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Resveratrol Induces Pro-apoptotic Endoplasmic Reticulum Stress in Human Colon Cancer Cells

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Resveratrol (3,4′,5 tri-hydroxystilbene), a naturally occurring polyphenolic compound highly enriched in grapes and red wine, has been shown to induce anti-proliferation and apoptosis of human cancer cell lines. Resveratrol induced dose-dependent apoptotic cell death in colon carcinoma cells, as measured by FACS analysis. Treatment of HT29 human colon carcinoma cells with resveratrol was found to induce a number of signature ER stress markers; phosphorylation of eukaryotic initiation factor-2a (eIF-2a), ER stress-specific XBP1 splicing, and CCAAT/enhancer-binding protein-homologous protein (CHOP). In addition, resveratrol induced up-regulation of glucose-regulated protein (GRP)-78, suggesting induction of ER stress. Furthermore, inhibition of caspase-4 activity by z-LEVD-fmk significantly reduced resveratrol-induced apoptosis. Taken together, the present study thus provides strong evidence to support an important role of ER stress response in mediating the resveratrol-induced apoptosis. This work was supported by the Korea Science & Engineering Foundation (KOSEF) (R13-2002-028-03001-0) and KRF-2005-070- C00100 from Korea Research Foundation.

Key words: Resveratrol, endoplasmic reticulum stress, apoptosis, CHOP, unfolded protein response

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Rosiglitazone Promotes Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL)-induced Apoptosis by Reactive Oxygen Species-mediated Up-regulation of Death Receptor 5 (DR5) and Down-regulation of c-FLIP

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Death receptor DR5 is an apoptosis-inducing membrane receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). In the present study, we show that rosiglitazone sensitize human renal cancer cells to TRAIL-mediated apoptosis, but not in normal human mesangial cells. Furthermore, this apoptosis induced by the combination of rosiglitazone and TRAIL is not interrupted by Bcl-2 overexpression. Since rosiglitazone-enhanced TAIL-mediatedapoptosis is induced in various types of cancer cells, this combinatory treatment may provide an attractive strategy for cancer treatment. We also found that treatment with rosiglitazone significantly induces DR5 expression both at its mRNA and protein levels, accompanying the generation of the reactive oxygen species (ROS). Both treatment with DR5/Fc chimeric protein and silencing of DR5 expression using small interfering RNA (siRNA) attenuated rosiglitazone plus TRAIL-induced apoptosis, showing that the critical role of DR5 in this cell death. Importantly, both TRAIL sensitization and up-regulation of DR5 induced by rosiglitazone treatment are likely PPARg-independent,because a dominant negative mutant of PPARg and a potent PPARg inhibitor GW9662 failed to block DR5 induction and apoptosis. However, pretreatmentwith GSH significantly inhibited rosiglitazone-induced DR5 upregulation and the cell death induced by the combined treatment with rosiglitazone and TRAIL. Interestingly, we also found that rosiglitazone treatment induced downregulation of c-FLIPs and ectopic expression of c-FLIPs lessened rosiglitazone plus TRAIL-mediated apoptosis. Taken together, the present study demonstrates that rosiglitazoneenhances TRAIL-induced apoptosis in various cancer cells by ROS-mediated DR5 up-regulation and downregulation of c-FLIPs. This work was supported by the Korea Science & Engineering Foundation (KOSEF) through the MRC at Keimyung University (R13-2002-028-03001-0), R01-2005-000-10786-0 and Korea Research Foundation grant KRF-2005-070-C00100.

Keywords: TRAIL, apoptosis, rosiglitazone, DR5, reactive oxygen species, c-FLIP