The expression of BRAK, which is also known as CXC chemokine ligand 14 (CXCL14), was down-regulated significantly by the treatment of HNSCC cells with EGF as observed by cDNA microarray analysis followed by reverse-transcriptase polymerase chain reaction analysis. The EGF effect was attenuated by the co-presence of a MEK inhibitor, thus suggesting that BRAK down-regulation is controlled by the EGF Receptor (EGFR)-Raf-MEK-ERK pathway. The rate of tumor formation in vivo by BRAK-expressing vector-transfected tumor cells in athymic nude mice was significantly lower than that of mock-vector-transfected ones. In addition, tumors formed in vivo by the BRAK-expressing cells were significantly smaller than those of the mock-transfected ones. These results indicate that BRAK down-regulation is beneficial for tumor suppression.

Next we addressed whether inhibition of EGFR activity would affect BRAK expression and growth of tumor cell xenografts. Gefitinib (ZD1839, Iressa), which is an inhibitor specific for the EGFR tyrosine kinase, has been shown to be effective for tumor suppression in non-small cell lung carcinoma patients with over activation of EGFRs. Thus we investigated the relationship between BRAK expression and gefitinib efficacy for tumor suppression. We found that EGF inhibited BRAK expression through the MEK-ERK pathway and that this inhibition was reversed by gefitinib in vitro and that oral administration of gefitinib reduced the tumor growth of xenografts in athymic nude mice, which reduction was accompanied by increased BRAK expression specifically in tumor tissue. The introduction of a BRAK ShRNA vector into HNSCC cells reduced both the expression of BRAK in the cells and the antitumor efficacy of gefitinib in vivo. Our data indicate that the gefitinib-induced increase in BRAK expression is beneficial for tumor suppression in vivo. Our data also provide a new strategy for chemokine-mediated cancer therapy using gefitinib [2].