Down-regulation of miR-210 enhances sensitivity towards 1'*S*-1'-acetoxychavicol acetate (ACA) in human cervical carcinoma cells.

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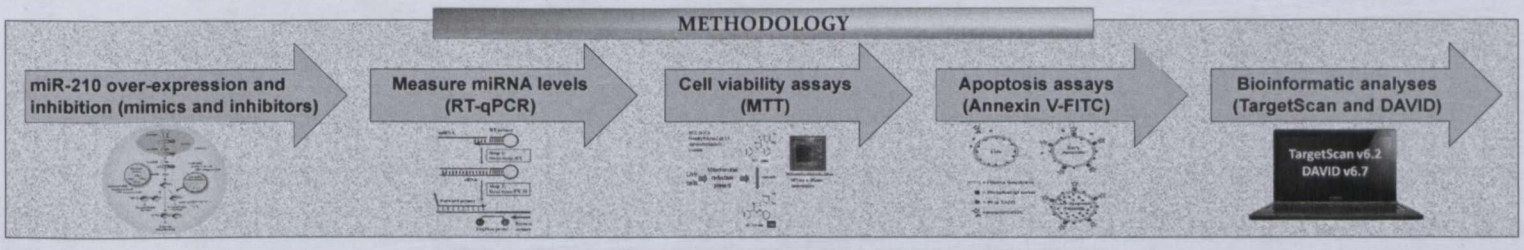
INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide after breast cancer[1], and the third most common cancer among Malaysian women after breast and colorectal cancer[2]. Although chemotherapy has led to improvement in the overall response and survival of cancer patients, drug resistance and toxicities remain major obstacles[3]. The 1'*S*-1'-acetoxychavicol acetate (ACA) is a natural compound isolated from *Alpinia conchigera* and has been shown to induce apoptosis and potentiates the effects of cisplatin in both *in vitro* and *in vivo* studies[4-6]. MicroRNAs (miRNAs) are short non-coding RNA that regulate genes negatively at post-transcriptional level, and has been implicated in diverse biological processes such as cell proliferation and apoptosis[7]. Various studies have shown that they play an important role in regulating response towards natural agents[8]. We have previously reported miR-210 to be among the differentially expressed miRNAs following treatment with ACA on human cervical carcinoma cells[6]. Hence, the aims of this study were to investigate the effects of miR-210 over-expression and inhibition in regulating response towards ACA on CaSki and SiHa human cervical carcinoma cells.

METHODOLOGY



RESULTS & DISCUSSION

(1) Transfection with miR-210 mimics and inhibitors alters the expression of miR-210 in human cervical carcinoma cells

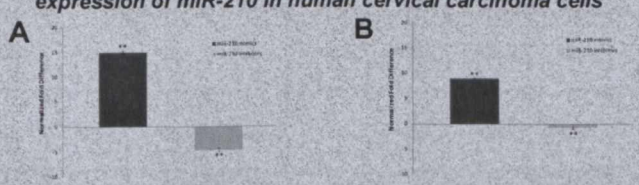


Fig. 1: RT-qPCR of miR-210 presented as normalized fold difference in miR-210 mimics- or inhibitors-transfected (A) CaSki and (B) SiHa cervical carcinoma cells, in comparison to cells transfected with negative controls. Data presented as mean ± standard error mean of three replicates. Note: ** indicates p value ≤ 0.05

(2) Inhibition of miR-210 increases sensitivity towards ACA on human cervical carcinoma cells

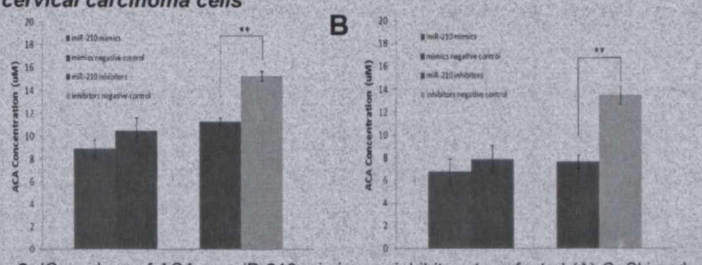


Fig. 2: IC_{50} values of ACA on miR-210 mimics- or inhibitors-transfected (A) CaSki and (B) SiHa cervical carcinoma cells, in comparison to cells transfected with negative controls. Data presented as mean ± standard error mean of three replicates. Note: ** indicates p value ≤ 0.05

(3) Inhibition of miR-210 increases percentage of apoptosis following treatment with ACA on human cervical carcinoma cells

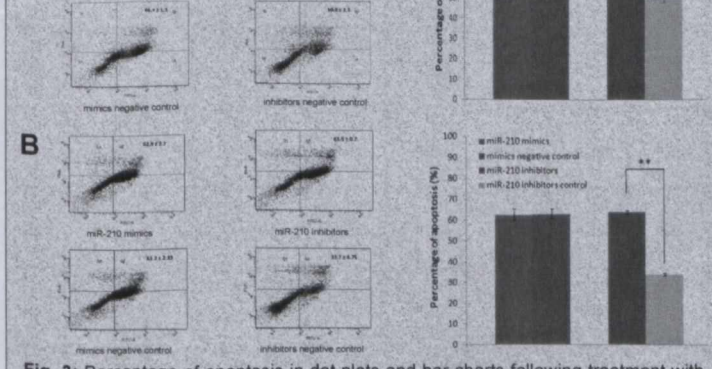


Fig. 3: Percentage of apoptosis in dot plots and bar charts following treatment with ACA in miR-210 mimics- and inhibitors-transfected (A) CaSki and (B) SiHa cervical carcinoma cells, in comparison to cells transfected with negative controls. Data presented as mean ± standard error mean of three replicates. Note: ** indicates p value ≤ 0.05

(4) Predicted targets of miR-210 involved in regulating cell proliferation and apoptosis

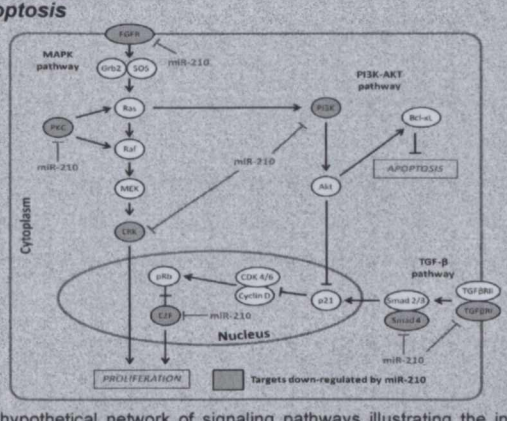


Fig. 4: A hypothetical network of signaling pathways illustrating the interaction of miR-210 with its predicted targets. Key signaling pathways involved are MAPK, PI3K-AKT and TGF-β, which regulates cell proliferation and apoptosis. Inhibitory relationships are denoted as flat arrow heads, whereas positive interactions are denoted as open arrow heads.

CONCLUSION

This study demonstrated that inhibition of miR-210 decreased cell viability and increased apoptotic cells following treatment with ACA in human cervical cancer cells, indicating that down-regulation of miR-210 enhances sensitivity towards ACA. We also showed that miR-210 targets genes involved in regulating cell proliferation and apoptosis. Therefore, our study provides a platform to study the roles of miR-210 in regulating response towards anti-cancer drugs and provide potential therapeutic approaches by exploiting the miRNA expression to improve efficacies in chemotherapy.

ACKNOWLEDGEMENT

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