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The plasminogen (Plg)/plasmin (Pla) system is associated with a variety of biological activities beyond the classical dissolution of fibrin clots, including cell migration, tissue repair, and inflammation. Although the capacity of Plg/Pla to induce cell migration is well defined, the mechanism underlying this process in vivo is elusive. In this study, we show that Pla induces in vitro migration of murine fibroblasts and macrophages (RAW 264.7) dependent on the MEK/ERK pathway and by requiring its proteolytic activity and lysine binding sites. Plasmin injection into the pleural cavity of BALB/c mice induced a time-dependent influx of mononuclear cells that was associated with augmented ERK1/2 and IκB-α phosphorylation and increased levels of CCL2 and IL-6 in pleural exudates. The inhibition of protease activity by using a serine protease inhibitor leupeptin or two structurally different protease-activated receptor-1 antagonists (SCH79797 and RWJ56110) abolished Pla-induced mononuclear recruitment and ERK1/2 and IκB-α phosphorylation. Interestingly, inhibition of the MEK/ERK pathway abolished Pla-induced CCL2 upregulation and mononuclear cell influx. In agreement with a requirement for the CCL2/CCR2 axis to Pla-induced cell migration, the use of a CCR2 antagonist (RS504393) prevented the Plg/Pla-induced recruitment of mononuclear cells to the pleural cavity and migration of macrophages at transwell plates. Therefore, Pla-induced mononuclear cell recruitment in vivo was dependent on protease-activated receptor-1 activation of the MEK/ERK/NF-κB pathway, which led to the release of CCL2 and activation of CCR2.