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Blood 142 (2023) 2598

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

321.COAGULATION AND FIBRINOLYSIS: BASIC AND TRANSLATIONAL

Cryo-EM Structure of Coagulation Factor VIII Bound to a Patient-Derived Anti-A2 Domain Antibody Inhibitor

Kenneth C Childers, PhD[1], *Jordan Vaughan, MS*[1], *John S. Lollar, MD*[2], *Christopher B Doering, PhD*[3], *Carmen Helena Coxon, PhD*[4], *P. Clint Spiegel Jr., PhD*[1]

[1] Chemistry Department, Western Washington University, Bellingham, WA
[2] Emory University, Children's Center, Atlanta, GA
[3] Department of Pediatrics, Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, GA
[4] National Institute of Biological Standards and Control, Potters Bar, GBR

Coagulation factor VIII (FVIII) promotes hemostasis by binding to activated factor IX on activated platelet surfaces to form the intrinsic tenase complex. The formation of inhibitory antibodies against FVIII occurs in approximately 30% of congenital hemophilia A patients receiving FVIII replacement therapy, significantly complicating treatments. By identifying the FVIII amino acids which bind to pathogenic inhibitory antibodies, FVIII replacement therapies can be engineered with reduced immunogenicity. Here, we aimed to structurally characterize FVIII bound to NB11B2, a patient-derived antibody inhibitor which binds to the A2 domain and disrupts tenase complex activity, using cryogenic electron microscopy (cryo-EM). The FVIII:NB11B2 structure was solved to a global resolution of 4.0 Å, representing the first structure of FVIII bound to an anti-A2 domain antibody inhibitor. Structural analysis revealed that NB11B2 binds to a discontinuous epitope encompassing FVIII residues S470-P472, R490-K493, and P502-E507. Furthermore, our structure identified a 20° swivel-like movement adopted by the C2 domain while the C1 domain remains immobile, consistent with a previous X-ray crystal structure of FVIII bound to an anti-C1 domain inhibitor. These results provide the structural basis for inhibition of FVIII by NB11B2 and elucidate a novel role for portions of the FVIII A2 domain in regulating tenase complex assembly and/or activity.

Disclosures Lollar: *Expression Therapeutics:* Current equity holder in private company. **Doering:** *Expression Therapeutics, inc:* Current equity holder in private company.

https://doi.org/10.1182/blood-2023-182304