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Inflammation, Extracellular Mediators, & Effector Molecules

MFG - E8 - derived peptide attenuates adhesion and migration of immune cells to endothelial cells

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Abstract

Milk fat globule - epidermal growth factor - factor 8 (MFG - E8) plays an immunomodulatory role in inflammatory diseases. MFG - E8 - derived short peptide (MSP68) greatly reduces neutrophil infiltration and injury in the lung during sepsis. In this study, we examined the effect of MSP68 on chemotaxis of various immune cells and its regulatory mechanism. Bone marrow - derived neutrophils (BMDNs) from C57BL/6 mice, human monocyte THP - 1 cell line, and human T lymphocyte Jurkat cell line were used for adhesion and migration assays using a Transwell method in the presence of MSP68. Treatment with MSP68 significantly inhibited the BMDN and THP - 1 cell but not Jurkat cell adhesion on the TNF - α - stimulated pulmonary artery endothelial cell (PAEC) monolayer dose - dependently. MSP68 also significantly reduced BMDN adhesion on VCAM - 1 - coated wells dose dependently. Surface plasmon resonance (SPR) analysis revealed that MSP68 efficiently recognized integrin $\alpha_4\beta_1$ (receptor for VCAM - 1) at the dissociation constant (K_D) of 1.53×10^{-7} M. These findings implicate that MSP68 prevents neutrophil adhesion to the activated endothelial cells by interfering with the binding between integrin $\alpha_4\beta_1$ on neutrophils and VCAM - 1 on endothelial cells. Moreover, MSP68 significantly attenuated the migration of BMDN and THP - 1 cells but not Jurkat cells to their chemoattractants. Pretreatment with MSP68 inhibited the transmigration of BMDNs across the PAECs toward chemoattractants, fMLP, MIP - 2, and complement fragment 5a (C5a) dose - dependently. Finally, we identified that the activation of p38 MAPK in BMDNs by fMLP was inhibited by MSP68. Thus, MSP68 attenuates extravasation of immune cells through the endothelial cell lining into inflamed tissue, implicating MSP68 to be a novel, therapeutic agent for inflammatory diseases caused by excessive immune cell infiltration.

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