A proposed mechanism for vaccine-induced thrombotic thrombocytopenia

What is this research about?

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a new, rare clotting disorder associated with administration of adenoviral vector vaccines against COVID-19 (e.g., ChAdOx1 nCoV-19, AstraZeneca). VITT causes moderate to severe thrombocytopenia (low platelet levels) and thrombosis (formation of blood clots) that mimics the response observed in patients with heparin-induced thrombocytopenia (HIT).

HIT occurs when immunoglobulin G (IgG) antibodies recognize novel epitopes (antibody binding sites) exposed after heparin binds to a platelet protein called platelet factor 4 (PF4). The antibodies bound to the PF4-heparin complex form an immune complex which activates platelets (by binding to a platelet receptor called FcγRIIa) and promotes clot formation. One idea is that VITT has a similar pathophysiology to HIT but without dependence on heparin. This study aims to better understand the mechanism behind clot formation observed in VITT patients.

IN BRIEF: This study provides an explanation for antibody-induced platelet activation that may contribute to clot formation in patients who received adenoviral vector vaccines against COVID-19.

What did the researchers do?

Samples from patients exposed to either heparin or the AstraZeneca vaccine were collected at the McMaster Platelet Immunology Laboratory for Diagnosis.

- VITT samples were taken from 5 patients (2 females, 3 males) who received a single dose of the AstraZeneca vaccine and developed thrombocytopenia and thrombosis. The mean age of patients was 44 years and mean time from first vaccine dose to sample collection was 28 days. Antibodies against PF4 were detected in all samples.
- HIT samples were taken from 10 patients (5 females, 5 males) who had thrombocytopenia after receiving heparin. Nine out of 10 patients experienced thrombosis. The mean age of patients was 69 years and mean time from heparin initiation to sample collection was 14.3 days. Antibodies against P4F-heparin were detected in all samples.
- Patterns of platelet reactivity in VITT and HITT samples were studied in vitro.
- 70 unique recombinant PF4 mutants—each differing by a single amino acid—were produced to identify the specific amino acid targets critical to binding of VITT antibodies on PF4.

What did the researchers find?

Both VITT and HIT samples had unique patterns of platelet reactivity in vitro:

- In VITT samples, platelet activation was not dependent on heparin but was strongly dependent on PF4 dose. Results indicate that VITT antibodies require PF4 for platelet activation and this is mediated by engagement of FcγRIIa receptors.
- In HIT samples, platelet activation occurred according to two distinct profiles: heparin-dependent (n=4) and heparin-independent (n=6). All HIT samples also activated platelets with the addition of PF4.

Researchers identified 8 surface amino acids considered essential to binding of anti-PF4-antibodies from patients with VITT; 4 of these 8 amino acids corresponded to amino acids on PF4 where heparin usually binds in HIT. This may account for the observation that adding heparin to VITT samples inhibits platelet activation, presumably by displacing VITT anti-PF4 antibodies.

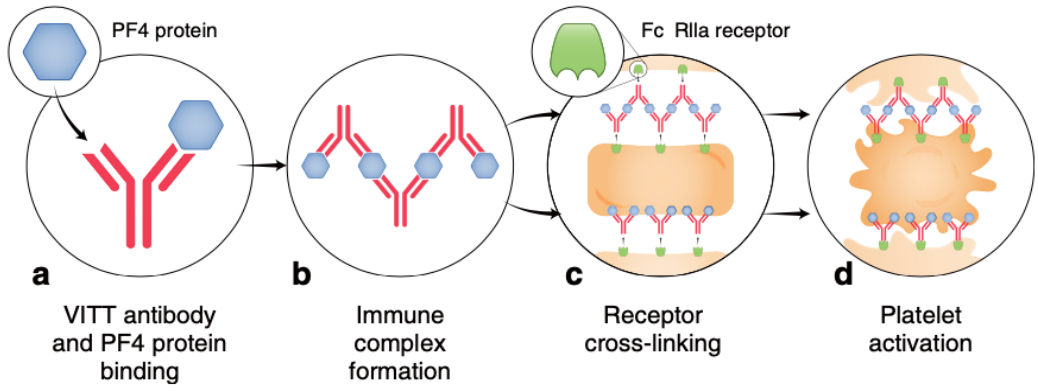

Figure 1: Proposed mechanism for VITT antibodies forming platelet-activating immune complexes (Source Huynh, A., Kelton, J.G., Arnold, D.M. et al. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature* 596, 565–569 (2021).

How can you use this research?

This paper shows for the first time a potential mechanism for platelet activation in a new, rare clotting disease. The findings are a major step forward in the diagnosis and treatment of patients with VITT.

This Research Unit is derived from the following publication:
Huynh, A., Kelton, J.G., Arnold, D.M. et al. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature* 596, 565–569 (2021). https://doi.org/10.1038/s41586-021-03744-4

Author: This Research Unit was written by **Dr. Khalid Batarfi**, Transfusion Medicine fellow at McMaster University.

About the research team: This research was led by **Dr. Angela Huynh**, Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

Acknowledgements: MCTR receives funding support from Canadian Blood Services (Transfusion Medicine Research Program Support Award), funded by the federal government (Health Canada) and the provincial and territorial ministries of health. The views herein do not necessarily reflect the views of Canadian Blood Services or the federal, provincial or territorial governments of Canada

Keywords: vaccine-Induced immune thrombotic thrombocytopenia, VITT, heparin-induced thrombocytopenia, HIT, epitopes

Want to know more? Contact Ishac Nazy at email: nazyi@mcmaster.ca