Deep vein thrombosis (DVT) is a major cause of cardiovascular death. The sequence of events that promote DVT remains obscure, largely as a result of the lack of an appropriate rodent model. We describe a novel mouse model of DVT which reproduces a frequent trigger and resembles the time course, histological features, and clinical presentation of DVT in humans. We demonstrate by intravital two-photon and epifluorescence microscopy that blood monocytes and neutrophils crawling along and adhering to the venous endothelium provide the initiating stimulus for DVT development. Using conditional mutants and bone marrow chimeras, we show that intravascular activation of the extrinsic pathway of coagulation via tissue factor (TF) derived from myeloid leukocytes causes the extensive intraluminal fibrin formation characteristic of DVT. We demonstrate that thrombus-resident
neutrophils are indispensable for subsequent DVT propagation by binding factor XII (FXII) and by supporting its activation through the release of neutrophil extracellular traps (NETs). Correspondingly, neutropenia, genetic ablation of FXII, or disintegration of NETs each confers protection against DVT amplification. Platelets associate with innate immune cells via glycoprotein Ib alpha and contribute to DVT progression by promoting leukocyte recruitment and stimulating neutrophil-dependent coagulation. Hence, we identified a cross talk between monocytes, neutrophils, and platelets responsible for the initiation and amplification of DVT and for inducing its unique clinical features.