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Activation of peroxisome proliferator-activated receptor gamma is a novel therapeutic means for giant cell tumor

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Introduction:
Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily. PPARγ plays a central role in the differentiation of adipocytes from precursor cells and is reported to exhibit anti-tumorigenic effects on a certain malignancy. Giant cell tumor of bone (GCTB) is a common primary benign tumor, but in some cases behaves aggressively, resulting in tumor recurrence. It is known that stromal cells of GCTB has a key role in the pathogenesis of the tumor rather than the multinucleated giant cell. However, effective therapies against GCTB have not been established to target the stromal cells. Moreover, the therapeutic effects of PPARγ activation on GCTB have not been fully clarified.
Methods:
We established primary cell lines of GCTB stromal tumor cells from fresh GCTB specimens surgically resected from two patients. These cell lines were treated with zaltoprofen, a nonsteroidal anti-inflammatory drug possessing an ability of activation of PPARγ, or troglitazone, a high-affinity agonist for PPARγ, at different concentrations and then subjected to WST-1 cell proliferation and TUNEL assays. The expression of PPARγ was assessed by immunofluorescent cytochemistry. The adipocytic differentiation of tumor cells was also examined using LipidTOX green neutral-lipid staining.
Results:
The treatment of 100 μM or 200 μM zaltoprofen significantly inhibited a cell proliferation of GCTB cells in a dose-dependent manner ($p < 0.001$). The apoptotic indices in TUNEL labeling were approximately 0% in control, 21.9% in 100 μM ($p < 0.001$) and 48.1% in 200 μM ($p < 0.001$) of zaltoprofen treatment. The labeling indices of PPARγ-positive cells were significantly higher than those in control after 24 hour of zaltoprofen treatment. Troglitazone treatment also demonstrated an inhibition of the cellular proliferation. Moreover, zaltoprofen treatment significantly increased labeling indices of LipidTOX Green neutral-lipid staining.
Conclusions:
These findings demonstrated that zaltoprofen could induce anti-tumor effects on GCTB cells, and also promoted the differentiation into an adipocytic lineage in remained tumor cells via an activation of PPARγ. This is the first study, to our knowledge, that activation of PPARγ could be a novel therapeutic tool against GCTB.

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