Inhibition of coagulation factor XI attenuates inflammation in myocardial ischemia/reperfusion injury

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Background: Increasing evidence suggests that FXI is an attractive target for antithrombotic therapy because it reduces thrombosis without increasing bleeding risk. Patients with decreased levels of FXI are at reduced risk of cardiovascular diseases and thromboembolic events. We have already revealed that depletion of FXI inhibits the vascular coagulation-inflammatory circuit in angiotensin II-induced arterial hypertension. However, the effect of FXI depletion on cardiac inflammation and vascular function in ischemia/reperfusion (I/R) injury is unknown.

Purpose: Using FXI-depleted mice to investigate the role of FXI in inflammation response post cardiac I/R injury.

Methods: 8–12 weeks old C57BL/6J male mice were injected intraperitoneally with FXI antisense oligonucleotide (FXI ASO) or scrambled controls for a period of 2 weeks. Then we temporarily ligated the left anterior descending (LAD) for 45 minutes to induce myocardial ischemia, followed by the reperfusion for 72 hours (ischemia/reperfusion injury, IRI). Myocardial inflammation and vascular function were analyzed by flow cytometry, real-time PCR, vascular relaxation studies from isolated aortic segment in organ chamber and chemiluminescence photon counting of oxidative burst in whole blood.

Results: FXI ASO treatment reduced hepatic FXI mRNA levels and prolonged activated partial thromboplastin time. Compared to scrambled ASO injected mice, oxidative burst from whole blood and endothelial dysfunction were decreased in FXI ASO injected mice with IRI. Compared to control groups, depletion of FXI attenuated cardiac infiltration of CD45+CD11b+ cells, especially LyG-LyChigh monocytes and LyG+ neutrophils at day 3 in I/R injury. Furthermore, the expression levels of adhesion molecules and expression of pro-inflammatory cytokines, such as Vcam-1, CCL2, IL-6 and IL-1b, in ischemic myocardium were significantly decreased in the FXI depleted mice of I/R injury.

Conclusion: Our results suggest that Inhibition of FXI leads to reduction of vascular dysfunction and ROS production in I/R injury, as well as attenuation of the inflammatory response and the influx of inflammatory cells in ischemic myocardium. This indicates that FXI could be a potential target for further treatment in cardiac IRI.