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"GLUTAMINE METABOLISM IN CANCER: INTEGRATING METABOLIC FLEXIBILITY AND IMMUNE EVASION FOR NOVEL THERAPEUTIC INTERVENTIONS"

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Glutamine, traditionally considered a non-essential amino acid, has emerged as a critical nutrient in cancer metabolism. Tumor cells reprogram their metabolic pathways to satisfy their increased demands for energy, biosynthetic precursors, and redox balance, and glutamine lies at the center of these adaptations. Cancer cells increase glutamine absorption by overexpressing certain transporters, including SLC1A5, SLC6A14, and SLC7A5. Following internalization (Glutaminolysis) , glutamine is converted by glutaminase (GLS1) to glutamate and then by GLUD1 or transaminase enzymes to alpha-ketoglutarate (α-KG), which feeds into the tricarboxylic acid cycle to produce ATP, biosynthetic intermediates, and preserve mitochondrial integrity. Beyond generating energy, glutamine also plays a key role in nucleotide synthesis, lipid biosynthesis, and the preservation of redox equilibrium through the creation of glutathione.

Glutamate reliance is further encouraged by genetic changes frequently observed in malignancies, including as MYC amplification, KRAS mutations, mTORC1 pathway activation, and hypoxia-induced HIF signaling. In addition to improving glutamine absorption and metabolism, these oncogenic drivers establish glutamine as a critical chemical in maintaining tumor development in hypoxic and nutrient-limited environments. But glutamine's significance goes beyond the survival of cancer cells. In particular, CD8+ T-cells and NK cells are effector immune cells that rely heavily on glutamine for activation, proliferation, and cytokine generation. Cancer cells frequently outcompete immune cells for glutamine in the tumor microenvironment (TME), impairing immune responses and encouraging immune evasion. A major obstacle in contemporary immunotherapy is the metabolic barrier that is produced by this glutamine competition, which prevents efficient anti-tumor immunity.

Targeting glutamine metabolism is an appealing therapeutic approach. By inhibiting GLS1 function, inhibitors like CB-839 (telaglinastat) have shown encouraging preclinical and early clinical results, depriving tumors of an essential resource. However, the long-term efficacy of monotherapies is limited by tumor metabolic flexibility, which is typified by the activation of alternate nutrition pathways and autophagy under glutamine shortage. Combinatorial strategies, which involve combining glutamine blockade with immunological checkpoint inhibitors, chemotherapeutics, or metabolic reprogramming drugs, are therefore being thoroughly studied.

Future treatment design requires a sophisticated grasp of glutamine's dual role in promoting immune cell activity and tumor survival. Achieving long-lasting clinical responses requires tactics that specifically disrupt tumor glutamine metabolism while maintaining or improving immune cell fitness. As studies progress, focusing on glutamine metabolism has the potential to revolutionize cancer treatment by combining immune system renewal with metabolic disturbance, providing fresh hope for potent and long-lasting therapeutic interventions.