Ras activation mediates WISP-1-induced increases in cell motility and matrix metalloproteinase expression in human osteosarcoma

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Abstract

WISP-1 is a cysteine-rich protein that belongs to the CCN (Cyr61, CTGF, Nov) family of matrix cellular proteins. Osteosarcoma is a type of highly malignant tumor with a potent capacity to invade locally and cause distant metastasis. However, the effect of WISP-1 on migration activity in human osteosarcoma cells is mostly unknown. In this study, we first found that the expression of WISP-1 in osteosarcoma patients was significantly higher than that in normal bone and corrected with tumor stage. Exogenous of osteosarcoma cells with WISP-1 promoted cell motility and matrix metalloproteinase (MMP)-2 and MMP-9 expression. In addition, the Ras and Raf-1 inhibitor or siRNA abolished WISP-1-induced cell migration and MMPs expression. On the other hand, activation of the Ras, Raf-1, MEK, ERK, and NF-κB signaling pathway after WISP-1 treatment was demonstrated, and WISP-1-induced expression of MMPs and migration activity were inhibited by the specific inhibitor, and mutant of MEK, ERK, and NF-κB cascades. Taken together, our results indicated that WISP-1 enhances the migration of osteosarcoma cells by increasing MMP-2 and MMP-9 expression through the integrin receptor, Ras, Raf-1, MEK, ERK, and NF-κB signal transduction pathway.