論 文 要 旨

GLI2 is a novel therapeutic target for metastasis of osteosarcoma

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Aberrant activation of the Hedgehog (Hh) pathway has been reported in several malignancies. We previously demonstrated that knockdown of GLI2 inhibited proliferation of osteosarcoma cells through regulation of the cell cycle. In this study, we analyzed the function of GLI2 in the pathogenesis of osteosarcoma metastasis. Immunohistochemical studies showed that GLI2 was overexpressed in patient osteosarcoma specimens. Knockdown of GLI2 inhibited migration and invasion of osteosarcoma cells. In contrast, the forced expression of constitutively active GLI2 in mesenchymal stem cells promoted invasion. In addition, xenograft models showed that knockdown of GLI2 decreased lung metastasis of osteosarcomas. To examine clinical applications, we evaluated the efficacy of arsenic trioxide (ATO), which is a Food and Drug Administration-approved antitumor drug, on osteosarcoma cells. ATO treatment suppressed the invasiveness of osteosarcoma cells by inhibiting the transcriptional activity of GLI2. In addition, the combination of Hh inhibitors including ATO, vismodegib and GANT61 prevented migration and metastasis of osteosarcoma cells. Consequently, our findings suggested that GLI2 regulated metastasis as well as the progression of osteosarcomas.
Inhibition of the GLI2 transcription may be an effective therapeutic method for preventing osteosarcoma metastasis.