Structure of Coagulation FXI bound to a Peptide Derived from Laminin

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Laminin is an extracellular matrix protein that is exposed when a blood vessel is damaged. Inoue *et. al.* showed that immobilized laminin is able to recruit platelets in the GP1bα-vWF dependent manner[1]. Recent work has also shown that laminin can contribute to the start of the coagulation cascade via the activation of coagulation FXII and that surface-associated laminin alone can trigger the formation of fibrin- and platelet-rich clots under shear [2]. Here, we present the first evidence that laminin is able to bind to coagulation FXI of the intrinsic pathway. We have determined the structure of a short 6-residue peptide from laminin bound to the apple 2 domain of the factor XI zymogen using protein x-ray crsytallography. The laminin peptide binds along a hydrophobic groove on the underside of the A2 domain of FXI. This is the same binding site which high molecular weight kininogen circulates bound to FXI in plasma. In addition, a hydrogen bond network between the laminin peptide and a number of basic residues on the A2 domain surface also appears important in mediating this interaction. The FXI-laminin complex crystal structure represents the first complex between factor XI and laminin. The structure reveals a key binding site for laminin with the apple 2 domain of FXI and also proposes a similar interaction between laminin and the apple 2 domain of the FXI homolog prekallikrein (PK). These molecular insights provide a scaffold for development of novel antithrombotics targeting the intrinsic pathway.

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2. White-Adams TC, Berny MA, Patel IA, et al. Laminin promotes coagulation and thrombus formation in a factor XII-dependent manner. *Journal of Thrombosis and Haemostasis*. 2010;8(6):1295-1301.

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