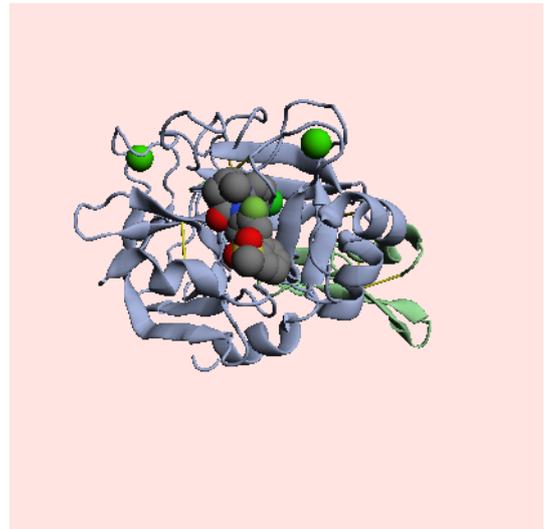


# Factor Xa

From Proteopedia [proteopedia.org/w/Factor\\_Xa](http://proteopedia.org/w/Factor_Xa)

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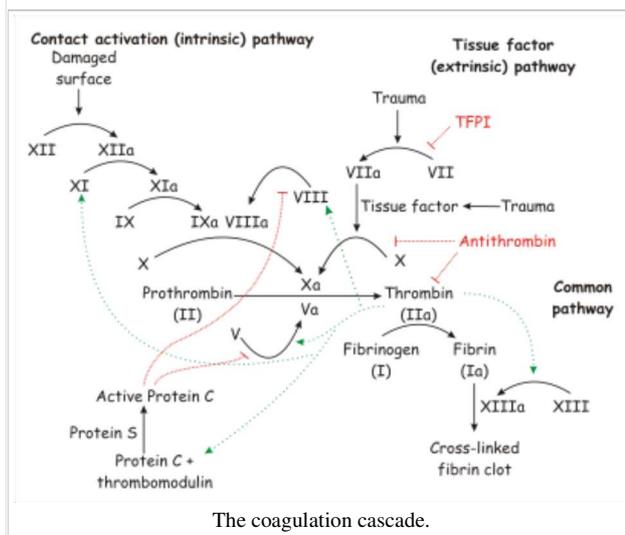


*Human factor X heavy chain (grey) and light chain (green) complex with pyrrolydine derivative inhibitor and Ca<sup>2+</sup> ions (green) (PDB code 2pr3)*

🖱️ Drag the structure with the mouse to rotate

Note: rotation and interaction with the structural model will only work if you view this document in a viewer that supports 3D-PDF format. (Not in a web browser)

## Introduction



**Factor X** is a vitamin K-dependent glycoprotein (<http://en.wikipedia.org/wiki/Glycoprotein>) that is synthesized in the liver. Zymogen (<http://en.wikipedia.org/wiki/Zymogen>) factor X circulates in plasma as a 2 chain molecule composed of a disulfide linked light chain (Mr = 16500) and heavy chain (Mr = 42,000). Factor X is activated to **factor Xa** by cleavage of the activation peptide. This reaction is catalyzed by factor VIIa ([http://en.wikipedia.org/wiki/Factor\\_VIIa](http://en.wikipedia.org/wiki/Factor_VIIa)) -tissue factor ([http://en.wikipedia.org/wiki/Tissue\\_factor](http://en.wikipedia.org/wiki/Tissue_factor)) (extrinsic Xase complex) and factor IXa ([http://en.wikipedia.org/wiki/Factor\\_ixa](http://en.wikipedia.org/wiki/Factor_ixa)) -factor VIIIa ([http://en.wikipedia.org/wiki/Factor\\_viii](http://en.wikipedia.org/wiki/Factor_viii)) (intrinsic Xase complex).<sup>[1]</sup>

**Factor Xa**, along with factor Va ([http://en.wikipedia.org/wiki/Factor\\_va](http://en.wikipedia.org/wiki/Factor_va)), calcium, and a phospholipid membrane surface to form the prothrombinase complex (<http://en.wikipedia.org/wiki/Prothrombinase>), and cleave prothrombin (<http://en.wikipedia.org/wiki/Prothrombin>) to its active form, thrombin (<http://en.wikipedia.org/wiki/Prothrombin>).<sup>[1]</sup>

## Relevance

Factor Xa is inhibited by Apixaban and Rivaroxaban which are anticoagulant medications.

