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## **A Peroxisome Proliferator-activated Receptor- $\gamma$ Agonist, Troglitazone, Facilitates Caspase-8 and -9 Activities by Increasing the Enzymatic Activity of Protein-tyrosine Phosphatase-1B on Human Glioma Cells\***

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Despite dramatic advances in adjuvant therapies, patients with malignant glioma face a bleak prognosis. Because many adjuvant therapies seek to induce glioma apoptosis, strategies that lower thresholds for the induction of apoptosis may improve patient outcomes. Therefore, elucidation of the biological mechanisms that underlie resistance to current therapies is needed to develop new therapeutic strategies. Here we proposed a novel mechanism of proapoptotic effect induced by a pharmacological peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) agonist, troglitazone, that facilitates caspase signaling in human glioma cells. Troglitazone activates protein-tyrosine phosphatase (PTP)-1B, which subsequently reduces phosphotyrosine 705 STAT3 (pY705-STAT3) via a PPAR $\gamma$ -independent pathway. Reduction of pY705-STAT3 in glioma cells caused down-regulation of FLIP (FADD-like IL-1 $\beta$ -converting enzyme-inhibitory protein) and Bcl-2. Furthermore, troglitazone induced Ser-392 phosphorylation of p53 via a PPAR $\gamma$ -dependent pathway and up-regulation of Bax in a p53 wild-type glioma. When given with tumor necrosis factor-related apoptosis-inducing ligand or caspase-dependent chemotherapeutic agents, such as etoposide and paclitaxel, troglitazone exhibited a synergistic effect by facilitating caspase-8/9 activities. A PPAR $\gamma$  antagonist, GW9662, did not block this effect, although a PTP inhibitor abrogated it. Knockdown of STAT3 by STAT3-small interfering RNA negated the inhibitory effect of PTP inhibitor on troglitazone, indicating that troglitazone uses a STAT3 inactivation mechanism that makes caspase-8/9 activities susceptible to cytotoxic agents in glioma cells and that PTP1B plays a critical role in the down-regulation of activated STAT3, as well as FLIP and Bcl-2. When taken with caspase-dependent anti-neoplastic agents, troglitazone may be a promising drug for use against malignant gliomas because it facilitates the caspase cascade, thereby lowering thresholds for the apoptosis induction of glioma cells.

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