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Prolonged survival of mice with established intracerebral glioma receiving combined treatment with peroxisome proliferator-activated receptor- γ thiazolidinedione agonists and interleukin-2-secreting syngeneic/allogeneic fibroblasts

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Abbreviations used in this paper: DMSO = dimethyl sulfoxide; ELISPOT = enzyme-linked immunospot; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; PPAR γ = peroxisome proliferator-activated receptor- γ ; SOD = superoxide dismutase; TZD = thiazolidinedione.

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Object

In this study the authors explored the benefits of treating C57Bl/6 mice with an established intracerebral glioma by combining immunotherapy with interleukin (IL)-2-secreting syngeneic/allogeneic fibroblasts administered into the tumor bed along with the chemotherapeutic agent pioglitazone, a thiazolidinedione (TZD). The TZDs are agonists of the peroxisome proliferator-activated receptor- γ . They have been found to exert antiproliferative effects on several transformed cell lines. Data from prior studies by these authors have revealed the immunotherapeutic properties of the IL-2-secreting fibroblasts in treating intracerebral gliomas in mice.

Methods

The sensitivity of GL261 glioma cells and primary astrocytes to pioglitazone was determined in vitro by incubating the cells with increasing amounts of the drug. Viability was assessed by measuring lactate dehydrogenase release, and effects on metabolism were determined by measuring superoxide production and levels of superoxide dismutase. The GL261 cells were injected intracerebrally into C57Bl/6 mice, followed by treatment with pioglitazone either orally or intracerebrally into the tumor bed. The effect of the combined therapy was determined by injecting C57Bl/6 mice with an established intracerebral GL261 glioma with IL-2-secreting allogeneic fibroblasts and pioglitazone directly into the tumor bed through a unique cannula system.

Pioglitazone was found to induce cell death in GL261 glioma cells grown in vitro while causing only modest damage to astrocytes. The application of pioglitazone also resulted in a significantly greater induction of cellular superoxide in glioma cells than in astrocytes, which can activate apoptotic pathways. Pioglitazone administered intracerebrally ($p < 0.05$) but not orally was found to prolong survival in mice harboring an intracerebral glioma. Synergistic effects of combination therapy on prolonging survival were found in mice receiving both pioglitazone and IL-2-secreting fibroblasts ($p < 0.005$, compared with untreated animals). Pioglitazone induces metabolic and oxidative stresses that are tolerated by astrocytes but not glioma cells, which could account for selective vulnerability and increased sensitivity to IL-2, suggesting potential for the use of this Food and Drug Administration-approved drug in the treatment of brain tumors.

Conclusions

The data indicate the beneficial effects of combination therapy using pioglitazone and immunotherapy in mice harboring intracerebral glioma.

KEYWORDS: glioma; interleukin-2; oxidative stress; apoptosis; thiazolidinedione; immunotherapy.

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