The Effect of Caspase-11 in Trauma-Induced Coagulopathy (TIC).

Joud Mulla[1], Nijmeh Alsaadi[1], Zachary Secunday,[1] Rohan Katti[1], Justin Curtis[1], Matthew D. Neal[1], Melanie J. Scott[1]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA

**Introduction:** Trauma is one of the leading causes of death globally in people 50 years and younger. Hemorrhagic shock following trauma can lead to hypoxia, loss of blood components, and the need for blood transfusion, all of which can lead to trauma-induced coagulopathy (TIC) and organ and tissue damage, resulting in multiple organ dysfunction (MODs). Caspase-4/11 is associated with disseminated intravascular coagulation (DIC) in sepsis by allowing tissue factor binding to cells and initiation of the coagulation cascade. However, its role in TIC is unknown. We sought to investigate the effects of caspase-11 in a murine polytrauma model on hemostasis and coagulation. **Method:** To induce coagulopathy, male C57BL/6J and caspase-$11^{-/-}$ mice, 8-12 weeks old, were subjected to a murine polytrauma model. The model consists of a blind cardiac puncture (25% of total blood volume is taken), laparotomy with liver crush, and bilateral pseudofractures (hindlimb crush injury followed by the injection of crushed bone solution from an age- and weight-matched syngeneic donor). Blood was collected and citrated at 3, 6 and 24 hours. Caspase-11, tissue factor, and fibrin expression were measured by Western blot (WB) of whole liver and lung lysates. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen were measured. **Results:** Polytrauma significantly increased aPTT levels (18.1$\pm$0.8 to 42.7$\pm$0.8 sec, $p<0.0001$) and fibrinogen levels (154$\pm$0.4 to 433$\pm$0.8 mg/dL, $p<0.0001$) after 24h, indicating TIC. Polytrauma induced expression of caspase-11 in the liver. After 24h of polytrauma, aPTT levels increased in WT mice but did not increase in caspase-$11^{-/-}$ mice (42.7$\pm$0.8 v.s 10.2 $\pm$1 sec, $p<0.0001$). Moreover, fibrinogen levels rose 3 fold in WT and caspase-$11^{-/-}$ mice with lesser post-injury values in caspase-$11^{-/-}$ mice compared to WT mice (331$\pm$0.8 v.s. 433$\pm$0.8 mg/dL, respectively). Caspase-11-deficiency increased tissue factor and decreased fibrin levels in both liver and lung at 6h in TIC compared with WT (Figures). **Conclusion:** Caspase-11 expression is induced by polytrauma and TIC. Caspase-11 signaling may regulate the coagulation profile in polytrauma as well as the localization of tissue factor. Inhibition of caspase-11 may therefore be a future therapeutic option for TIC.

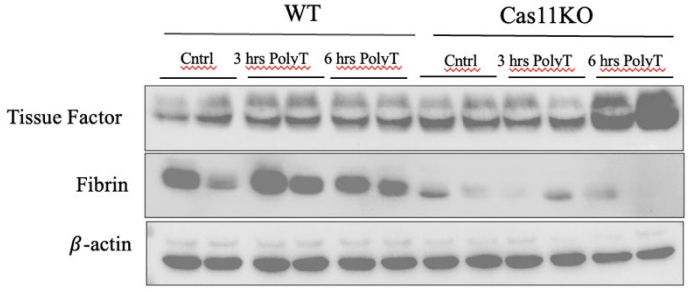


Figure 1: Western blot of whole lung lysate in WT and caspase-$11^{-/-}$ following 3 and 6 hours polytrauma (PolyT). $\beta$-actin as control.

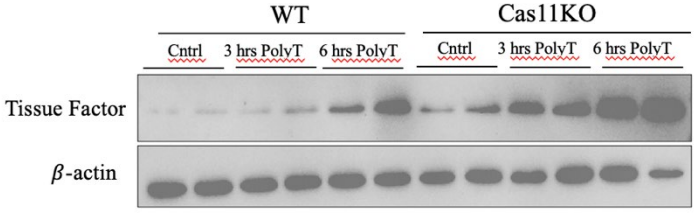


Figure 2: Western blot of whole liver lysate in WT and caspase-$11^{-/-}$ following 3 and 6 hours polytrauma (PolyT). $\beta$-actin as control.