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Chemokine BRAK stimulates apoptosis elicited by gefitinib in oral squamous cell carcinoma
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Objectives: The chemokine BRAK/CXCL14, a non ELR-motif chemokine, is expressed in many normal tissues, but absent or down regulated in transformed cells and cancerous tissues including oral carcinoma. We reported previously that BRAK had suppressive activity toward tumor progression of oral carcinoma in vivo when over-expressed in tumor cells. In this study, we investigated whether BRAK expression is associated with the tumor suppression by gefitinib, an inhibitor of the epidermal growth factor receptor (EGFR).

Methods: To examine the mechanism of the tumor suppression in vivo, we xenografted nude mice with HSC-3 cells that had been transfected with control Sh-scrambled vector or ShRNA of BRAK to down-regulate BRAK mRNA expression. In order to investigate the cell proliferation and/or apoptosis with regard to the suppression of tumorigenicity, we prepared paraffin sections and used them for immunohistochemical detection of Ki-67, a marker of cell proliferation and for the TUNEL method to detect apoptosis.

Results: As to the cell proliferation, the number of Ki-67-positive cells in both Sh-Scrambled-treated control tissue sections and Sh-BRAK-treated one was decreased, when the animals were treated with gefitinib. There was no difference between Sh-Scrambled vector-treated tumor cells and Sh-BRAK vector-treated ones with respect to the responsiveness to gefitinib. On the other hand, with respect to apoptosis, we found a significant increase (P<0.05) in the number of apoptotic cells in the Sh-Scrambled vector-treated control tumor cells concomitant with the suppression of tumor mass after the mice had been treated with gefitinib. In contrast, gefitinib affected neither the number of apoptotic cells nor tumor volume suppression in the case of Sh-BRAK vector-treated tumor cells.

Conclusions: These results suggest that a BRAK dependent signal(s) was essential for the stimulation of apoptosis by gefitinib and reduction in tumor volume in vivo.