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Extended Abstract

Hypoxia induced ferritin light chain (FTL) promoted epithelia mesenchymal transition and chemoresistance of glioma.

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Abstract

Background: Hypoxia, a fundamental characteristic of glioma, is considered to promote tumor malignancy by inducing process of epithelial mesenchymal transition (EMT). Ferritin Light Chain (FTL) is one of the iron metabolism regulators and is overexpressed in glioma. However, relationship between hypoxia and FTL expression and its role in regulating EMT remains unclear.

Methods: Immunohistochemistry (IHC), western blot and public datasets were used to evaluate FTL level in glioma. Wound healing, transwell assays, CCK8, annexin V staining assay were used to measure migration, invasion, proliferation and apoptosis of glioma cells in vitro. Interaction between HIF1A and FTL was assessed by luciferase reporter and Chromatin immunoprecipitation (ChIP) assays. Subcutaneous xenograft model was established to investigate in vivo growth.

Results: FTL expression was enriched in high grade glioma (HGG) and its expression significantly associated with IDH1/2 wildtype and unfavorable prognosis of glioma patients. FTL expression positively correlated with HIF1A in glioma tissues and obviously increased in U87 and U251 cells under hypoxia in a time-dependent manner. Mechanistically, HIF-1α regulates FTL expression by directly binding to HRE-3 in FTL promoter region. Furthermore, we found that knockdown FTL dramatically repressed EMT and reduced migration and invasion of glioma by regulating AKT/GSK3β/ β-catenin signaling both in vitro and in vivo. Moreover, our study found downregulation FTL decreased the survival rate and increased the apoptosis of glioma cells treated with temozolomide (TMZ). FTL expression segregated glioma patients who were treated with TMZ or with high MGMT promoter methylation into survival groups in TCGA dataset. Patients with methylated MGMT who had high FTL expression presented similar prognosis with patients with unmethylated MGMT.

Conclusion: Our study strongly suggested that hypoxia-inducible FTL was a regulator of EMT and acted not only as a prognostic marker but also a novel biomarker of response to TMZ in glioma.

Keywords: Ferritin light chain, Hypoxia, Epithelial mesenchymal transition, Chemoresistance, Glioblastoma, Prognosis

Glioma originated from the neuroectoderm and accounts for approximately 81% of primary malignant brain tumors. Glioma is graded I-IV according to the 2016 World Health Organization classification of central nervous system tumors. Glioblastoma is the most common and malignant subtype and the dismal 2-year and 5-year survival rate are < 40 and < 10%, respectively. Low grade gliomas (WHO I-II) usually progress to higher grade and eventually have poor outcomes despite treating with standard care (surgical resection combined with postoperative radiotherapy and chemotherapy).

Therefore, it is urgent to understand the key molecular mechanisms in the malignancy progression of glioma to develop more effective treatments. Hypoxia is a common pathological feature in glioma. Increasing grade of gliomas correlate with an increase in absence of oxygen. Chronic hypoxia often leads to necrosis in tumor tissues, which is one of the most distinct characteristics of glioblastoma. Hypoxia microenvironment promotes glioma cells aggressive phenotype by upregulating hypoxia-inducible factor (HIF) family [5–7].HIF1A is highly expressed in glioblastoma and significantly correlated with IDH1/2 mutation. Moreover, previous studies have demonstrated that hypoxia environment could induce the epithelialmesenchymal transition (EMT) during the progression of glioma by regulating several pathways, such as Wnt/β-catenin, transforming growth factor β (TGF-β) [10] and Sonic Hedgehog (SHH) pathway. This phenotype transition facilitated glioma cells easier to infiltrate the adjacent brain tissues and more resistance to chemo/radiotherapy. However, the specific mechanism underlying which hypoxia promoting glioma malignancy remains to be further illustrated. Ferritin was consisted of 24 units of heavy chain (FTH) and light chain (FTL). FTL had been widely recognized as one of the iron metabolism regulators for a long time.

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