Ciglitazone Enhances Ovarian cancer cell death via inhibition of Glucose Uptake Transporter-1

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Peroxisome proliferator-activated receptor (PPARs)

- Members of the nuclear hormone receptor family, the largest family of transcription factors

- Subfamily: $\alpha$, $\delta$ (also called $\beta$, NUC-1 or FAAR) and $\gamma$

- Activated: by naturally occurring fatty acids or fatty acid derivates
  → plays in glucose homeostasis and insulin sensitivity
Peroxisome proliferator-activated receptor (PPARs)

- **PPAR-γ expression**
  - increased in several epithelial cancer cells
  - physiological function in normal epithelial cells largely unknown.

- **PPAR-γ activation**
  - reported to inhibit the proliferation of malignant cells from different lineages
  - liposarcoma, breast adenocarcinoma, prostate carcinoma, colorectal carcinoma, pancreatic carcinoma, bladder cancer cells, and gastric carcinoma cells.
Targeting PPAR γ for prevention and treatment of cancer

Nat Rev Cancer. ; 12(3): 181–95
Potential targeting PPAR α for prevention and treatment of cancer

Nat Rev Cancer. ; 12(3): 181–95
OBJECTIVES

- To determine the effect of ciglitazone on cell proliferation and evaluate whether the expression of GLUT 1 in human ovarian cancer cells lines.
MATERIAL AND METHOD

Chemicals:
- PPAR gamma agonist (Ciglitazone)

Cell line:
- Ovarian cancer cells (A2780) were purchased from European Collection of Cell Culture (ECACC).

In vitro condition:
- Cells were cultured and incubated at 37°C temperature in 5% CO₂.
A2780 cells were cultured for 24 h to allow their adhesion to the plates.

Culture media was changed to experimental media supplemented with ciglitazone in different concentrations.

48 h treatment

Cell or cell lysets were harvested for different purposes.

Glucose uptake test
Immunofluorescence
DAPI & FACS analysis
Western blot analysis
In Vivo (NSG mouse)
RESULTS

Glucose uptake test & Hexokinase activity

Fig. 1 Cigлитазон inhibits Glucose uptake in ovarian cancer cell
Fig. 2 Ciglitazone decreased GLUT-1 expression

**Immunofluorescence (A) & Western Blot analysis (B)**
Fig. 3 Ciglitazone increased apoptosis of ovarian cancer cell lines

A

CTL  CGT 1 μM  CGT 10 μM  siGLUT-1

B

0.0  2.0  4.0  6.0  8.0  10.0

CTL  CGT 1 μM  CGT 10 μM  siGLUT-1
Immunohistochemical staining in ovarian ca sample
A,C) High grade serous adenocarcinoma
B,D) Low grade serous adenocarcinoma

A) H&E, X200
B) H&E, X200
C) GLUT1, X200
D) GLUT1, X200
Western Blot analysis

Fig. 4 Ciglitazone increased apoptosis of ovarian cancer cell lines

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[Western Blot images for CGT, Sp-1, β-catenin, β-actin at different concentrations]
In vivo (NSG mouse)

Fig. 5 Ciglitazone could decreased ovarian cancer mass

A

Control  Ciglitizone

B

Tumor Volume (mm$^3$)

Day 10  Day 13  Day 16  Day 19  Day 22

Control  Ciglitizone

Con  Cig

Keimyung University Dongsan Medical Center
Cancer cell metabolism

Nature reviews 2011
GLUT-1

愎 GLUT1 expression
  : the most common GLUT in humans, overexpressed in several tumors
  : tumor development, and unfavourable prognosis of several tumors

愎 GLUT1 as therapeutic target
  : Amann and Hellerbrand et al.
    -- the inhibition of GLUT1 expression in vitro by siRNA and by using the antisense oligodeoxynucleotide in HCC
  : Rastogi et al.
    -- antibodies against GLUT1 induce growth arrest and apoptosis
    -- inhibited proliferation by 50% in non-small cell lung ca,
      75% in the breast Ca cell line
    -- also potentiate the anti-proliferative effects of cisplatin
CONCLUSION

- Ciglitazone inhibited glucose uptake in ovarian cancer cell lines.
- Ciglitazone induced cancer cell apoptosis via decreasing GLUT-1 expression.
- These results suggest ciglitazone is a candidate for anti-cancer drug.