PP-11

CHM-1 Induces Apoptosis via p38-Mediated Up-regulation of DR5 Expression in Human Ovarian Cancer SKOV3 Cells

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Ovarian cancer is a leading cause of death due to neoplasm of the female genital tract. Treatment for advanced-stage disease remains limited, and an effective drug for ovarian cancer is urgently needed today. In the present study, MTT assay was used to evaluate the anti-proliferative effect of the 2-phenyl quinolone derivatives for developing new anti-ovarian cancer drugs. CHM-1 was the most active compound, and it exhibited potent anti-proliferative activity against human ovarian cancer cells. CHM-1 inhibited the growth of SKOV3 cells and induced apoptosis in a concentration-dependent manner, but it was less cytotoxicity to human diploid skin fibroblast Detroit 551 cells. The western blot experiments showed that CHM-1 caused the up-regulation of death receptor (DR) 5 and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Interestingly, CHM-1-mediated cellular apoptosis was found to be closely involved with the p38-mediated up-regulation of DR5 expression. In an SKOV3 subcutaneous xenograft model, both CHM-1 and its phosphate, CHM-1-P caused significant dose- and time-dependent tumor regression. Furthermore, CHM-1 inhibited tumor growth and prolonged the lifespan in the SKOV3 ip1/luc orthotopic xenograft model. Intravenous administration of CHM-1-P significantly prolonged the survival time in the SKOV3/ICR-Foxn1nu orthotopic xenograft model. Based on their excellent antitumor activity with interesting mechanism of action, CHM-1 and CHM-1-P were considered new anti-ovarian cancer drug candidates.

Key Words: *apoptosis; CHM-1; death receptor 5; ovarian cancer; p38*