Peroxisome proliferator-activated receptor gamma (PPARYγ) agonists, such as the antidiabetic drug thiazolidinediones (TZDs), have been demonstrated to affect anti-proliferation, differentiation, and apoptosis of various cancer cell types. Recently in vitro and in vivo studies suggest the importance of specific PPARγ ligands as cell cycle modulators for cancer treatment. To investigate the mechanism of the anticancer effect of TZDs on human ovarian cancers, TZDs were tested on various human ovarian cancer cell lines.

The treatment of human ovarian cancer cells (NIH:OVCAR3, SKOV3, SNU-8, SNU-840, SNU-251, 2774) with troglitazone, a synthetic PPARγ ligand, induced a dose-dependent inhibition of ovarian cancer cell growth. Furthermore, when ovarian cancer cells were treated with additional PPARγ ligands (pioglitazone, ciglitazone), they showed similar results; however, no significant inhibition was induced in human normal cells. Human ovarian cancer cells exhibited various expression levels of PPARγ mRNA and protein by RT-PCR and Western analysis. Although these compounds (troglitazone) bind to PPARγ transcription factors as agonists, our evidence suggests that the PPARγ ligand acts independently of PPARγ in many functions, including apoptosis. Flow cytometry showed that the cell cycle was arrested at G1 phase and revealed by the appearance of a sub-G1 peak. PPARγ ligands were found to increase the number of apoptotic cells in 2774, SKOV3 and NIH:OVCAR3 cell lines. In addition, DNA ladder formation was observed in NIH:OVCAR3, SKOV3 and 2774 after treatment with troglitazone for 72h. This observation was corroborated by the finding of increased Bax and p21 protein levels in cells treated with troglitazone. In previous reports, p53 has been implicated in the TZDs-mediated control of the cell cycle, cell differentiation, DNA repair, programmed cell death. However, the growth inhibition does not seem to be dependent on p53 protein in human ovarian cancers. Because 2774 and NIH:OVCAR3 express a mutant form of p53 and SKOV3 is a p53-null. The p63γ (p51A) protein is similar to p53 in structure and function. In particular, the p63γ protein is capable of inducing p53-responsive genes and can elicit growth arrest and apoptosis. Treatment of human ovarian cancer cells with troglitazone up-regulated the expression of p63γ and p73γ proteins. In contrast, the levels of other p53 family proteins, p63 γ and p73γ, are unchanged or reduced. These results suggest that troglitazone may induce growth suppression and apoptosis via p63γ and p73γ in human ovarian cancer cells. The our study has demonstrated that PPARγ ligands were able both to induce growth suppression in ovarian cancer cells via a p53-independent and PPARγ-independent pathway as well as to regulate p63γ and p73γ proteins. The tumor suppressive effects of PPARγ ligands and their very low toxicity make them candidates for use in combination with chemotherapeutic drugs.

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