Temozolomide Reverses Doxorubicin Resistance by Inhibiting P-glycoprotein in Glioma Cells

Rong Zhang MD; Ryuta Saito; Ichiyo Shibahara; Masayuki Kanamori; Yukihiko Sonoda; Teiji Tominaga MD, PhD

Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

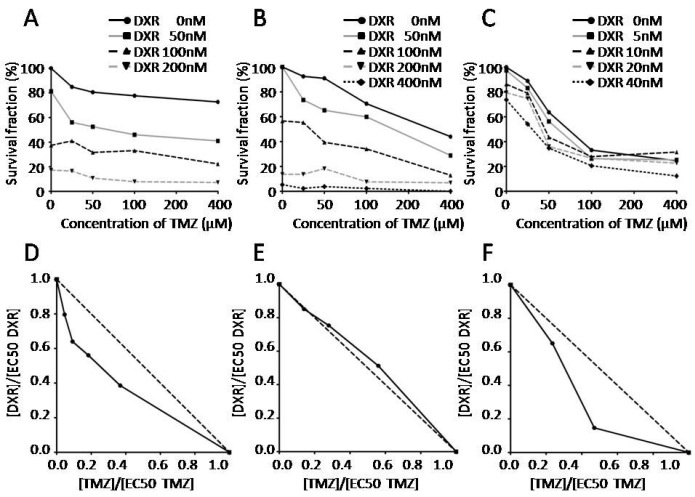
Introduction

Although temozolomide is utilized as standard chemotherapeutant against malignant gliomas, the treatment represents one of the most formidable challenges in oncology. Combination chemotherapy using temozolomide with other anti-tumor compounds are under investigation.

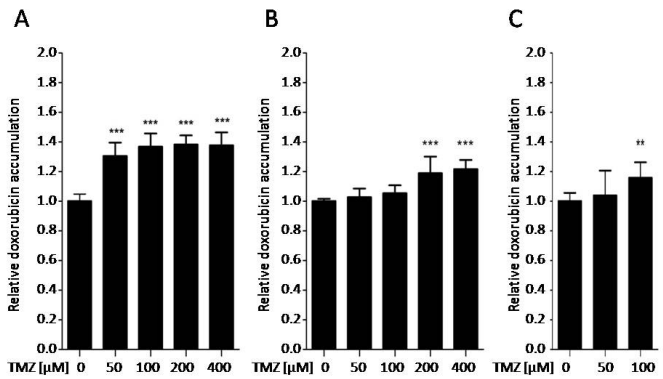
Methods

- Glioma cells : 9L gliosarcoma cells, doxorubicin (adriamycin) resistant 9L gliosarcoma cells (9L/ADR), T98G cells and U251MG cells
- Drugs: temozolomide/ doxorubicin/ pegylated liposomal doxorubicin
- Synergism: Isobologram assay
- P-glycoprotein (P-gp) expression: Western-blot
- P-glycoprotein activity: ATPase-assay
- Intracellular accumulation of doxorubicin: FACS
- Survival study: 9L glioma intracranial xenograft rat model

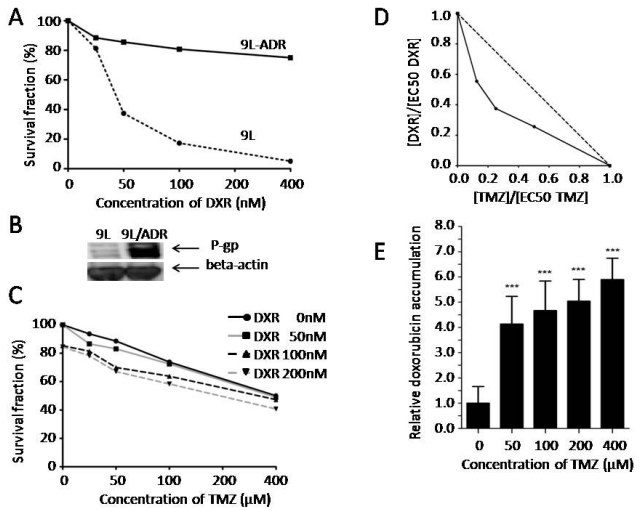
Result 1. Isobologram analysis showing the drug interaction effect of temozolomide (TMZ) with doxorubicin (DXR) in vitro.



Result 2. Flow cytometric analysis showing the intracellular accumulation of doxorubicin with or without temozolomide.



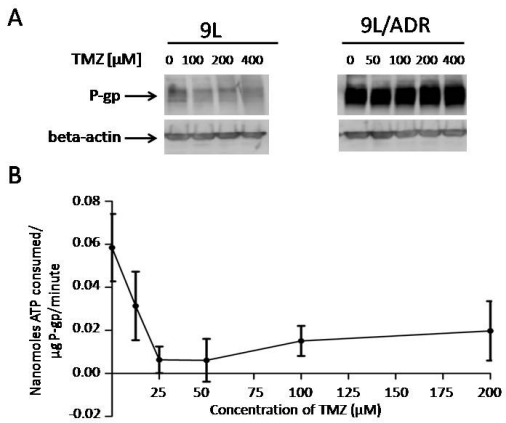
Result 3. Establishment of the 9L/ADR cell line.



Conclusions

We conclude that TMZ reverse doxorubicin resistance by directly affecting p-gp transport activity, and TMZ combine with other chemotherapeutic agents may be effective against gliomas in clinical applications.

Result 4. (A) Effect of temozolomide (TMZ) on the expression of P-gp protein. (B) ATPase activity of P-gp.



Result 5. Effect of combination therapy of temozolomide (TMZ) with PLD on the intracranial xenograft 9L tumor rat model.