ANGPTL4 Induces TMZ Resistance of Glioblastoma by Promoting Cancer Stemness Enrichment via the EGFR/AKT/4E-BP1 Cascade

Yu-Ting Tsai1, Chiung-Yuan Ko2, Wen-Chang Chang1, Tsung-I Hsu2
1Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan.
2Ph.D. Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University and National Health Research Institutes, Taipei, Taiwan.

Figure 1. Effect of angiotensin-like 4 (ANGPTL4) on temozolomide (TMZ) sensitivity in glioblastoma (GBM).

Figure 2. Effect of ANGPTL4 on glioma stem-like cell (GSC) enrichment.

Figure 3. Effect of specificity protein (Sp4) on ANGPTL4 and GBM.

Figure 4. ANGPTL4-induced phosphorylation cascade for GSC enrichment.

Figure 5. Effect of Sp4 and ANGPTL4 in the clinical relevance of GBM.

Abstract

Glioblastoma (GBM) is the most aggressive brain tumor, with a strong invasiveness and high tolerance to chemotherapy. With the current standard treatment combining temozolomide (TMZ) and radiotherapy, glioblastoma can be incurable due to drug resistance. The existence of glioma stem-like cells (GSCs) is considered the major reason for drug resistance. However, the mechanism of GSC enrichment remains unclear. Herein, we found that the expression and secretion of specificity protein-lik4 (ANGPTL4) were obviously increased in GSCs. The overexpression of ANGPTL4 induced GSC enrichment that was characterized by BMI-1 and SOX2 expression, resulting in TMZ resistance in GBM. Furthermore, epidermal growth factor (EGFR) phosphorylation induced 4E-BP1 phosphorylation that was required for ANGPTL4-induced GSC enrichment. In particular, ANGPTL4 induced 4E-BP1 phosphorylation by activating PI3K/AKT and ERK cascades for inducing stemness. To elucidate the mechanism contributing to ANGPTL4 upregulation in GSCs, chromatin immunoprecipitation coupled with sequencing (ChIP-Seq) revealed that specificity protein 4 (Sp4) associates with the promoter region, −979 to −606, and the luciferase reporter assay revealed that Sp4 positively regulates activity of the ANGPTL4 promoter. Moreover, both ANGPTL4 and Sp4 were highly expressed in GBM and resulted in a poor prognosis. Taken together, Sp4-mediated ANGPTL4 upregulation induces GSC enrichment through the EGFR/AKT/4E-BP1 cascade.

Aim

1. To investigate the role of ANGPTL4 in GBM drug resistance
2. To investigate whether ANGPTL4 is involved in the enrichment of GSCs
3. To investigate the signaling pathway involved in ANGPTL4-induced GSC enrichment

Figure 4. ANGPTL4-regulated phosphorylation cascade for GSC enrichment

Reference


This research was supported by the Ministry of Science and Technology of Taiwan (MOST 106-2320-B-038 -003 -MY2, 107-2320-B-038-001, and 108-2628-B-038-005-.)