SSADH

SSADH, or succinic semialdehyde dehydrogenase, is an enzyme that plays a critical role in the metabolism of the neurotransmitter gamma-aminobutyric acid (GABA) in the brain. GABA is a major inhibitory neurotransmitter that helps regulate neuronal activity in the brain.

SSADH catalyzes the final step in the metabolism of GABA, converting succinic semialdehyde (SSA) to succinate. Mutations in the gene that encodes for SSADH can result in a rare genetic disorder called SSADH deficiency. This disorder is characterized by a buildup of SSA in the brain and other tissues, which can lead to seizures, developmental delays, intellectual disability, and other neurological symptoms.

Research has also suggested that alterations in SSADH activity may be involved in the development of certain neurological and psychiatric disorders. For example, decreased SSADH activity has been associated with an increased risk of developing schizophrenia, and changes in SSADH expression have been observed in the brains of individuals with autism spectrum disorders.

Understanding the role of SSADH in the brain and its potential involvement in various neurological and psychiatric disorders is an active area of research. New therapies and interventions targeting SSADH activity may hold promise for the treatment of these disorders.

Cell populations with differing proliferative, stem-like, and tumorigenic states co-exist in most tumors and especially malignant gliomas. Whether metabolic variations can drive this heterogeneity by controlling dynamic changes in cell states is unknown. Metabolite profiling of human adult glioblastoma stem-like cells upon loss of their tumorigenicity revealed a switch in the catabolism of the GABA neurotransmitter toward enhanced production and secretion of its by-product GHB (4-hydroxybutyrate). This switch was driven by succinic semialdehyde dehydrogenase (SSADH) downregulation. Enhancing GHB levels via SSADH downregulation or GHB supplementation triggered cell conversion into a less aggressive phenotypic state. GHB affected adult glioblastoma cells with varying molecular profiles, along with cells from pediatric pontine gliomas. In all cell types, GHB acted by inhibiting α-ketoglutarate-dependent Ten-eleven Translocations (TET) activity, resulting in decreased levels of the 5-hydroxymethylcytosine epigenetic mark. In patients, low SSADH expression was correlated with high GHB/α-ketoglutarate ratios and distinguished weakly proliferative/differentiated glioblastoma territories from proliferative/non-differentiated territories. The findings support the active participation of metabolic variations in the genesis of tumor heterogeneity [1)].

Modulation of SSADH was shown to impact glioma cell properties, such as proliferation, self-renewal and tumorigenicity.

The purpose of a study by Piperi et al. was to investigate the clinical significance of SSADH expression in human gliomas. Using public single-cell RNA-sequencing data from glioma surgical resections, Piperi et al. initially grouped cancer cells according to ALDH5A1 (Aldehyde dehydrogenase 5 family member A1) expression, which encodes SSADH. Gene ontology enrichment analysis of genes differentially expressed between cancer cells expressing high or low levels of ALDH5A1, highlighted enrichment in genes implicated in the cell morphogenesis and motility. In glioblastoma cell lines,

ALDH5A1 knockdown inhibited cell proliferation, induced apoptosis, and reduced their migratory potential. This was accompanied by a reduction in the mRNA levels of the adherens junction molecule ADAM-15 and deregulation in the expression of EMT biomarkers, with increased CDH1 and decreased vimentin mRNA levels. Evaluation of SSADH expression in a cohort of 95 gliomas using immunohistochemistry showed that SSADH expression was significantly elevated in cancer tissues compared to normal brain tissues, without any significant correlation with clinicopathological characteristics. In summary, data show that SSADH is upregulated in glioma irrespective of the histological grade, and its expression sustains glioma cell motility [2)]

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