Background:
Factor (f)XI, the precursor of the protease fXIa, is an important component of the coagulation system; deficiency in fXI (hemophilia C) results in bleeding problems. Although two proteases produced at sites of vascular injury, fXIIa and thrombin, have been shown to catalyze the activation of fXI, significant controversy exists concerning the efficiency of thrombin activation of fXI and the need for cofactors. To address this controversy, we performed kinetic analyses of fXI activation by several catalysts and assessed potential cofactors.

Methods:
FXI activation was monitored using small peptide substrates. Reaction mixtures containing activators (thrombin, fXIa, fXIIa) with/without potential cofactors were constructed. The synthetic polymer dextran sulfate (DS) was used as a positive cofactor control. Platelets were isolated from phlebotomy blood and the following preparations were made as potential sources of cofactors: unactivated platelets, lysed platelets, lysed platelet releasate, and thrombin-activated platelet releasates.

Results:
Measured second-order rate constants (average of three experiments) for fXI activation by thrombin, fXIa, and fXIIa in the presence/absence of DS were:

Activator	No Dextran Sulfate	Dextran Sulfate
Thrombin	$<163 M^{-1}sec^{-1}$	$2.4x10^{5} M^{-1}sec^{-1}$
fXIa	$<694 M^{-1}sec^{-1}$	$4.7x\ 10^{4} M^{-1}sec^{-1}$
fXIIa	$1.7x10^{3} M^{-1}sec^{-1}$	$6.4x10^{4} M^{-1}sec^{-1}$

In the absence of DS, fXIIa was at least ten times more efficient than thrombin in activating fXI. No fXI activation by thrombin was detected without the use of DS. In the presence of the different platelet preparations fXIa formation was only detected in the releasate from thrombin-activated platelets, and was characterized by a second-order rate constant of $1.3x10^{4} M^{-1}sec^{-1}$. However, the addition of high molecular weight kininogen (which is bound to fXI in blood) to the reactions containing thrombin-activated platelet releasate or DS blocked fXI activation by thrombin.

Conclusion: In the absence of a cofactor, fXIIa is a better activator of fXI than thrombin. A physiologically relevant cofactor for thrombin activation of fXI remains to be identified.