Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines
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1211 POSTER

Peroxisome proliferator-activated receptor Gamma responsible for TGF

mediated growth inhibition and also promoted TGF 
g

suggested that PPAR

g

b

TGF

b

treated H460 and found that not only survival of H460 was decreased,

and exacerbate tumor metastasis. TGF

b

expression level after the treatment, either.

P38/ERK/cPLA2

and 14. The results clearly demonstrated a TGF

-b

induced EMT in H460. Seven days after TGF

b

treatment followed by a morphological shift (from round to fibroblast or spindle-like shape) at day 7 and 14. The results clearly demonstrated a TGF

-b

induced EMT in H460. Seven days after TGF

b

treatment, the migration and invasion of H460 was significantly increased in accompany with the induced expression of PPAR

g

b

and cell survival. The up-stream regulators (P38, ERK, cPLA2

and COX-2) of PPAR

g

b

were also activated (phosphorylated) by TGF

b

at early time points (1−6 h). To further confirm the role of PPAR

g

b

in TGF

b

mediated growth inhibition and also promoted TGF

-b

induced EMT and cell invasion in H460, we added PPAR

b

inhibitor (GW9662) into TGF

-b

-treated H460 and found that not only survival of H460 was decreased, TGF

-b

induced EMT and cell invasion were also interrupted. The results suggested that PPAR

g

b

were also activated (phosphorylated) by TGF

b

at early time points (1−6 h). To further confirm the role of PPAR

g

b

in TGF

b

mediated growth inhibition and also promoted TGF

-b

induced EMT and cell invasion in H460. In overall, TGF

-b

induced EMT and cell invasion in H460 have been confirmed and proved to be PPAR

g

b

dependent. Results from the study not only provided information about the drug resistance and metastasis of H460 in response to TGF

-b

treatment but also implied the therapeutic value of PPAR

g

b

inhibitor (GW9662) in the treatment of NSCLCs.

Conclusions: It is suggested that Compound3 should be considered for further exploration and development and that induction of monoastral formation would be critical in a predictive biomarker. Taken together, a novel mitotic kinesin Eg5 inhibitor Compound3 may have other mechanisms of action for its growth inhibitory effect on cancer cells and further investigation on alternative biomarkers is necessary to develop Eg5 inhibitors as an anticancer drug.

1213 POSTER

Plumbagin induces ROS-mediated apoptosis in human myeloid leukemia cells in vivo

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Plumbagin, a naphthoquinone from the roots of Plumbago zeylanica, known to possess anticancer and antibacterial activity. Based on the former finding in vitro, we further investigated the effects of Plumbagin on the growth of human myeloid leukemia NB4 cells that had been transplanted subcutaneously into NOD/SCID mice.

Material and Methods: In order to elucidate the molecular mechanism involved in plumbagin-induced apoptosis, we studied the effect of Plumbagin with IC50 (9 μM) by monitoring the activity of the caspase-3 and caspase-9, the change of mitochondrial membrane potential (ΔΨm), the expression of the Bcl-2 family as well as ROS change in plumbagin-induced apoptosis. The efficacy of Plumbagin was evaluated with intraperitoneal injection of plumbagin (2 mg/kg body weight) daily for three weeks using subcutaneous NB4 xenograft in NOD/SCID mice, comparing with the vehicle and Doxorubicin (1 mg/kg thrice a week). The tissue samples were applied to hematoxylin and eosin histological staining as well as TUNEL assay.

Results: We revealed that plumbagin triggered the mitochondrial apoptotic pathway, as indicated by the increase in Bax/Bcl-2 ratios, resulting in the induction of mitochondrial membrane potential decrease and corresponding caspase activation. We also found that the generation of ROS was a critical mediator in plumbagin-induced cell apoptosis, which would be abrogated completely by the antioxidant, NAC. Furthermore, compared with the control, Plumbagin presented a ~60% reduction of tumor volume and a marked increase in tumor apoptosis; There was no overt manifestation of toxicity such as weight loss, tissue damage and behavior change as showed in Doxorubicin-treated mice.

Conclusion: Our data support that Plumbagin has potential as a novel therapeutic agent for myeloid leukemia with minimal side-effects.

1214 POSTER

Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines


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Artemisinin derivatives are well-tolerated anti-malaria drugs that also exert anti-cancer activity. Here, we investigated artemisinin and its derivatives dihydroartemisinin and artesunate in a panel of chemosensitive and chemoresistant human neuroblastoma cells as well as in primary neuroblastoma cultures.

Materials and Methods: Cell viability was determined by MTT assay or by determination of ATPase activity. Apoptosis was examined by staining for activated caspase-3 and detection of cells with low DNA content (sub-G1) by flow cytometry. Bioinformatic analysis of gene microarray data was used to identify genes relevant for neuroblastoma cell response to artesunate. Results: Only dihydroartemisinin and artesunate affected neuroblastoma cell viability with artesunate being more active. Of 16 cell lines and two primary cultures, only UKF-NB-3′3′CDP100 showed low sensitivity to artesunate. Artesunate induced apoptosis and reactive oxygen species in neuroblastoma cells. L-Buthionine-S,R-sulfoximine, an inhibitor of GCL (glutamate-cysteine ligase), resensitised in part UKF-NB-3′3′CDP100 cells to artesunate. This finding together with bioinformatic analysis of expression of genes involved in glutathione metabolism showed that this pathway is involved in artesunate resistance.

Conclusion: These data indicate that neuroblastoma represents a artesunate-sensitive cancer entity including chemoresistant cells. Characteristic gene expression signatures based on a previous analysis of artesunate resistance in the NCI60 cell line panel clearly separated UKF-NB-3′3′CDP100 from the other cell lines.