Spindle Cells Expressed by Stem Cells As The Origin of Rat Glioblastoma Have High Energy

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Introduction

Recurrence of glioblastoma multiforme (GBM) after total resection is speculated to originate from precursor cells that pre-existed in surrounding brain tissue. To simulate human GBM, the authors studied morphology and metabolism of rat GBM.

Learning Objectives

By the conclusion of this session, participants should be able to: **1)** understand the concept of GBM precursor. Describe the importance of Experimental rat GBM has the same morphological and molecular biological behavior, **2)** Discuss, in small groups, the importance of experimental results and conclusion **3)** Identify an effective treatment targeted to the spindle cells in experimental animal model, and to precursor cells in humans.

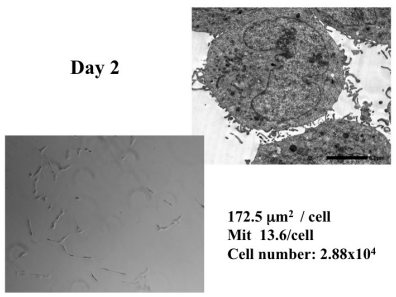
Methods

The following studies were carried out: **1)** culture of C6 rat GBM monoclone cells in plate wells and brain implant for morphological studies, **2)** temozolomide (TMZ) treatment of plate-cultured cells, **3)** immonohistochemical (CD15) staining of C6 cells. **4)** EM studies of C6 cell mitochondria, and **5)** mitochondrial volume study by flow cytometry.

Results

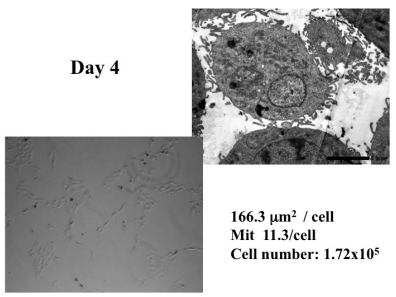
1) Both plate-culture and implant cells began to grow spindle cells, followed by syncytium formation, then by rapid transformation to multiform undifferentiated cells. **2)** Spindle cells were histologically identical to primative spongioblasts, which Bailey and Cushing claimed to be the origin of human glioblastoma (1926). **3)** Spindle cells were stained by CD15, and proved to be stem-like cells. **4)** After TMZ treatment of C6 cells, spindle cells mostly survived to transform to multiforme GBM cells. **5)** EM study showed normal appearance of mitochondria in the early stage (spindle cells), but began to show disintergration of cristae in the syncytium stage, and further progress to destruction in the late stage (undifferentiiated cells) **(Figure 1).** Additionally, the number of mitochondria/cell was greatest in spindle cells after TMZ treatment **(Figure 2). 6)** After TMZ treatment, the mitochrondial volume of spindle cells increased as the TMZ concentration increased **(Figure 3).**

Figure 1 Mitochondria by EM



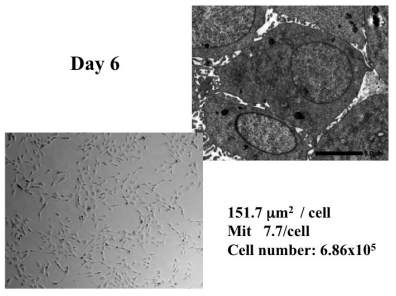
Normal Mitochondria Day 2

Mitrochondria by EM



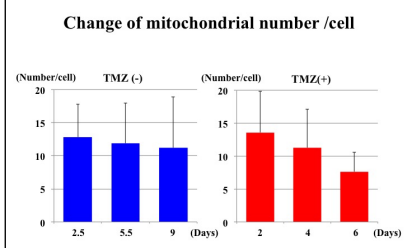
Mitrochondria Structural changes Day 4

Mitochondria by Em



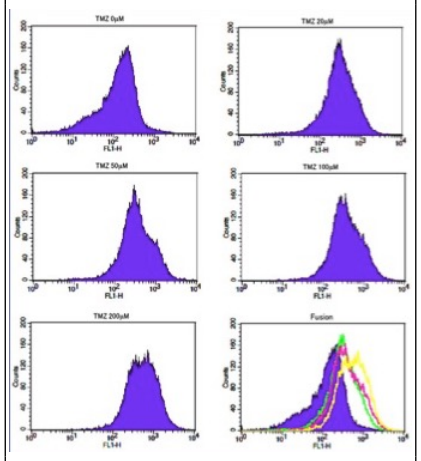
Mitochrondia Structural Changes Day 6

Figure 2 Number of Mitochondria



With and Without TMZ RX

Figure 3 Mitochondrial Volume



After TMZ Rx of Spindle Cells

Conclusions

1) CD15 stained spindle cells are capable of producing undifferentiated cells in rat GBM, similar to the primative spongioblasts in human GBM. **2)** After TMZ treatment, spindle cells survived , and grew to multiform cells. However, they lose mitochondrial function as they become histologically malignant. 3**)** The spindle cells can resist TMZ treatment with the higher than the lower concebtration. The EM findings suggest that spindle cells are more resistant to TMZ than undifferentiated C6 cells. Therefore, therapeutic agents must be targeted to spindle cells.

References

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