

Sulfasalazine suppresses drug resistance and invasiveness of lung adenocarcinoma cells expressing AXL.

賴基銘

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摘要

Abstract

Metastasis and drug resistance are the major causes of mortality in patients with non-small cell lung cancer (NSCLC). Several receptor tyrosine kinases (RTKs), including AXL, are involved in the progression of NSCLC. The AXL/MER/SKY subfamily is involved in cell adhesion, motility, angiogenesis, and signal transduction and may play a significant role in the invasiveness of cancer cells. Notably, no specific inhibitors of AXL have been described. A series of CL1 sublines with progressive invasiveness established from a patient with NSCLC has been identified that positively correlates with AXL expression and resistance to chemotherapeutic drugs. The ectopic overexpression of AXL results in elevated cell invasiveness and drug resistance. Nuclear factor-kappaB (NF-kappaB) signaling activity is associated with AXL expression and may play an important role in the enhancement of invasiveness and doxorubicin resistance, as shown by using the NF-kappaB inhibitor, sulfasalazine, and IkappaB dominant-negative transfectants. In the current study, sulfasalazine exerted a synergistic anticancer effect with doxorubicin and suppressed cancer cell invasiveness in parallel in CL1 sublines and various AXL-expressing cancer cell lines. Phosphorylation of AXL and other RTKs (ErbB2 and epidermal growth factor receptor) was abolished by sulfasalazine within 15 min, suggesting that the inhibition of NF-kappaB and the kinase activity of RTKs are involved in the pharmacologic effects of sulfasalazine. Our study suggests that AXL is involved in NSCLC metastasis and drug resistance and may therefore provide a molecular basis for RTK-targeted therapy using sulfasalazine to enhance the efficacy of chemotherapy in NSCLC.