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Research

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STI571 reduces TRAIL-induced apoptosis in colon cancer cells: c-Abl activation by the death receptor leads to stress kinase-dependent cell death

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Abstract (provisional)

Background

In an effort to achieve better cancer therapies, we elucidated the combination cancer therapy of STI571 (an inhibitor of Bcr-Abl and clinically used for chronic myelogenous leukemia) and TNF-related apoptosis-inducing ligand (TRAIL, a developing antitumor agent) in leukemia, colon, and prostate cancer cells.

Methods

Colon cancer (HCT116, SW480), prostate cancer (PC3, LNCaP) and leukemia (K562) cells were treated with STI571 and TRAIL. Cell viability was determined by MTT assay and sub-G1 appearance. Protein expression and kinase phosphorylation were determined by Western blotting. c-Abl and p73 activities were inhibited by target-specific small interfering (si)RNA. In vitro kinase assay of c-Abl was conducted using CRK as a substrate.

Results

We found that STI571 exerts opposite effects on the antitumor activity of TRAIL. It enhanced cytotoxicity in TRAIL-treated K562 leukemia cells and reduced TRAIL-induced apoptosis in HCT116 and SW480 colon cancer cells, while having no effect on PC3 and LNCaP cells. In colon and prostate cancer cells, TRAIL caused c-Abl cleavage to the active form via a caspase pathway. Interestingly, JNK and p38 MAPK inhibitors effectively blocked TRAIL-induced toxicity in the colon, but not in prostate cancer cells. Next, we found that STI571 could attenuate TRAIL-induced c-Abl, JNK and p38 activation in HCT116 cells. In addition, siRNA targeting knockdown of c-Abl and p73 also reduced TRAIL-induced cytotoxicity, rendering HCT116 cells less responsive to stress kinase activation, and masking the cytoprotective effect of STI571.

Conclusions

All together we demonstrate a novel mediator role of p73 in activating the stress kinases p38 and JNK in the classical apoptotic pathway of TRAIL. TRAIL via caspase-dependent action can sequentially activate c-Abl, p73, and stress kinases, which contribute to apoptosis in colon cancer cells. Through the inhibition of c-Abl-mediated apoptotic p73 signaling, STI571 reduces the antitumor activity of TRAIL in colon cancer cells. Our results raise additional concerns when developing combination cancer therapy with TRAIL and STI571 in the future.

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