**Objectives:** Coronavirus-associated coagulopathy is postulated to be driven by systemic macrophage activation after severe acute respiratory syndrome coronavirus 2 infection and presents with an increased risk of thrombogenesis and hyperfibrinolysis. Previous work shows that the histone deacetylase inhibitor KMT2A overexpression is a key mediator of inflammatory signaling in monocytes and macrophages (Mo/Ms). In this study, we sought to identify the regulation of factors important in coronavirus-associated coagulopathy by MLL1.

**Methods:** Mice with myeloid specific knockout of MLL1 (Cre1) and littermate controls (Cre0) underwent intranasal inoculation of 2 × 105 pfu of the murine coronavirus MVA59. An established model which phenocopies severe acute respiratory syndrome coronavirus 2 infection. Splenic Ms (surrogate for circulating Mo/Ms) were isolated and RNA and protein levels of urokinase (Plau; probrinolytic), urinase receptor (Plaur; profibrinolytic), and tissue factor (F3/TF; procoagulant) were analyzed using quantitative reverse-transcriptase polymerase chain reaction and enzyme-linked immunosorbent assay, respectively. Thromboelastography on whole blood and urinase activity assays from mouse plasma were performed. Urokinase and tissue factor activity assays were performed on plasma from human samples.

**Results:** RNA (Figure, top panel) and protein (Figure, bottom) levels of Plau, Plaur, and F3 were suppressed in the splenic Ms harvested from Cre1 animals (white bars) compared with splenic Ms harvested from Cre0 animals (blue bars; Figure A). Cre1 mice displayed a shortened reaction time as measured by thromboelastography (Figure B) and elevated plasma urinase activity levels (not shown). Hospitalized coronavirus disease 2019-positive patients displayed elevated plasma urinase and tissue factor activity levels (Figure C).

**Conclusions:** We identify a role for MLL1 for basal expression and for coronavirus-mediated induction of factors important for fibrinolysis and coagulation in murine Mo/Ms and in disease coagulopathy. Our results suggest that MLL1 blockade may be an attractive strategy to combat coronavirus-associated coagulopathy.