趨化激素 CCL5 調控腫瘤淋巴管新生之研究

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Chondrosarcoma is the second most frequently occurring type of bone malignancy that is characterized by the distant metastasis propensity. Vascular endothelial growth factor-C (VEGF-C) is the major lymphangiogenic factor, and makes crucial contributions to tumor lymphangiogenesis and lymphatic metastasis. Several chemokines have been indicated to facilitate cancer metastasis by promoting lymphangiogenesis in tumor microenvironment. However, the effect of chemokine CCL5 on VEGF-C regulation and lymphangiogenesis in chondrosarcoma has largely remained a mystery. In this study, we showed a clinical correlation between CCL5 and VEGF-C as well as tumor stage in human chondrosarcoma tissues. We further demonstrated that CCL5 promoted VEGF-C expression and secretion in human chondrosarcoma cells. The conditioned medium (CM) from CCL5-overexpressed cells significantly induced tube formation of human lymphatic endothelial cells (LECs). Otherwise, knockdown of CCL5 attenuated CM-induced LECs tube formation, indicating CCL5 enhanced lymphangiogenesis by VEGF-C production in chondrosarcoma cells. Mechanistic investigations showed that CCL5 activated VEGF-C-dependent lymphangiogenesis by down-regulating miR-507. Moreover, we found that CCL5 dramatically increased VEGF-C expression and decreased miR-507 expression in the chondrosarcoma xenograft animal model. Collectively, we document for the first time that CCL5 induces tumor lymphangiogenesis by the induction of VEGF-C in human cancer cells. Our present study reveals miR-507/VEGF-C signaling as a novel mechanism in CCL5-mediated tumor lymphangiogenesis. Targeting both CCL5 and VEGF-C pathways might serve as the potential therapeutic strategy to inhibit tumor progression and metastasis of chondrosarcoma.