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A Brief Summary of Mechanisms Underlying VITT

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Abstract

Several mechanisms for vaccine-induced immune thrombotic thrombocytopenia are proposed. The variability of the proposed mechanisms is disappointing particularly because generally underlying mechanisms pave the way to drug policies and treatments. We quickly overview the main mechanisms and then we propose some feasible solutions that may trigger topographic studies and domain/epitope mappings.

Keywords: Vaccine-induced immune thrombotic thrombocytopenia; mechanism; Covid-19.

Editorial

Several mechanisms underlying vaccine-induced immune thrombotic thrombocytopenia (VITT) are proposed [1]. Different hypotheses might support this phenomenon and could trigger further investigations. We briefly outline the novel hypothetic mechanisms that are currently known to underlie VITT form different perspective. We then comment on a plausible causative relationship and underlying mechanisms that might elucidate the link between VITT and the A2 domain of von Willebrand factor. Finally, we propose some feasible solutions that may trigger topographic studies and domain/epitope mappings which can shed light on molecular interactions and provide atomic-level structural information to improve our understanding of the interaction between SARS-CoV-2 vaccination and assists the structure-based new mRNA vaccines design that is urgently needed. A full description of the mechanism justifying these hypotheses is beyond the scope of a short editorial, due to the space limits, but can be made available by the author on request.

According to a model proposed by McGonagle et al [2], electrochemical DNA-PF4 interactions and PF4-heparin interactions, albeit at different locations, may partially represent the common denominator in VITT compared to natural COVID-19 infection.

Marchandot et al [3] recently proposed another hypothesis stating that the pathogenesis of VITT may involves (a) a FcγRIIA receptors pathway with circulating PF4 antibodies complexes that bind platelets and monocytic FcγRIIA receptors, thereby causing cell monocytic activation and release of procoagulant MPs (b) a direct activation of the endothelium by heparin-induced thrombocytopenia Ab complexes which may lead to increased thrombogenicity through the release of E-selectins, P-selectins, von Willebrand factor and IL-6.

A recent extensive review by Favalaro et al concluded that COVID-19 is characterized in many well-conducted studies as an imbalance in the VWF/ADAMTS-13 "axis," i.e., the most severely affected patients with COVID-19 manifest a relatively high VWF/ADAMTS-13 ratio, which may promote (micro)thrombosis [4].

Maayan et al [5] just recently published a case series of patients, who developed VITT within several days of receiving the BNT162b2 vaccine. Normalization of ADAMTS13 activity was confirmed in three out of five cases. ADAMTS13 activity was significantly enhanced and ADAMTS13 antibodies were significantly decreased within 5 weeks of treatment after the vaccination. This study may provide the first experimental evidence supporting Favalaro et al [4] hypothesis that a further increase in VWF/ADAMTS-13 ratio –above a physiological commensurate -may at least partially explain the severe VITT in compared to natural COVID-19 infection.

aTTP is caused by development of auto- antibodies to the Von Willebrand cleaving protein, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) [6].

Anti-ADAMTS13 auto-antibodies are previously shown to block proteolysis of von Willebrand factor and/or induce ADAMTS13 clearance from the blood circulation [7,8].

Furthermore, conformation-sensitivity against the A2 domain of von Willebrand factor is previously shown to alter its proteolysis by ADAMTS13. Zhang et al [9] demonstrated that a conformation-sensitive monoclonal antibody (SZ34) against the A2 domain of von Willebrand factor significantly reduces its proteolysis by ADAMTS13. Decreased amount of the high and intermediate molecular weight multimers are drastically decreased by murine monoclonal antibodies (mAb) SZ34 in a concentration-dependent fashion under shear stress, confirming the role of SZ34 in decreasing the susceptibility of VWF to proteolytic cleavage by ADAMTS13 under physiologically relevant conditions [9].

This later study is very suggestive; because it might be conjectured that similar scenario happens following COVID-19 vaccination and results in VITT- at least in susceptible individuals who have congenital deficiency of ADAMTS13 [10].

It might be argued that "You can have your hypothesis, but how do you find which is the one that caused an event in maybe 1 in 100,000 people?". The answer is that molecular topology of the SARS-CoV-2 spike monomer is now determined [11]. As a practical solution to find out the underlying mechanism behind the VITT, we need (i) to determine molecular and biologically characterize the human monoclonal antibodies binding to the spike and nucleocapsid proteins of SARS-Cov-2, (ii) to find out ant conformation-sensitivity against the A2 domain of von Willebrand factor, and most importantly, (iii) to investigate the effects of COVID-19 vaccination against various domains of VWF on its proteolysis by ADAMTS13, (iv) identifying new mRNA vaccine induced epitopes and (v) mapping antibody epitope specificity after immunization using SARS-CoV-2 spike protein peptide arrays in severely affected patients.

A greater understanding of the molecular pathways behind the VITT might facilitate the discovery of better preventive measures and therapeutic agents for the management severely affected patients. Since deficiency of ADAMTS13 can be either congenital or acquired [10], it is equally important to consider this point in exploratory studies, because the acquired form can occur spontaneously or secondary to an existing inflammatory condition.

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