HDAC4 as target for epigenetic imaging and therapy of glioblastomas.

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A recent report demonstrated that level of expression of HDAC4 negatively correlates with overall survival rates after temozolomide (TMZ) combined with radiation therapy irrespective of MGMT promoter methylation and level of MGMT expression. However, another study reports that GBM patients with high expression of HDAC4 and methylated MGMT promoter have better survival with TMZ and radiation therapy. Other studies demonstrated that shRNA-mediated silencing of HDAC4 radiosensitizes tumor cell lines by promoting DNA double-strand break (DSBs) and by affecting DSBs repair molecular machinery. HDAC4 positively regulates HIF-1α stability and transcriptional activity and negatively regulates transcriptional activity of MEF2, hence suppresses KLF4 leading to leakage of blood brain barrier (BBB). Therefore, pharmacologic inhibition of HDAC4, effectively monitored using PET/CT/MRI with [18F]TFAHA, with selective inhibitors represents a potential approach to improving the outcomes of chemo-radiation therapy of GBM in clinical studies.

Figure 1. Immunohistochemical staining for HDAC4, HIF1α and KLF4 in 9L and U87 gliomas and in contralateral hippocampus or cortex.

Figure 2. (A) PET/CT/MR images of [18F]TFAHA accumulation in 9L tumor and in normal brain structures before and after single dose of MC1568. (B) SUV (C) distribution volume (by Logan plot analysis) (D) tumor-to-cortex (contralateral) ratio.