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Endothelin-1 promotes vascular endothelial growth factor-dependent angiogenesis in human chondrosarcoma

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Chondrosarcoma is the second most common sarcoma in bone malignancy and is characterized by a high metastatic potential. Angiogenesis is essential for the cancer metastasis. Endothelin-1 (ET-1) has been implicated in tumor angiogenesis and metastasis. However, the relationship of ET-1 with vascular endothelial growth factor (VEGF) expression and angiogenesis in human chondrosarcoma cells is mostly unknown. Here, we found that the expression of ET-1 and VEGF were correlated with tumor stage and were significantly higher than that in the normal cartilage. Exogenous ET-1 with chondrosarcoma cells promoted VEGF expression and subsequently increased migration and tube formation in endothelial progenitor cells. ET-1 increased VEGF expression and angiogenesis through ETAR, integrin-linked kinase (ILK), Akt and hypoxia-inducible factor-1α (HIF-1α) signaling cascades. Knockdown of ET-1 decreased VEGF expression and also abolished chondrosarcoma conditional medium-mediated angiogenesis in vitro as well as angiogenesis effects in the chick chorioallantoic membrane and Matrigel plug nude mice model in vivo. In addition, in the xenograft tumor angiogenesis model, knockdown of ET-1 significantly reduced tumor growth and tumor-associated angiogenesis. Taken together, these results indicate that ET-1 occurs through ETAR, ILK and Akt, which in turn activates HIF-1a, resulting in the activation of VEGF expression and contributing to the angiogenesis and tumor growth of human chondrosarcoma cells.