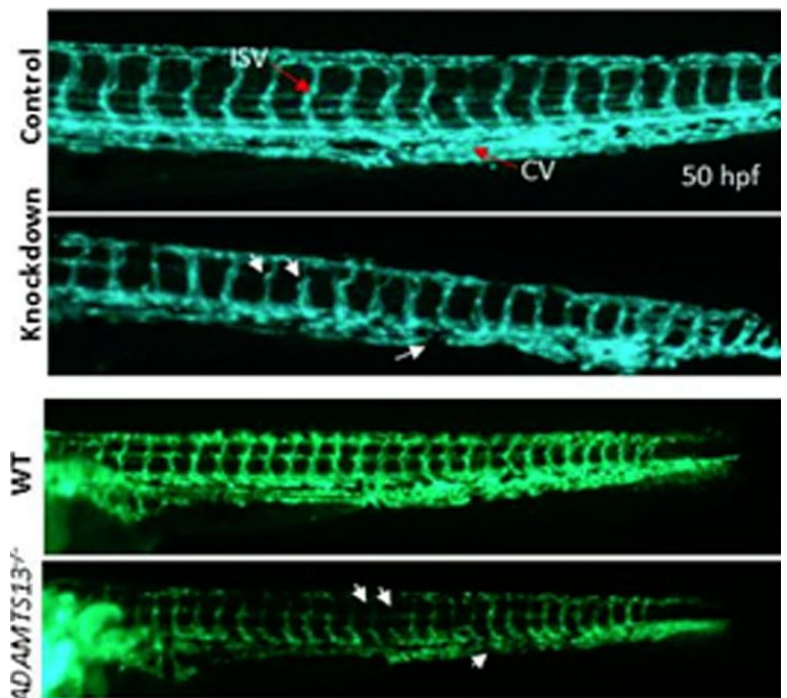


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Thrombotic thrombocytopenic purpura, a potentially fatal blood disorder – Lesson learned from Zebrafish to human

Thrombotic thrombocytopenic purpura (TTP) is caused by severe deficiency of ADAMTS13, a plasma metalloprotease that cleaves endothelial von Willebrand factor (VWF). However, severe ADAMTS13 deficiency alone is often not sufficient to cause an acute episode, suggesting that additional factors may be required to trigger the disease. To further understand the pathogenesis of TTP, we created and characterized several novel zebrafish lines carrying a null mutation in *adatms13*, *vwf*, and both using the CRISPR/Cas9; we then assessed the direct role lysine-rich histone in triggering acute TTP in zebrafish. The results demonstrate that *adats13*^{-/-} zebrafish have increased plasma levels of *vwf* antigen, multimer size, and the ability of thrombocytes to adhere to fibrillar collagen surface under arterial flow. Also, *adats13*^{-/-} zebrafish exhibit an increased rate of forming occlusive thrombi in the caudal venules after oxidative injury. More importantly, the *adats13*^{-/-} zebrafish show a ~30% reduction in the number of all, mature, and immature thrombocytes with an increased number of erythrocyte fragmentation. Furthermore, an intraperitoneal administration of a lysine-rich histone, an inflammatory mediator, results in more persistent thrombocytopenia and significantly higher mortality rate in *adats13*^{-/-} zebrafish than in wild-type controls. Finally, both spontaneous and histone-induced TTP in *adats13*^{-/-} zebrafish is abrogated when *vwf* is genetically deleted. Together, these results demonstrate a potential mechanistic link from infections or inflammation and neutrophil activation to the onset of acute TTP; these novel zebrafish lines may help accelerate the discovery of novel therapeutics for TTP and perhaps other arterial thrombotic disorders.



Zheng and Zheng, 2016 Blood 128 (22): 1446