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Amino Acid Addiction Diagnosis in Cancer

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Introduction

Gliomas, which are astrocytic in origin, are the most common malignant brain tumours, with the most aggressive being glioblastoma. Despite efforts, medicine has made no progress in terms of glioma prognosis and life expectancy. Multiple genetic mutations leading to reprogramming of their metabolism give those highly proliferating cells an advantage over healthy cells underpin the malignant phenotype of gliomas.The so-called glutamine addiction is a metabolic adaptation that supplements oxidative glycolysis in order to provide nutrients and energy to neoplastic cells under hypoxic conditions [1].

Over 100 histologically distinct types of primary central nervous system tumours exist, each with its own set of clinical manifestations, treatments, and outcomes. Gliomas are tumours of the central nervous system that develop from glial or precursor cells. Gliomas make up about 25% of all primary CNS tumours and more than 80% of malignant ones. The most common gliomas are those of astrocytic origin, with glioblastoma accounting for more than 57% of these neoplasms. Gliomas have a high mortality rate due to their localization, high proliferative potential, infiltrative growth pattern, and intratumoral heterogeneity. Only 30% of anaplastic astrocytoma patients and less than 7% of GBM patients survive five years after diagnosis [2].

This information has helped to improve the diagnostics and classification systems. Somatic mutations in the isocitrate dehydrogenase residue of the isocitrate dehydrogenase 2 gene are frequently found in WHO grade II or III gliomas and oligodendrogliomas. These mutations are also found in GBMs that have evolved from lower grade gliomas, but they are uncommon in GBM patients who do not have a clinical diagnosis of a lower grade precursor neoplasm. Tumors with IDH1 or IDH2 mutations have distinct genetic and clinical characteristics, and patients with these tumours have a longer overall survival time than patients with wild-type gliomas. IDH enzymes convert isocitrate to -ketoglutarate, and mutations at R132 in IDH1 or R172 in IDH2 confer neomorphic enzyme activity that catalyses the reduction of KG into the oncometabolite D-2-hydroxyglutate [3].

Description

Cancer stem cells play a critical role in tumour relapse and metastasis, according to a growing body of evidence. Glioblastoma stem cells, discovered for the first time in brain tumours by Singh et al., have the ability to proliferate, self-renew, and differentiate, as well as to initiate tumours in vivo. Although their biology is not fully understood, GSCs have been shown to be involved in therapy resistance, angiogenesis, invasion, and recurrence. The targeting of GSCs is most likely required to achieve long-term therapeutic effects.

GS is important in nitrogen metabolism because it uses ammonia derived from amino acid degradation. GS is expressed exclusively in astrocytes in the brain, making them solely responsible for glutamine synthesis and ammonia detoxification. Furthermore, as a component of the glutamine-glutamate cycle, GS participates in neurotransmitter glutamate recycling, clearance from the synaptic cleft, and precursor synthesis. 70% of the glutamate neurotransmitter pool is derived from astrocytic GS-generated glutamine. Human GA is encoded by two genes: GLS, which encodes the kidney-type KGA and GAC isoforms, and GLS2, which encodes the liver-type GAB and LGA isoforms. Such oncogenes may influence GLS gene expression [4].

The ability of gliomas.The to maintain high-rate pyrimidine synthesis may be limiting, and targeting this pathway resulted in decreased viability of GBM stem cells. Furthermore, decreased nutrient availability activates the catabolic process, which provides substrates for biosynthesis. As a result, the TCA cycle intermediates used as macromolecule precursors must be replenished. Pyruvate carboxylation and glutaminolysis are two anaplerotic pathways that serve this purpose. However, in most neoplasms, the reaction catalysed by pyruvate carboxylase, which generates oxaloacetate from pyruvate, is down regulated. In contrast to the SF188 GBM cell line, which had initially low PC activity, cells with experimentally unregulated PC became glutamine independent, and silencing GA expression had no effect on their growth [5].

Conclusion

The genetic mutations that cause neoplastic transformation affect the key metabolic pathways in gliomas, allowing them to compete with healthy cells. The robust aerobic glycolysis provides undeniable benefits, such as survival in hypoxic conditions and elevated lactate, which facilitates invasiveness, but it necessitates the implementation of anaplerotic mechanisms, which are required for supporting anabolic and catabolic processes and are amplified in highly proliferative cells. Glutamine addiction becomes a treatment option. Increased transport provides glutamine as a carbon source for the TCA cycle, and it can then be redirected via the malate shuttle to become a source of extra energy and lactate. Furthermore, glutamine becomes necessary for nucleotide synthesis and improves the capability of the GSH redox system, allowing gliomas to resist radiotherapy and chemotherapy. Although the aforementioned mechanisms are relatively well understood, clinically targeting them remains a challenge for medicine, and not just because of drug side effects. The reasons for this are the neoplasms' high heterogeneity in terms of genetic background and metabolic strategy on the one hand, and their remarkable plasticity, which allows them to adjust their metabolism to changing growth conditions and nutrient supplies on the other. It invariably implies the need for combined personalised treatment based on the genetic profile of each individual glioma case.

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Conflict of Interest

There is no conflict of interest by author.

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