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Clinicopathological and Prognostic Significance of p53 and TGF-Beta 1 in Patients With Gastric Cancer

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Background: The p53 protein is a molecule with numerous functions. However, mutation of p53 and accumulation of mutated p53 protein, which have no normal function, are common in human cancers. On the other hand TGF-beta1 may be implicated in the pathogenesis of the tumours, since it is expressed in neoplastic tissue.
The aim of this study is to investigate p53 value and it relationship with TGF-beta1 expression, clinicopathological parameters and survival in patients with gastric cancer.
Material and Methods: In 53 patients who had undergone gastrectomy for gastric cancer, the expression levels of p53 and TGF-beta1 in gastric cancer tissues were examined immunohistochemically (IHC). p53 gene alterations were examined by fluorescence microscope after in situ hybridization performing. Finaly the clinicopathological parameters such as gender, age, operation type, TNM stage and size of the tumour, histology and Lauren classification, and survival were analyzed retrospectively.
Results: We found p53 expression in all of gastric cancer specimens. Also, 47.2% of specimens were TGF-beta1 expression positive. Our data demonstrate a relationship between survival and p53 expression. The patients with p53 expression had worse prognosis after surgical therapy compared to those without. The median survival of p53-positive patients was 4.8 months whereas the median survival of p53-negative patients was 9.1 months ($p = 0.027$; log-rank test). Also, 88.9% from patients with p53-positive status is in T1-T2 stage vs. 37.8% in T3-T4 ($\chi 2 = 7.88$, $p = 0.005$). Finally we found that 56.1% from p53 expressive tumours have TGF-beta1 expression and 16.7% were non-expressive ($\chi 2 = 5.79$, $p = 0.016$). There was no statistically significant correlation between p53 expression and the other clinicopathological parameters.
Conclusions: In conclusion our results suggest that low expression of p53 and TGF-beta1could be useful as a marker of poor prognosis and had prognostic value for gastric cancer patients.

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Suppression of Stat3 Activity Sensitizes Gefitinib-resistant Non Small Cell Lung Cancer Cells

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Epidermal growth factor receptor (EGFR) is a proven therapeutic target to treat a small subset of non small cell lung cancer (NSCLC) harboring activating mutations within the EGFR gene. However, many NSCLC patients are not sensitive to EGFR inhibitors, suggesting that other factors are implicated in survival of NSCLC cells. Signal transducers and activators of transcription 3 (Stat3) function as transcription factor to mediate cell survival and differentiation and the dysregulation of Stat3 has been discovered in a number of cancers. In this study, we found that a small molecule, reactivation of p53 and induction of tumour cell apoptosis (RITA), showed anti-cancer activity against gefitinib-resistant H1650 cells through a p53-independent pathway. Stat3 suppression by RITA attracted our attention to investigate the role of Stat3 in sustaining survival of H1650 cells. Pharmacological and genetic approaches were employed to down-regulate Stat3 in H1650 cells. WP1066, a known Stat3 inhibitor, was shown to exhibit inhibitory effect on the growth of H1650 cells. Meanwhile, apoptosis activation by siRNA-mediated down-regulation of Stat3 in H1650 cells provides more direct evidence for the involvement of Stat3 in viability maintenance of H1650 cells. Moreover, as a novel identified Stat3 inhibitor, RITA increased doxorubicin sensitivity of H1650 cells in vitro and in vivo, suggesting that doxorubicin accompanied with Stat3 inhibitors may be considered as an alternative strategy to treat NSCLC patients who have inherent resistance to doxorubicin. Overall, our observations reveal that targeting Stat3 may be an effective treatment for certain NSCLC cells with oncogenic addition to Stat3.

