What do we know about the molecular mechanisms of fibrin(ogen)-dependent inflammation?

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Recruitment of leukocytes from the circulation to sites of inflammation is an integral part of the inflammatory response and transendothelial migration of leukocytes is a key step in such recruitment. Although numerous data indicate that fibrin(ogen) and its degradation products modulate leukocyte transmigration and thereby inflammation, there is still no clear understanding of the molecular mechanisms underlying this phenomenon. The first molecular mechanism proposed more than two decades ago (reviewed by Altiery, 1999) suggests that fibrinogen promotes leukocyte transmigration by bridging leukocytes to the endothelium through the interaction with leukocyte receptor Mac-1 and endothelial receptor ICAM-1. However, subsequent studies revealed that fibrinogen in solution, which mimics its state in the circulation, does not interact with Mac-1. The second molecular mechanism proposed later (Petzelbauer et al., 2005) suggests that naturally occurring fibrin degradation product E1 fragment promotes transendothelial migration of leukocytes by bridging them to the endothelium through the interaction with leukocyte integrin CD11c and endothelial VE-cadherin. However, in the circulation, the E1 fragment may exist only in a complex with the D-D dimer and the CD11c-binding site in such complex is inaccessible for interaction with CD11c. Several years ago we discovered that fibrin promotes leukocyte transmigration through the interaction with the very low density lipoprotein (VLDL) receptor (Yakovlev et al., 2012), but until now the underlying molecular mechanism remained unclear. Our recent in vitro and in vivo studies clarified this mechanism. The results obtained suggest that fibrin-VLDL receptor interaction may trigger a signaling pathway through src kinase Fyn which results in the loss of function of the endothelial barrier and increased leukocyte transmigration.