Abstract

Cancer is a hyperproliferative disorder that results from tumour initiation and promotion. Several genes that are involved in cellular transformation, proliferation, invasion, and angiogenesis are regulated by NF-κB. NF-κB is a transcription factor that exists in the cytoplasm in an inactive form, as a result of their association with IκB proteins. The degradation of IκB allows NF-κB to translocate to the nucleus and bind their cognate DNA binding sites to promote gene expression. Research within the last few years has revealed that chemotherapeutic agents such as cisplatin and paclitaxel activate NF-κB. Interestingly, however, most chemopreventive agents appear to suppress the activation of the NF-κB through inhibition of NF-κB signalling pathway and also sensitize the tumour to chemotherapeutic agents through abrogation of NF-κB activation. Therefore, this study was carried out to determine whether ACA in combination with cisplatin could induce a higher level of efficacy with lower side effects than ACA or cisplatin standalone treatments and to compare the synergistic effect of AEA as a chemosensitizer when used in combination with paclitaxel over ACA alone or paclitaxel standalone treatments on oral and breast cancer xenografts.

Introduction

Previous in vitro studies have reported that 1'-S-1'-acetoxychavicol acetate (ACA) and its analogue, 1'-S-1'-acetoxyeugenol acetate (AEA) isolated from rhizomes of the Malaysian ethno-medicinal plant Alpinia conchigera Griff (Zingiberaceae) induces apoptosis-mediated cell death in tumour cells via dysregulation of the NF-κB pathway. ACA and AEA were also found to synergistically enhance the apoptotic effects of cisplatin and paclitaxel when used in combination on HSC-2 and MCF-7 cells respectively. In this study, synergistic effect of both agents on human oral and breast cancer xenografts. Nu/Nu mice were shown that mice exposed to combined treatments displayed higher reductions in tumour volume and also demonstrated milder signs of toxicity such as loss in body weight compared to standalone treatments. In addition to this, immunohistochemical analysis on xenograft tumors showed that dual-drug combination regimes displayed superior inhibition of NF-κB compared to standalone agents.

Methodology

Cell culture  
Tumour Induction  
Treatment  
Termination & harvesting  
Tissue fixation & sectioning  
Immunohistochemistry

Results & Discussion

Figure 1: In vivo effects of ACA and CDDP through assessment of Nu/Nu mice tumour volume and body weight post-implantation across 35 days. (A) Photographs of Nu/Nu mice harvested 35 days post-implantation with human oral SCC (HSC-4) xenografts and 21 days post-treatment with various ACA/CDDP treatment regimes. (B) Photographs of AEA and Tumours from different treatment regimes. (C) Tumour volume changes of HSC-4 xenograft mice treated with AEA and CDDP. (D) Mice body weight with HSC-4 xenografts treated with AEA and CDDP. All data shown are a representative of mean values (n=3 ±SD, with commencement of treatment regimes on 14 days post-implantation (dpi).

Figure 2: In vivo effects of AEA and paclitaxel through assessment of Nu/Nu mice tumour volume and body weight post-implantation across 35 days. (A) Photographs of Nu/Nu mice harvested 28 days post-implantation with human breast adenocarcinoma cells (MCF-7) xenografts and 14 days post-treatment with various ACA/Paclitaxel treatment regimes. (B) Photographs of AEA and Tumours from different treatment regimes. (C) Tumour volume changes of MCF-7 xenograft mice treated with AEA and Paclitaxel. (D) Mice body weight with MCF-7 xenografts treated with AEA and Paclitaxel. Location of all tumour sites are indicated by closed arrows.

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References


Conclusion

Combined drug regimes employing ACA & AEA were successful in enhancing the efficacy of pre-existing anti-cancer drugs by preventing dose limiting toxicity in oral and breast cancer treatments via NF-κB pathway dysregulation.

Further research question

How ACA/AEA affects the tumour growth and how this activity may differ from its action in combination with cisplatin/paclitaxel?

![Figure 3: Effects of ACA and CDDP on the pathology of tumour samples for oral squamous carcinoma. Magnification, 400x](image-url)