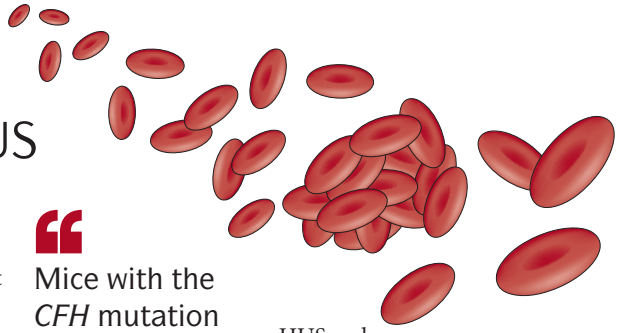
THROMBOTIC MICROANGIOPATHIES

Complement factor H: beyond aHUS



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Complement activation is usually controlled by regulatory factors such as complement factor H (CFH) and alteration of this process causes severe diseases such as atypical haemolytic uraemic syndrome (aHUS). New research by Wenchao Song and colleagues shows that a point mutation that impairs CFH function at the cell surface but not in the plasma leads to aHUS and systemic thrombophilia through activation of the alternative complement pathway.

To study the function of CFH at the cell surface and the mechanisms underlying aHUS, the researchers generated an animal model that recapitulates the human disease. "First, we tried to delete short consensus repeats (SCRs) 19 and 20; unfortunately (or fortunately), that led to a low production of truncated CFH and resulted in C3 glomerulopathy instead of aHUS," explains Song. "In this study, we took a different approach by introducing a specific point mutation in SCR 20 (Trp1206Arg) that corresponds to that found in some patients with aHUS (Trp1183Arg)."

The point mutation impaired CFH interaction with host cells but did not affect its ability to regulate complement in the plasma. Mice with the *CFH* mutation developed severe aHUS with altered endothelial and vascular smooth muscle function, but also systemic thrombophilia. "We expected these mice to develop aHUS, but this model showed us that there is a strong effect of complement dysregulation on macrovessel injury, thrombosis and coagulation abnormalities —the extent of which surprised us," comments Song. Genetic deficiency of complement factor C3 and complement factor D, two proteins of the alternative pathway, prevented aHUS and systemic thrombophilia in *CFH* mutant mice.

> "Mice with the *CFH* mutation developed severe aHUS … but also systemic thrombophilia"

The researchers now plan to use their new mouse model to test novel anti-complement agents in aHUS and systemic thrombophilia and to investigate the mechanisms underlying these diseases. "Specifically, we are interested in investigating which complement effectors are responsible for each phenotype and in understanding how activated complement interacts with the coagulation pathway to cause systemic thrombophilia," says Song.

Andrea Aguilar

ORIGINAL ARTICLE Ueda, Y. *et al.* Murine systemic thrombophilia and hemolytic uremic syndrome from a factor H point mutation. *Blood* http://dx.doi.org/10.1182/blood-2016-07-728253 **(2017)**