Factor XI Structure reveals a Novel Receptor Mediated Activation Pathway

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Factor XI (FXI) is an essential component to normal blood hemostasis and inherited deficiency is associated with excessive bleeding complications after surgery or trauma. FXI functions to cleave factor IX within the intrinsic coagulation pathway. The FXI protease is activated through a unique mechanism of binding to the leucine rich repeat receptor Glycoprotein Ib (GpIb) on the surface of platelets. It is then cleaved by thrombin also bound to a different region of the GpIb receptor.

We have crystallised the intact recombinant FXI zymogen and determined the structure to 3Å resolution. Each FXI monomer has four homologous subunits called apple domains (designated A1, A2, A3, and A4, from the N terminus) which mediate protein-protein interactions. At the C-terminus there is a serine protease with a typical catalytic triad. The structure reveals a remarkable "flying saucer" quaternary arrangement with the four apple domains forming a ring and the serine protease domain positioned on top. The structure of the individual apple domains is represented by a novel topological motif. The FXI structure combined with our previous structural analysis of the Glycoprotein Ib receptor domain[1] allows us to construct a model of the activating ternary complex formed with thrombin.

[1] Uff et al., *J. Biol. Chem.,* 2002, **277**, 35657 - 35663.

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