

**Troglitazone-mediated catalase induction decreases radiation sensitivity in HeLa**Z. An<sup>a</sup>, X. Liu<sup>a</sup>, W.D. Kim<sup>a</sup>, J.R. Yu<sup>b</sup> and W.Y. Park<sup>a</sup><sup>a</sup>*Chungbuk National University College of Medicine, 410 Sungbong-Ro Heungduk-Gu, 361-763 Cheongju, Republic of Korea;* <sup>b</sup>*Department of Environmental and Tropical Medicine, Konkuk University School of Medicine, 143-701 Seoul, Republic of Korea*  
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Background: Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is a critical transcription factor in the regulation of glucose and lipid metabolism. In addition, PPAR $\gamma$  is of particular interest as a potential anticancer agent because of its effect on cellular differentiation, proliferation, and tumorigenesis. Troglitazone (TRO) is a synthetic PPAR $\gamma$  agonist and has been studied well on its antiproliferative activities against many human cancer cells in vitro and in vivo. TRO induces G1 arrest and this may increase radiation sensitivity. In the other hand, activated receptor complexes of TRO can induce catalase through binding to its promoter region and this may decrease radiation sensitivity via reactive oxygen species (ROS) scavenging. However, many reports have used high dose of TRO and showed ROS overproduction as one of the cytotoxic mechanism of TRO. Here, we investigated the combined effect of clinically relevant low dose TRO and radiation. Materials and methods: HeLa was incubated with different concentrations of TRO. Catalase activity was quantitated spectrophotometrically following the decomposition of H<sub>2</sub>O<sub>2</sub> at 240nm. Intracellular production of ROS was measured using the fluorescent dye, 2',7'-dichlorodihydrofluorescein-diacetate at 488/530 nm. Radiation sensitivity was measured by clonogenic assay. Results: Catalase activity was increased as TRO increased up to 5  $\mu$ M for 24 hrs (1.3 fold) and it was decreased with higher dose. The increased catalase activity via TRO was decreased partially by a PPAR $\gamma$  inhibitor, GW9662 and this means that there is another pathway for TRO-mediated catalase induction. Increased ROS via 4 Gy of radiation was decreased by TRO, but this was not changed with the addition of GW9662. Decreased ROS via TRO was inhibited partially by a catalase inhibitor, 3-amino-1,2,4-triazole (ATZ) and this means that TRO-induced catalase contributes to scavenge ROS which was produced by radiation. When the cells were incubated with 5  $\mu$ M of TRO for 24 hrs before irradiation clonogenic cell survival by radiation was increased more than expected (1.4 fold). Conclusion: Low dose TRO may decrease radiation sensitivity through the induction of catalase. Some of PPAR $\gamma$  agonists (rosiglitazone, pioglitazone) are clinically used for the control of Type II diabetes. Therefore, we need to have concern about how PPAR $\gamma$  agonists affect on the treatment results of patients undergoing radiation therapy.