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MiR-126 reverses drug resistance to TRAIL through inhibiting the expression of c-FLIP in cervical cancer

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Abstract

TNF-related apoptosis-inducing ligand (TRAIL) represents one potential and ideal anti-tumor drug, because it kills cancer cells specifically without targeting normal cells. However, acquired drug resistance to TRAIL usually impedes the clinical use of TRAIL on cancer patients. In the present study, we established in vitro TRAIL-resistant cervical cancer cell lines through long-term exposure to TRAIL. Interestingly, we observed significant upregulation of c-FLIP in TRAIL-resistant Hela and SiHa cells (Hela-TR and SiHa-TR) compared to their parental Hela and SiHa cells. Although Hela-TR and SiHa-TR cells exhibited low-sensitivity to TRAIL treatment, knockdown of c-FLIP significantly increased the cytotoxicity of TRAIL to them. In contrast to high protein level of c-FLIP, expression of miR-126 was significantly downregulated in Hela-TR and SiHa-TR cells. Results of western blot analysis, luciferase assays and and bioinformatics proved that c-FLIP was the target of miR-126. Furthermore, as c-FLIP is the cellular antagonist to caspase-8, transfection with miR-126 promoted the activation of caspase-8 induced by TRAIL. As a result, miR-126 increased the TRAIL-induced apoptosis in Hela-TR and SiHa-TR cells. In