Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines
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We have previously demonstrated that non-small cell lung cancer cell, H460, had strong drug resistance to TGFβ and can grow and metastasize successfully in animal model. Despite the fact TGFβ can suppress the growth of gastric carcinoma and hepatoma cells, it also promotes the epithelial mesenchymal transition (EMT) and/or metastasis of liver and breast cancers. We therefore were interested to know would TGFβ also promote the EMT and/or metastasis in NSCLC cells (H460) and excarcerate tumor metastasis. TGFβ-triggered signaling pathway, p38/ERK1/2, and its downstream target, PPARγ, were also analyzed in H460 with or without TGFβ to link with the induced EMT and/or tumor invasion. According to our early observation, PPARγ was already known to play a critical role in the early development of TGFβ resistance of H460. Our current results showed that TGFβ-induced cell scattering of H460 first appeared at day 3 after the TGFβ treatment followed by a morphological shift (from round to fibroblast or spindle-like shape) at day 7 and 14. The results clearly demonstrated a TGFβ-induced EMT in H460. Seven days after TGFβ treatment, the migration and invasion of H460 were significantly increased in accompany with the induced expression of PPARγ and cell survival. The up-stream regulators (p38, ERK, p38/ERK1/2, and COX-2) of PPARγ were also activated (phosphorylated by TGFβ) at early time points (1−6 h). To further confirm the role of PPARγ in TGFβ-induced EMT and cell invasion in H460, we added PPARγ inhibitor (GW9662) into TGFβ treated H460 and found that not only survival of H460 was decreased, TGFβ-induced EMT and cell invasion were also interrupted. The results suggested that PPARγ was critical for the protection of H460 from TGFβ-mediated growth inhibition and also promoted TGFβ-induced EMT and cell invasion in H460. In overall, TGFβ-induced EMT and cell invasion in H460 have been confirmed and proved to be PPARγ dependent. Results from the study not only provided information about the drug resistance and metastasis of H460 in response to TGFβ treatment but also implied the therapeutic value of PPARγ inhibitor (GW9662) in the treatment of NSCLCs.

Background: Mitotic kinase Eg5 plays an important role in mitosis, as it is critical for proper bipolar spindle assembly. After the discovery of the first Eg5 inhibitor monastrol, a number of Eg5 inhibitors have been developed as therapeutic value of PPARγ in the treatment of NSCLCs. Anti-cancer effects of artesunate in a panel of chemoresistant neuroblastoma cell lines


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Background: 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’-CDDP100 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’-CDDP100 cells to artesunate. This finding together with bioinformatic analysis of gene expression signatures showed that this pathway is involved in artesunate resistance. Conclusion: These data indicate that neuroblastoma represents a chemoresistant 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’-CDDP100 from the other cell lines.