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Hypoxia induced LBH overexpression accelerates malignant progression in glioma

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Glioma is a world-wide health issue and is the most common, most malignant neoplasm in the central nervous system. Nowadays, comprehensive treatment has been developed involving surgical resection, concurrent chemo-and radio-therapy and supplementation with targeting therapy. However, glioma is still untreatable, bearing a poor median survival of 14.4 months [1]. This is mainly due to the undiscovered molecular mechanism, especially in the complicated tumor microenvironment.

The hypoxic tumor microenvironment regulates the aggressive progression in tumors, especially in glioma and breast tumor [2], but the detailed regulatory relationship between hypoxia and glioma progression is still unsolved. In this issue, Jiang et al. reported that HIF-1/LBH/VEGFA signaling axis drives tumor progression by promoting angiogenesis and oncogenesis in glioma [3]. The authors used various *in vitro* and *in vivo* experiments to demonstrate that LBH mediates the angiogenesis and oncogenesis in the hypoxic status regulated by HIF-1.

Since the anti-VEGF targeting therapy, such as bevacizumab, showed little effect in primary glioma treatment, novel targets should be developed and exploited. Here, Jiang et al. focused on LBH, which was upregulated by HIF-1 in hypoxia and regulated the VEGFA/ERK pathway subsequently. This implied that LBH might be a potential target of interest for research. In earlier studies, LBH was found to participate in early limb and heart development [4]. Then, it was found to be related to immune-related diseases, such as rheumatoid arthritis, and systemic lupus erythematosus, functioning as a risk gene [5]. While researchers have focused on the role of LBH in oncology research for some years, the conclusion remains controversial. It promotes the progression of gastric cancer and breast cancer by activating the downstream Akt and Wnt pathway [6,7], but suppresses the tumorigenesis in lung adenocarcinoma and nasopharyngeal carcinoma through regulating integrin family members and arresting cell cycling [8,9]. Thus far, the impact of LBH in gliomas has not been researched.

Analysis of clinical information from patients revealed the specific higher expression of LBH in gliomas with higher malignance. This phenomenon was verified with the immunohistochemical result obtained by the authors, implying the potential biomarker role of LBH in diagnosis and prognosis prediction for gliomas. Unfortunately, the authors included patients of all grade together, which may ignore the difference between different categories divided by 2016 WHO classification. Further research should investigate the expression difference in each subtype defined by newly published guidelines. The subsequent experiments confirmed angiogenesis and tumorigenesis was influenced by upregulation of LBH and the regulating effect of HIF-1 to LBH in hypoxia. The glioma conditioned medium (GCM) model used here is an interesting method to observe the effect of glioma cells on Human Brain Microvascular Endothelial cells (hBMECs), which lowered the difficulty normally associated with detecting features of hBMECs. The conditioned medium not only supplied cytokines secreted by glioma, but also excluded the influence of cell leakage induced by cell coculture, which had been shown to be effectual in published researches [10]. The most interesting finding in this manuscript is the circuit from hypoxia to dramatic angiogenesis and tumorigenesis and back to central ischemic necrosis and hypoxia status. The positive regulation cycle gradually promotes the tumor progression.

However, several questions remain. The authors of the current manuscript did not investigate the direct interactive relationship between LBH and VEGFA, which is still unclear. Also, the patient derived xenograft (PDX) model, the most powerful model for com-

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plicated tumor microenvironment, is absent here. In the future research, the authors should cover this deficiency. And lastly, but most significantly, the authors focused on LBH, which is an intermediate molecular component in the circuit. The targeting therapy may be ineffective, for the downstream receptor tyrosine kinase network is so complicated and full of crosslinks. The targeting inhibition may be covered by other activated kinase in the network.

Taken together, the authors highlighted the role LBH may play in the upregulation of VEGFA and ERK signal axis and result in the angiogenesis and tumorigenesis of glioma. This study is valuable in terms of understanding the link between hypoxia and malignant tumor progression. Furthermore, consideration of the context dependent role of LBH in glioma pathogenesis, may mean that it possesses strong potential as a biomarker or could participate in an instructive gene signature. However, the effectiveness of specifically targeting LBH in therapy should be reconsidered.

Declaration of Competing Interest

None.

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