## Structure

**Factor Xa** is a member of the chymotrypsin-like clan within the serine protease family. Other clans within the mammalian family are the subtilisin-like and  $\alpha/\beta$ -hydrolase fold serine proteases. **Structural homology** is seen in the mammalian serine protease family, and is particularly conserved in the active site geometry of the catalytic triad. The mammalian serine protease family is an example of divergent evolution from a common ancestor. <sup>[2]</sup>

Bacterial subtilisin serine protease shows no sequence or structural homology to the mammalian serine protease family, but is functionally identical. Subtilisin uses a His, Asp, Ser catalytic triad with the same mechanism of catalysis. This is an example of convergent evolution.<sup>[2]</sup>

## Light Chain

The factor Xa light chain contains a  $\gamma$ -carboxyglutamic acid (Gla) domain  $\gamma$ -carboxyglutamic acid (Gla) ([http://en.wikipedia.org/wiki/Gla\\_domain](http://en.wikipedia.org/wiki/Gla_domain)) (11 gla residues) as well as two epidermal growth factor (EGF)-like domains epidermal growth factor (EGF) ([http://en.wikipedia.org/wiki/Epidermal\\_growth\\_factor](http://en.wikipedia.org/wiki/Epidermal_growth_factor)).<sup>[3]</sup> The vitamin K-dependent GLA-domain is a post-translational modifications of many glutamate residues by vitamin K-dependent carboxylation to form gamma-carboxyglutamate. <sup>[4]</sup> <sup>[5]</sup> This domain begins at the N-terminus of the protein and ends with a conserved aromatic residue. There is also a conserved Gla-X(3)-Gla-X-Cys motif <sup>[6]</sup>, located in the middle of the GLA domain, and appears to be important for recognition by the vitamin K-dependent carboxylase. The Gla residues are responsible for the high-affinity binding of calcium ions. Based on 3D structures of several Gla domains it that the binding of calcium ions induce conformational changes in the domain and are necessary for proper folding of this region. <sup>[7]</sup> A common structural feature of Gla domains is the clustering of N-terminal hydrophobic residues into a hydrophobic patch that mediates interaction with the cell surface membrane. <sup>[8]</sup> The Gla domain enables factor X/Xa to bind phospholipid (i.e. cell surfaces) in a calcium dependent manner; a requirement for assembly of the prothrombinase complex. Factor Xa from which the Gla domain has been removed by limited chymotryptic digestion does not bind to phospholipid-factor Va and is virtually inactive. <sup>[9]</sup> Additional detgails in Calcium ions the Gla domain.

EGF-like domains have a length of approximately 40 amino acids and are characterized by a conserved arrangement of six cysteine residues that form 3 evenly spaced disulfide bonds.<sup>[10]</sup> Factor X contains two of them located between the membrane-proximal  $\gamma$ -carboxyglutamic acid (Gla)- containing domain and the serine protease domain. The first EGF-like domain in these proteins contains 1 Ca<sup>2+</sup> binding site. <sup>[11]</sup> The side chains of two Asp, one of which may be  $\beta$ -hydroxylated, and one Gln residue and two backbone carbonyl oxygens have been identified as Ca<sup>2+</sup> ligands in the first EGF-like domain. <sup>[12]</sup> The affinity of this site in factor X is represented by a dissociation constant (Kd) of about 0.1 mM in the intact protein. <sup>[13]</sup> In contrast, Ca<sup>2+</sup> binding to the isolated EGF-like domain has a 20-fold higher Kd <sup>[14]</sup>. The biological function of EGF-like domains are largely unknown, some proteins containing them, may have some EGF-like functions also. Recent crystal structures suggest that the N-terminal epidermal growth factor (EGF)-like domain is flexibly, while the second EGF domain maintains contacts with the catalytic domain.

## Heavy Chain

The factor Xa heavy chain contains the activation peptide (no crystal structures of inactive Factor X containing the activation peptide have been solved) and the trypsin-like serine protease domain.

The members of the trypsin-like serine protease family have two homologous greek key  $\beta$ -

Partial content taken from  
[https://proteopedia.org/w/Factor\\_Xa](https://proteopedia.org/w/Factor_Xa)