Vascular Endothelial Growth Factor C Upregulates Trans-Lymphatic Metastasis in the Murine Liver by Recruiting Bone Marrow-Derived Cells

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Abstract

Colorectal cancer liver metastasis (CRCLM) is a major cause of death from colorectal cancer; however, the mechanism of intrahepatic dissemination (trans-lymphatic metastasis) is not fully elucidated. It is possible that lymphangiogenesis is the mechanism of dissemination; however, this requires confirmation, especially in the liver. In this study, we attempted to clarify the mechanism using a syngeneic murine CRCLM model, focusing on vascular endothelial growth factor C (VEGFC), a major promoter of lymphangiogenesis. We confirmed 1) intrahepatic CRCLM occurs via lymphatic vessels and upregulation of lymphangiogenesis in the CRCLM-bearing liver, 2) the degree of lymphangiogenesis and CRCLM was significantly correlated with the expression of VEGFC in colorectal cancer (CRC) cells, and 3) macrophage inflammatory protein-1α (MIP-1α) was released from CRC cells under VEGFC stimulation and induced migration of immature bone marrow-derived cells into the liver and differentiation into macrophages, which promoted dissemination of CRCLM. From these findings, we suggest a therapeutic strategy targeting VEGFC/MIP-1α to reduce CRCLM.

Key words: colorectal cancer, liver metastasis, lymphangiogenesis, vascular endothelial growth factor C, macrophage inflammatory protein-1α, tumor associated macrophage