Chava Kimchi-Sarfaty, J Blood Disord Transfus 2018, Volume 9
DOI: 10.4172/2155-9864-C1-031

Assay-dependent results of ADAMTS13 activity in sickle cell disease

Chava Kimchi-Sarfaty
CBER - Food and Drug Administration, USA

Background: von Willebrand factor (VWF) is an adhesive multimeric plasma protein that is acutely elevated in sickle cell disease vaso-occlusive crisis (VOC) and may play a mechanistic role in the genesis of vaso-occlusion. However, discrepant findings concerning the functionality of ADAMTS13, the VWF-cleaving plasma protease, have been reported in sickle cell disease (SCD).

Objectives: To characterize ADAMTS13 activity in adult sickle cell patients using multiple *in vitro* assays and assess for alternative VWF-cleaving plasma proteases.

Methods: Plasma samples were obtained from adult sickle cell patients undergoing regular exchange transfusion (n=20) and healthy control patients (n=15). Plasmatic ADAMTS13 activity was determined by two VWF A2 domain peptidyl-based assays (FRETS VWF73 and VWF73 GST) and a shear-based assay employing the full length VWF molecule. Plasma matrix metalloprotease-9 (MMP-9) was quantitated by ELISA.

Results: Using peptidyl-based assays, sickle cell disease plasma displayed significantly lower ADAMTS13 activity relative to healthy controls (0.695 vs. 1.109 IU/mL, respectively, for VWF73 GST ELISA, P<0.0001). By contrast, the cleavage potential against the full length VWF molecule was normal or enhanced in sickle cell disease patient plasma. Plasma MMP-9 was elevated in SCD plasma and displayed preferential cleavage of the full length VWF molecule over peptidyl substrates.

Conclusions: Our findings demonstrate assay-dependent results of ADAMTS13 activity measurements in sickle cell disease, and imply the possible existence of alternative blood proteases capable of VWF cleavage. These findings may have implications for the interpretation of ADAMTS13 activity in sickle cell disease and for the monitoring of ADAMTS13 activity in clinical trials.

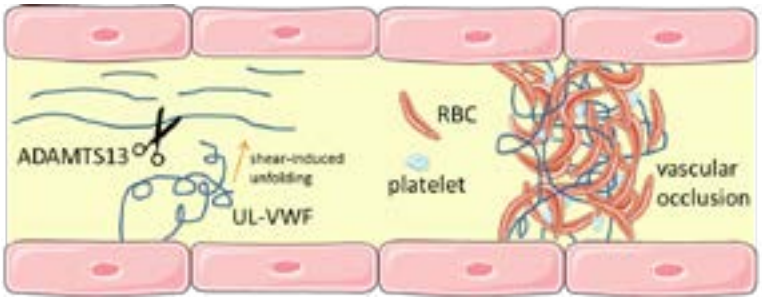

Figure 1: *Mechanistic role for VWF-ADAMTS13 in vaso-occlusion.*

Recent Publications

1. Simhadri V, Hamasaki Katagiri N, Lin B C, Hunt R C, Jha S, Tseng S C, Bentley A A, Zichel R, Lu Q, Zhu L, Freeberg D I, Monroe D N, Sauna Z E, Peters R, Komar A A and Kimchi Sarfaty C (2016) Single synonymous mutation in factor IX alters protein properties and underlies haemophilia B. J Med Genet. 54:338-345.
2. Hamasaki Katagiri N, Lin B C, Simon J, Hunt R C, Schiller T, Russek Cohen E, Komar A A, Bar H and Kimchi Sarfaty C (2017) The importance of mRNA structure in determining the pathogenicity of synonymous and non-synonymous mutations in haemophilia. Haemophilia 23:8-17.

3. Hunt R C, Yalamanoglu A, Tumlin J, Schiller T, Hyen Baek J, Wu A, Fogo A, Yang H, Wong E, Miller P, Buehler P and Kimchi Sarfaty C (2017) A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood 129:896-905.
4. Lagassé H A, Alexaki A, Simhadri V L, Katagiri N H, Jankowski W, Sauna Z E and Kimchi Sarfaty C (2017) Recent advances in (therapeutic protein) drug development. F1000Research 6:113.
5. Athey J, Alexaki A, Rostovtsev A, Santana Quintero L, Katneni U K, Simonyan V and Kimchi Sarfaty C (2017) A new and updated resource for codon usage tables. BMC Bioinformatics 18:391.

Biography

Chava Kimchi-Sarfaty currently leads a group at the FDA within the Division of Plasma Protein Therapeutics, Office of Tissues and Advanced Therapies (OTAT) that investigates various blood coagulation factors with a specific focus on the genetic determinants of coagulation factor biosynthesis and structure. She is also the Acting Deputy Associate Director for Research of the Office. She reviews and chairs pre-INDs, INDs and BLAs for recombinant proteins and plasma derivatives products such as von Willebrand factor, ADAMTS13, factor VIII, FIX, thrombin and fibrinogen.

Chava.kimchi-sarfaty@fda.hhs.gov

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