Asparagine synthetase

Asparagine synthetase (ASNS) is a gene on the long arm of chromosome 7 that is copy number amplified in the majority of glioblastomas. ASNS copy number amplification is associated with a significantly decreased survival. Using patient-derived glioma stem cells (GSCs), Thomas et al. showed significant metabolic alterations occur in gliomas when perturbing the expression of asparagine synthetase, which is not merely restricted to amino acid homeostasis. ASNS-high GSCs maintained a slower basal metabolic profile yet readily shifted to a greatly increased capacity for glycolysis and oxidative phosphorylation when needed. This led ASNS-high cells to a greater ability to proliferate and spread into brain tissue. Finally, we demonstrate that these changes confer resistance to cellular stress, notably oxidative stress, through adaptive redox homeostasis which led to radiation resistance. Furthermore, ASNS overexpression led to modifications of the one-carbon metabolism to promote a more antioxidant tumor environment revealing a metabolic vulnerability that may be therapeutically exploited. Implications: This study reveals a new role for ASNS in metabolic control and redox homeostasis in glioma stem cells and proposes a new treatment strategy that attempts to exploit one vulnerable metabolic node within the larger multilayered tumor network [1].

1)
Thomas TM, Miyaguchi K, Edwards LA, Wang H, Wollebo H, Aiguo L, Murali R, Wang Y, Braas D, Michael JS, Andres A, Zhang M, Khalili K, Gottlieb RA, Perez JM, Yu JS. Elevated Asparagine Biosynthesis Drives Brain Tumor Stem Cell Metabolic Plasticity and Resistance to Oxidative Stress. Mol Cancer Res. 2021 Apr 16:molcanres.0086.2020. doi: 10.1158/1541-7786.MCR-20-0086. Epub ahead of print. PMID: 33863814.