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Editorial

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Serine and Urinary Tumors

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Serine is an amino acid, it comes in two forms: L-serine and D-serine. L-serine is consumed in the diet and D-serine is made in the body from L-serine. The body uses D- and L-serine to make proteins. It is a vital contributor to the folic acid cycle and serves as an important single-carbon source for tumor cells. It also supports the biosynthesis of purine and pyrimidine, participates in the methionine cycle, methylation reactions, and the generation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) for antioxidant defense and the growth and proliferation of cancer. The cells' reprogramming accelerates the breakdown of serine [1]. Serine Hydroxymethyltransferase (SHMT) 2 plays a significant role in the onset of Bladder Cancer (BLCA). The expression level of SHMT2 was found to be negatively associated with patient survivability. In vitro experiments demonstrated that bladder malignancy cells exhibited reduced motility when SHMT2 expression levels decreased. In addition, it was observed that the low levels of SHMT2 expression blocked the bladder tumor cell cycle in the G2/M phase, which led to decreased cell proliferation and increased apoptosis. SHMT2, as one of the serine hydroxymethyltransferase isozymes, is a potential cancer driver due to its influence on bladder cancer development, migration, and apoptosis.Many tumor cells show dependence on exogenous serine. Dietary serine and glycine starvation can inhibit the growth of these cancers and extend survival. In vitro, inhibition of Phosphoglycerate Dehydrogenase (PHGDH) combined with serine starvation leads to a defect in global protein synthesis, which blocks the activation of an ATF-49 (Activating Transcription Factor 4). *ATF4* is a Protein Coding *gene* response and more broadly impacts the protective stress response to amino acid depletion. However, the defect in ATF4-response. *ATF4* is a Protein Coding *gene)* and is seen in vitro following complete depletion of available serine. The results indicate that inhibition of PHGDH will augment the therapeutic efficacy of a serine-depleted diet [2].

Metabolic pathways leading to the synthesis, uptake, and usage of the nonessential amino acid serine are frequently amplified in cancer. Serine encounters diverse fates in cancer cells, including being charged onto tRNAs for protein synthesis. Many genetic and pharmacologic experiments to date have been performed in xenograft models in immunodeficient mice, which may present an overestimation of the therapeutic efficacy of targeting this pathway [3]. The conversion of serine and glycine that is accomplished by Serine Hydroxymethyltransferase 2 (SHMT2) in mitochondria is significantly upregulated in various cancers to support cancer cell proliferation urinary or otherwise [4,5]. The expression, function, and underlying mechanisms of SHMT2 in clear cell renal cell carcinoma (ccRCC) remain largely unknown. It was shown that SHMT2 was upregulated in ccRCC tissues compared with controls and associated with patient survival. SHMT2 knockdown inhibited proliferation, migration, and invasion in ccRCC cells. Research revealed that SHMT2 functions as an oncogenic gene to promote ccRCC progression. SHMT2 depletion induces apoptosis by causing LMP through excessive activation of the autophagy-lysosome pathway via metabolic reprogramming [6]. Altered metabolism is a common feature of new and recurring malignancies. Further reports indicated that upregulation of the Serine, Glycine, One-Carbon (SGOC) metabolic network is required for neuroendocrine prostate cancer, a castration-resistant aggressive form of the disease, and presents a targetable vulnerability [7]. Further study showed that Serine/Threonine Kinase 3 (STK3) is an essential member of the highly conserved Hippo tumor suppressor pathway that regulates Yes-Associated Protein 1 (YAP1) and TAZ. STK3 and its paralog STK4 initiate a phosphorylation cascade that regulates YAP1/TAZ inhibition and degradation, which is important for regulated cell growth and organ size. In the context of Prostate Cancer (PC), STK3 has a pro-tumorigenic role [8]. SHMT2 knockdown inhibited proliferation, migration, and invasion in ccRCC cells [9]. In summary, the inhibition of the serine synthesis pathway and dietary serine depletion synergistically inhibit one-carbon metabolism and cancer cell growth. Serine and glycine are essential metabolites for cancer cells and provide precursors for macromolecules and antioxidant defense. Metabolic enzymes of serine and glycine biosynthesis are upregulated in cancer. They are biosynthetically linked, and together provide the essential precursors for the synthesis of proteins, nucleic acids, and lipids that are crucial to cancer cell growth. Dietary serine and glycine starvation can inhibit the growth of these cancers and extend survival. Serine is found in soybeans, nuts (especially peanuts, almonds, and walnuts), eggs, chickpeas, lentils, meat, and fish (especially shellfish).

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