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Title: Overcome the EGFR-TKIs resistance with cucurbitacin BE compound by targeting STAT3, ERK1/2 and AKT

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Body: Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) therapy, but acquired resistance eventually develops at about 9-12 months. Overcoming the drug resistance is of great clinical and scientific significance. In this study, We showed that STAT3,ERK1/2 and AKT were persistently activated in the resistant cells with T790M mutation(PC9/ER) and 52 tumor samples from EGFR-TKIs resistant NSCLC patients.The growth inhibition of the triterpenoid compound cucurbitacin BE (Cu BE) was tested in vitro and in vivo against PC9/GR cells. Cu BE can inhibit the growth of PC9 and PC9/GR cells in a dose- and time-dependent manner, resulting in G2/M phase arrest and apoptosis. This was associated with inhibition of activated Stat3,ERK1/2 and AKT, increased level of autophagy(LC3B expression), and down-regulated the expression of caspase 3 and survivin. Moreover, in a nude mouse tumor xenograft model, Cu BE decreased the PC9/GR tumor volume by 46.4% ($P < 0.05$) compared with the mice treated with erlotinib. These data suggest that treatment with CuBE, which can inhibite the activation of STAT3,ERK1/2 and AKT, appears to be an effective strategy for NSCLC patients with EGFR-TKIs resistance.