TGF-β-Activated Kinase 1 (TAK1) Is an In Vivo Druggable Target for Reverting Pancreatic Cancer Chemoresistance

Carmine Carbone¹, Geny Piro², Anna Tamburrino¹, Maria Mihaela Mina², Silvia Zanini², Giampaolo Tortora², Davide Melisi¹

¹Digestive Molecular Clinical Oncology Research Unit, and ²Laboratory of Oncology and Molecular Therapy; Medical Oncology, “Azienda Ospedaliera Universitaria Integrata” and University of Verona, Verona, Italy

Context TAK1, a mitogen-activated protein kinase kinase kinase, functions in the activation of nuclear factor kappaB (NF-kappaB) and activator protein-1, which can suppress proapoptotic signaling pathways and thus promote resistance to chemotherapeutic drugs. However, it is not known if inhibition of TAK1 is effective in reducing chemoresistance to therapeutic drugs against pancreatic cancer. Methods: NF-kappaB activity was measured by luciferase reporter assay in human pancreatic cancer cell lines AsPc-1, PANC-1, and MDAPanc-28, in which TAK1 expression was silenced by small hairpin RNA. TAK1 kinase activity was targeted in AsPc-1, PANC-1, MDAPanc-28, and Colo357FG cells with exposure to increasing doses of a selective small-molecule inhibitor, LYTAK1, for 24 hours. To test the effect of LYTAK1 in combination with chemotherapeutic agents, AsPc-1, PANC-1, MDAPanc-28 cells, and control cells were treated with increasing doses of oxaliplatin, SN-38, or gemcitabine in combination with LYTAK1. In vivo activity of oral LYTAK1 was evaluated in an orthotopic nude mouse model (n=40, 5 per group) with luciferase-expressing AsPc-1 pancreatic cancer cells. Results AsPc-1 and MDAPanc-28 TAK1 knockdown cells had a statistically significantly lower NF-kappaB activity than did their respective control cell lines. TAK1 inhibitor LYTAK1 had potent in vitro cytotoxic activity in AsPc-1, PANC-1, MDAPanc-28, and Colo357FG cells, with IC₅₀ between 5 and 40 nM. LYTAK1 also potentiated the cytotoxicity of chemotherapeutic agents oxaliplatin, SN-38, and gemcitabine in AsPc-1, PANC-1, and MDAPanc-28 cells compared with control cells. In nude mice, oral administration of LYTAK1 plus gemcitabine statistically significantly reduced tumor burden and prolonged survival duration. Conclusions The results of this study suggest that genetic silencing or inhibition of TAK1 kinase activity in vivo is a potential therapeutic approach to reversal of the intrinsic chemoresistance of pancreatic cancer.