Down-regulation of microRNA-210 confers sensitivity towards 1's-1'-acetoxychavicol acetate (ACA) in cervical cancer cells by targeting SMAD4

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Abstract

MicroRNAs (miRNAs) are short non-coding RNAs that regulate genes posttranscriptionally. Past studies have reported that miR-210 is up-regulated in many cancers including cervical cancer, and plays a pleiotropic role in carcinogenesis. However, its role in regulating response towards anti-cancer agents has not been fully elucidated. We have previously reported that the natural compound 1'S-1'- acetoxychavicol acetate (ACA) is able to induce cytotoxicity in various cancer cells including cervical cancer cells. Hence, this study aims to investigate the mechanistic role of miR-210 in regulating response towards ACA in cervical cancer cells. In the present study, we found that ACA down-regulated miR-210 expression in cervical cancer cells, and suppression of miR-210 expression enhanced sensitivity towards ACA by inhibiting cell proliferation and promoting apoptosis. Western blot analysis showed increased expression of markers against desmoplakin isoform 6 (SMAD6), which was predicted as a target of miR-210 by target prediction programs. Following treatment with ACA, luciferase reporter assay confirmed that miR-210 binds to sequences in 3'UTR of SMAD6. Furthermore, decreased in SMAD4 protein expression was observed when miR-210 was overexpressed. Conversely, SMAD4 protein expression increased when miR-210 expression was suppressed. Lastly, we demonstrated that overexpression of SMAD4 augmented the anti-proliferative and apoptosis-inducing effects of ACA. Taken together, our results demonstrated that down-regulation of miR-210 conferred sensitivity towards ACA in cervical cancer cells by targeting SMAD4. These findings suggest that combination of miRNAs and natural compounds could provide new strategies in treating cervical cancer.

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