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Antiproliferative and Apoptotic Effects of Black Currant Juice (Ribes Nigrum) on Lymphoblastic Leukemia Cells

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Background: Polyphenols are a group of naturally occurring compounds widely present in fruits and vegetables in human daily diets. These compounds have been reported to show anticancer and anti-mutagenic activities. Black currant juice (*Ribes nigrum*) is a rich source of polyphenols containing about 4.1 g/L. The aim of the present study was to determine whether black currant juice inhibits the proliferation of acute lymphoblastic leukemia cells (Jurkat cells) and, if so, to determine the underlying mechanism.
Material and Methods: Human acute lymphoblastic leukemia Jurkat cell line was used in the study. MTS assay, Cell cycle phase distribution and Apoptosis analysis were performed to study the effect of Black currant juice on proliferation, cell cycle and apoptosis in Jurkat cells respectively. The formation of ROS was determined by staining with dihydroethidine (DHE). Western blot experiments were performed to detect pJNK, p38 MAPK, pERK, pAkt, p73, Cyclin B1, Caspase 3 and UHRF1.
Results: Black currant juice inhibited the proliferation and induced cell cycle arrest in G2/M phase that led to a strong apoptotic effect. Cell cycle arrest and apoptotic effects were accompanied by an upregulation of p73 and caspase-3, and down-regulation of UHRF1. These findings indicate that black currant juice is a strong inducer of apoptosis in Jurkat cells. Mechanistic studies revealed that black currant juice significantly increased the formation of reactive oxygen species (ROS). The formation of ROS was accompanied with a strong upregulation of stress-related kinases (pJNK, p38 MAPK, pERK and pAkt) in a time-dependent manner. Intracellular inhibitors of ROS such as MnTMPyP, N-acetylcysteine and PEG-catalase inhibited the black currant juice-induced formation of ROS and upregulation of stress-related kinases.
Conclusion: The role of black currant juice-induced formation of ROS and upregulation of stress-related kinases in apoptosis still remains to be explored. These results indicate that black currant juice is a potent inducer of apoptosis in acute lymphoblastic leukemia cells and, hence, may be of potential in leukemia therapy.

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Antimycin A Sensitizes TRAIL-induced Apoptosis Through Down-regulation of C-FLIP and Bcl-2 Proteins

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Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) has been paid attention as a potential anti-cancer drug, because it induces apoptosis in a wide variety of cancer cells but not in most normal human cell types. Here, we showed that co-treatment with subtoxic doses of antimycin A (AMA), an inhibitor of electron transport and TRAIL induced apoptosis in human renal cancer cells, Caki cells, but not in normal tubular kidney cells. Treatment of Caki cells with AMA down-regulated c-FLIP and Bcl-2 proteins in dose- and time-dependent manners. AMA-induced decreases in c-FLIPL and c-FLIPs protein levels were involved in the increased protein instability, which was confirmed by the result that treatment with protein biosynthesis inhibitor, CHX, reduced c-FLIPL and c-FLIPs proteins level by AMA. We also found that AMA induced down-regulation of Bcl-2 at the transcriptional level. Pretreatment with N-acetyl-l-cysteine (NAC) slightly inhibited the expression levels of DR5 up-regulated by the treatment of AMA, suggesting that AMA appears to be partially dependent on the generation of ROS for up-regulation of DR5. Taken together, the present study demonstrates that AMA enhances TRAIL-induced apoptosis in human renal cancer cells by DR5 up-regulations, as well as cFLIP and Bcl-2 down-regulations.

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Gabexate Mesilate Induces the Apoptosis of HepG2cells

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Background: We happened to administer gabexate mesilate(GM)to patients with pancreatitis complicated by HCC. We found GM had a inhibiting effect on HCC. Therefore, an experimental study was performed to evaluate the mechanism of the inhibition.
Materials and Methods: HepG2 cells (HGC) were cultured. DNA fragments from cultured cells were extracted and electrophoresed. The cell were stained using TUNEL method. The immunohistochemical staining(IHCS)for P53, ss-DNA, bcl2 and caspase 3 (C3) in cultured for 24 hours were performed using polymer method with monoclonal antibody.