Defective cofactor function of FVIIIa variant

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 78

This document contains 1 pathway and 1 reaction (see Table of Contents)
Defective cofactor function of FVIIIa variant ↗

Stable identifier: R-HSA-9672396

Compartments: extracellular region, plasma membrane

Diseases: factor VIII deficiency

Factor VIII (FVIII) in its activated form, FVIIIa, acts as a cofactor to the serine protease FIXa, in the conversion of the zymogen FX to the active enzyme (FXa). Missense mutations within the S577-Q584 region of FVIII have been associated with mild/moderate hemophilia A (HA) (Amano K et al. 1998; Celie PH et al. 1999; Jenkins PV et al. 2002). A functional assay demonstrated that the mutations S577F, V578A, D579A, and Q584R interfere with FVIIIa:FIXa-mediated stimulation of FX activation thus the effect of the mutations is to reduce the cofactor potential of FVIII in FXa generation. The Reactome event describes failed generation of FXa as the functional consequence of the FIXa interaction with HA-associated FVIIIa variants due to reduced ability of defective FVIII to act as a cofactor for FIXa within the intrinsic tenase complex.

Literature references


Editions

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The coagulation factor VIII (FVIII) in its activated form, FVIIIa, acts as a cofactor to the serine protease FIXa, in the conversion of the zymogen FX to the active enzyme (FXa). Factors VIIIa and IXa associate on cell surfaces to form a complex that very efficiently catalyzes the activation of factor X, the so-called "intrinsic tenase complex". In vitro, negatively charged phospholipids can provide an appropriate surface. In the body, the surface is provided by the plasma membranes of activated platelets (Gilbert and Arena 1996). FVIII interaction with FIXa was localized to residues S577-Q584 (Fay P et al. 1994; O'Brien LM et al. 1995) and K726-N733 (Griffiths AE et al. 2013) in the A2 domain and to residues E1830-K1837 in the A3 domain (Lenting PJ et al. 1996; Bloem E et al. 2013). Missense mutations within the S577-Q584 region have been associated with mild/moderate hemophilia A (HA) (Amano K et al. 1998; Celie PH et al. 1999; Jenkins PV et al. 2002). A functional assay demonstrated that the effect of the mutations S577F, V578A, D579A, and Q584R is not to alter the affinity of FVIIIa for FIXa but rather to directly affect the catalytic rate constant of the complex, and thus the effect of the mutations is to reduce the cofactor potential of FVIII in FXa generation. (Jenkins PV et al. 2002). This conclusion is supported by fluorescence anisotropy data showing defective interaction of fluorescein-modified FIXa with mutant FVIIIa in the presence of FX (Jenkins PV et al. 2002). Other missense mutations in this region include a substitution of isoleucine to threonine at residue 585 (I585T) that creates a new N-linked glycosylation site at asparagine residue 583 resulting in defective procoagulant activity (Aly AM et al. 1992). Structural modeling showed that I585T creates a new asparagine-linked glycosylation site and S577F introduces a bulky side chain, both of which could create steric hindrance impairing FIXa interaction with the S577-Q584 region (Amano K et al. 1998). In addition, in the three-dimensional FVIII model residues 530–549 are located in close proximity to residues S577-Q584 (Pemberton S et al. 1997). Mutations in this segment, for example R546W, could also interfere with FVIIIa:FIXa-mediated stimulation of FX activation (Celie PH et al. 1999). The Reactome event describes failed generation of FXa as the functional consequence of the FIXa interaction with HA-associated FVIIIa variants due to reduced ability of defective FVIII to act as a cofactor for FIXa within the
intrinsic tenase complex.

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[https://reactome.org](https://reactome.org)
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