論　文　要　旨

Suppression of Osteosarcoma Cell Invasion by Chemotherapy Is Mediated by Urokinase Plasminogen Activator Activity via Up-Regulation of EGR1

松野下　幸弘

Abstract

Background: The cellular and molecular mechanisms of tumour response following chemotherapy are largely unknown. We found that low dose anti-tumour agents up-regulate early growth response 1 (EGR1) expression. EGR1 is a member of the immediate-early gene group of transcription factors which modulate transcription of multiple genes involved in cell proliferation, differentiation, and development. It has been reported that EGR1 act as either tumour promoting factor or suppressor. We therefore examined the expression and function of EGR1 in osteosarcoma.

Methods: We investigated the expression of EGR1 in human osteosarcoma cell lines and biopsy specimens. We next examined the expression of EGR1 following anti-tumour agents treatment. To examine the function of EGR1 in osteosarcoma, we assessed the tumour growth and invasion in vitro and in vivo.

Results: Real-time PCR revealed that EGR1 was down-regulated both in osteosarcoma cell lines and osteosarcoma patients' biopsy specimens. In addition, EGR1 was up-regulated both in osteosarcoma patient' specimens and osteosarcoma cell lines following anti-tumour agent treatment. Although forced expression of EGR1 did not prevent osteosarcoma growth, forced expression of EGR1 prevented osteosarcoma cell invasion in vitro. In addition, forced expression of EGR1 promoted downregulation of urokinase plasminogen activator, urokinase receptor, and urokinase plasminogen activity. Xenograft mice models showed that forced expression of EGR1 prevents osteosarcoma cell migration into blood vessels.

Conclusions: These findings suggest that although chemotherapy could not prevent osteosarcoma growth in chemotherapy-resistant patients, it did prevent osteosarcoma cell invasion by down-regulation of urokinase plasminogen activity via up-regulation of EGR1 during chemotherapy periods.