Defective F8 cleavage by thrombin

D'Eustachio, P., Shamovsky, V., Zhang, B.
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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 75

This document contains 1 pathway and 1 reaction (see Table of Contents)
Defective F8 cleavage by thrombin

**Stable identifier:** R-HSA-9672391

**Compartments:** extracellular region

**Diseases:** factor VIII deficiency


**Literature references**


**Editions**

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In normal human plasma factor VIII (FVIII) complexed to von Willibrand factor (vWF) is cleaved into several smaller polypeptides that remain associated. While several proteases are capable of catalyzing these cleavages in vitro, only thrombin is active on FVIII:vWF complexes under physiological conditions (Eaton D et al. 1986; Hill-Eubanks DC et al. 1989; Lollar P et al. 1988; Pieters et al. 1989). Thrombin cleaves FVIII after arginine residues 391 (A1-A2 domain junction) and 759 (A2-B domain junction) to yield heavy chain fragments and at R1708 (a3-A3 junction) to yield the light chain fragment (Eaton D et al. 1986; Hill-Eubanks DC et al. 1989; Kaufman et al. 1997). Cleavage at R759 is rapid relative to the other two sites and results in the liberation of the B domain or its fragments from the factor VIII heavy chain (Hill-Eubanks DC & Lollar P 1990). The cleavage at R759 is thought to facilitate cleavages at R391 and R1701, which lead to FVIII activation (Newell JL & Fay PJ 2007). Cleavage at R391 exposes a cryptic functional factor IXa-interactive site in the A2 domain (Fay PJ et al. 2001). Proteolysis at R1708 results in the release of the acidic polypeptide (a3 subdomain) on the aminoterminal side of the A3 domain of the light chain. However, as this polypeptide mediates the association of FVIII with vWF, the active factor VIII dissociates from vWF. Thus, cleavage after R1708 is required to release the active FVIIIA from vWF (Lollar P et al. 1988; O’Brien DP & Tuddenham EG 1989; Aly AM & Hoyer LW 1992). The active FVIIIA acts as a cofactor for factor IXa that converts factor X to the activated form Xa and eventually leads to the formation of a blood clot.

Mutations affecting arginine residues located at the thrombin cleavage sites result in mild/moderate hemophilia A (HA) (Pattinson JK et al. 1990; Arai M et al. 1990; Schwaab R et al. 1991). Substitution of Arg391 was reported to impair thrombin cleavage of the heavy chain (Shima M et al. 1989; Arai M et al. 1989; O’Brien DP et al. 1990; Nogami K et al. 2005). Similarly, substitution of R1708 prevents cleavage of the FVIII light chain by thrombin (O’Brien DP & Tuddenham EG 1989; Arai M et al. 1990; Newell JL & Fay PJ 2009). The substitution of arginine for cysteine at position 1708 (FVIII R1708C, also known as East Hartford, FVIII-EH) has been identified in 5% of all patients with HA (Lazarchick and Hoyer 1978). Un-
cleaved FVIII R1708C variant was not released from vWF and thereby blocked procoagulant function of FVIII (O’Brien DP & Tuddenham EG 1989; Aly AM & Hoyer LW 1992). The incubation of plasma of FVIII R1708C hemophilic patients with cysteamine, a small aminothiol endogenously derived from coenzyme A degradation, caused dose- and time-dependent increases in FVIII activity and restored light chain cleavage by thrombin (Aly AM et al 1992). It has been suggested that C1708 is present in a disulfide bond which is converted by cysteamine treatment to a positively charged lysine analogue recovering the thrombin cleavage site (Aly AM et al 1992; Gallego-Villar L et al. 2017). In addition, mutations close to thrombin cleavage sites may also disrupt the activation of FVIII (Johnson DJ et al. 1994; Mumford AD et al. 2002). For example, FVIII Y365C variant plasma showed delayed thrombin activation and a greater subsequent rate of decay than wild-type FVIII (Mumford AD et al. 2002). This hypothesis is supported by the observations that the mutation Y365F, generated by site directed mutagenesis, results in a delayed thrombin-mediated activation of FVIII, because sulfation of this residue is crucial for thrombin cleavage at position 391 (Michnick DA et al. 1994). The Reactome event describes failed thrombin-mediated activation of HA-associated FVIII variants (such as R391C, R391H, S392L) due to defects at or close to thrombin cleavage sites.

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