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The BRAK Box Is Opening
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In order to find a suppressor(s) of tumor progression in vivo for head and neck squamous cell carcinoma (HNSCC), we searched for molecules down-regulated in HNSCC cells when the cells were treated with epidermal growth factor (EGF), whose receptor is frequently over-activated in HNSCC.

The expression of BRAK, which is also known as MEK-ERK pathway. The rate of tumor formation in 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 expression is beneficial for tumor suppression in vivo.

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 siRNA 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].

REFERENCES

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Metabolic characteristics of cancer microenvironment and its implication in malignant progression of cancer

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Objective: Unlimited and unregulated cell proliferation is characteristics of cancer and to support this sufficient supply of oxygen and nutrients is regarded pivotal. Contrary to this, poor blood supply is often associated with poor patient outcome. An extreme example is pancreatic cancer. To understand how deprivation of nutrient is inversely correlated with progression, cancer microenvironment was analyzed from metabolic viewpoint.

Methods: Human materials were obtained after surgical treatments and the protocol was approved by Ethical committee of National Cancer Center. Metabolomic analysis was carried out mainly by CE-MS method established by Soga et al.

Results: Glucose concentration in many cancer tissues was found far less than blood glucose level being less than 0.1mg/ml in average. In contrary, amino acid concentrations were comparable to those of corresponding normal tissues. In vitro experiments using pancreatic cancer cell lines showed that they have a capacity to operate fumarate respiration, an energy production pathway by parasites without oxygen. Glucose deprivation has been shown to induce various types of proteases including cathepsin and MMPs. Immunohistochemical analysis revealed that cancer cells activates autophagy in early stage.

Conclusion: By intrinsic and environmental reasons, cancer cells acquire ability to survive glucose and oxygen deprivation by degrading protein to yield amino acid, leading to invasiveness.