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CD99L2 as a Major Regulator in Human Transendothelial Migration

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Transendothelial Migration (TEM) is a crucial step in the inflammatory response as it is the process in which leukocytes leave the bloodstream to enter the inflamed tissues. Adhesion/signaling molecules such as PECAM and CD99 are important for the initiation and completion of TEM. We and others have shown that CD99-like 2 (L2), a highly glycosylated 52 kD type-1 membrane protein that is the only molecule in the genome related to CD99 is also important for TEM. However, L2 is different enough from CD99 (60% larger and with only 38% sequence identity) that it is not clear whether it regulates TEM by the same mechanism as CD99. Furthermore, all of the published studies on L2 have been performed in mice. The role of L2 in human cells is not known. In order to study the mechanism used by L2 and the relevance to human inflammation, we studied the role of L2 on human cells in vitro.

Our data show that similar to PECAM and CD99, human L2 is constitutively expressed at the borders of endothelial cells and on the surface of leukocytes; treatment with proinflammatory cytokines changes neither its surface expression nor its distribution. Blocking L2 using antibodies significantly reduces transmigration of human neutrophils and monocytes across human endothelial cells. Blockade of either leukocytes or endothelial cells blocks equivalently to blocking both, consistent with a homophilic mechanism of interaction. Furthermore, knockdown of L2 using shRNAs dose-dependently reduces TEM of neutrophils and monocytes across endothelial cells. TEM is restored by re-expression of L2. Our data also show that L2 regulates a step in TEM after PECAM and before CD99. Consistent with this, preliminary data suggest that L2 can promote TEM by engaging either the signaling pathway used by PECAM or the one used by CD99. Similar to PECAM and CD99, L2 promotes transmigration by recruiting the lateral border recycling compartment to the site of TEM. Ongoing studies are focused on identifying unique signaling pathways (if any) used by L2 to promote TEM.

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