Repurposing artesunate for targeting cancer cells and circulating tumor cells (ctcs)

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Abstract

Background

CTCs are the key players in metastatic procedure, making them crucial targets for precision medicine. Their resistance to conventional therapies highlights the need for novel treatments. Artesunate (AS), an antimalarial drug, shows promising anticancer properties. It is also an inhibitor of AP-1 family including JUNB. Furthermore, JUNB controls the expression of the Immune checkpoint molecule PD-L1. AS also increases the expression of Vimentin in cancer cells. We have recently shown that JUNB, PD-L1, and Vimentin are poor prognostic factors when overexpressed in patients' CTCs.

Objective

This study aimed to examine the effect of AS on adherent and non-adherent (CTC-model) cancer cells. It also evaluated AS treatment on small-cell lung cancer (SCLC) patient-derived CTCs, using TetherChip technology to address the anti-metastatic efficacy of this drug.

Methods

Lung (H1299, A549, DMS-454), breast (MDA-MB-231, MDA-MB-436, MCF-7), colon (HT-29, SW-620), and patient-derived CTC-MCC-41 cells, were cultured under adherent and non-adherent conditions and treated with AS and 5-FU (10 μM 24 h). Cell viability was assessed using an MTT assay. TetherChip technology was used to analyze CTCs, derived from 5 SCLC patients, before and after AS treatment. Immunofluorescence (IF) staining used the following combinations of antibodies: CK/PD-L1/CD45, CK/CXCR4/JUNB, CK/VIM/GLU, and CK/M30 (apoptotic marker)/CD45. Samples were analyzed with VyCAP platform.

Results

AS reduced the viability of all adherent and non-adherent cell lines in a time- and concentration-dependent manner. However, non-adherent cells were less sensitive to therapy. Notably, CTC-MCC-41 cells exhibited the highest sensitivity to AS. These results stress the potential efficacy of AS on metastatic dissemination. In addition, AS demonstrated greater cytotoxicity compared to the common therapeutic agent 5-FU on adherent and most non-adherent cancer cells. Moreover, SCLC patients' CTCs were significantly reduced after AS treatment ($p=0.001$). AS also significantly decreased the aggressive subclones: [(CK+/CXCR4+/JUNB-) $p=0.01$], [(CK+/CXCR4-/JUNB+) $p=0.034$), and [(CK+/VIM+/GLU+) $p<0.001$]. Finally, apoptotic (M30-positive) CTCs were statistically increased ($p=0.021$) after therapy, reinforcing the anti-metastatic potential of AS.

Conclusion

AS demonstrates antitumor activity on adherent and non-adherent cancer cells, exhibiting remarkable effectiveness against patients' CTCs. Its capacity to diminish the aggressive phenotypes of CTCs and promote apoptosis underscores its potential as an anti-metastatic agent.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.