Endothelial intracellular molecule *LSP1* regulates the chemotactic directionality of extravascular migrating neutrophils

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The recruitment of leukocytes from the flowing bloodstream into inflamed tissue is of key importance in inflammation. This recruitment is characterized as the initial tethering and rolling of leukocytes along the endothelium, followed by leukocyte activation and firm adhesion to the endothelium, leukocyte transmigration across the endothelium (diapedesis), and chemotactic migration of emigrated leukocytes toward the site of infection or injury (chemotaxis) in tissue. The role of intracellular signaling molecules in leukocytes and endothelial cells involved in leukocyte recruitment is investigated in the microvasculature *in vivo*. *LSP1* (leukocyte-specific protein 1), an F-actin-binding, intracellular phosphoprotein, is expressed in leukocytes and endothelial cells with different intracellular localization pattern. In endothelial cells, *LSP1* is mainly expressed in the nucleus with small proportion as cytosolic and cytoskeletal protein. The role of endothelial *LSP1* in neutrophil recruitment is investigated and endothelial *LSP1*-regulated mechanism for extravascular neutrophil chemotaxis is revealed in our study. Using intravital microscopy in *LSP1*-deficient and *LSP1*-chimeric mice, we show that endothelial *LSP1* plays a permissive role in controlling neutrophil transendothelial migration during neutrophil recruitment and regulates extravascular migration directionality but not the migration velocity of emigrated neutrophils. We found that the expression of $\alpha 6\beta 1$ integrins on the emigrated neutrophils was blunted when *LSP1* was deficient in the endothelium of LSP1-deficient or chimeric mice, and that neutrophil $\alpha 6\beta 1$ integrin expression dictated the directionality of emigrated neutrophils *in vivo* and *in vitro*. *LSP1*-deficiency or *LSP1*-targeted siRNA silencing in endothelial cells reduced endothelial adhesion molecule PECAM-1 expression through GATA-2-dependent mechanism. *LSP1* overexpression in endothelial cells has unregulated endothelial PECAM-1 expression. It was the reduced endothelial PECAM-1 expression in *LSP1*-deficient endothelium that down-regulated $\alpha 6\beta 1$ integrin expression on the transmigrating neutrophils and that, through PECAM-1-sensitive, down-regulated $\alpha 6\beta 1$ integrin expression, mitigated the migration directionality of transmigrated neutrophils in tissue. Thus, endothelial *LSP1* regulates vascular PECAM-1-sensitive and neutrophil integrin $\alpha 6\beta 1$ dependent directionality of extravascular neutrophil migration in inflamed tissue during neutrophil recruitment.

Biography

Liu Lixin had research training with Dr. Dirk Roos (CLB, The Netherlands) and completed his PhD study with Dr. Per Venge at Uppsala University (Sweden). In Europe, he has studied the regulatory mechanisms of granulocyte transmigration across epithelial cell monolayer. Thereafter, as a Post-doctoral Fellow, he has joined the lab of Dr. Paul Kubes in the University of Calgary, in Alberta, Canada, where he became experienced in the techniques of intravital microscopy and started to explore the role of intracellular protein molecules in neutrophil transendothelial migration and chemotaxis. In late 2006, he has joined the faculty in the University of Saskatchewan (Saskatchewan, Canada) and currently he is Associate Professor in Pharmacology. Using intravital microscopy and other imaging techniques and biochemical and cell biological approaches, his lab is now investigating the role of intracellular signaling molecules in neutrophil-endothelial cell interactions, with current research interests in the signaling mechanisms of *LSP1* (leukocyte-specific protein 1) and PI3K (phosphoinositide 3-kinases) in neutrophil recruitment during inflammation.

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