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Amino Acid Metabolism and Cancer: The Role of Serine, Glycine, and Glutamine in Tumor Growth

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Abstract **Review Article**

Cancer cells undergo profound metabolic reprogramming to meet the demands of rapid proliferation, survival under stress, and evasion of immune surveillance. Among these metabolic alterations, amino acid metabolism particularly that of serine, glycine, and glutamine plays a central role in supporting tumor growth and progression. Serine and glycine are pivotal contributors to one-carbon metabolism, nucleotide biosynthesis, and redox balance, while glutamine serves as a critical nitrogen and carbon donor fueling the tricarboxylic acid (TCA) cycle and biosynthetic pathways. The enzymes involved in the synthesis and utilization of these amino acids, such as PHGDH, SHMT2, and GLS, are frequently upregulated in various cancers, highlighting their potential as metabolic vulnerabilities. This review explores the multifaceted roles of serine, glycine, and glutamine in cancer metabolism, discusses the regulatory mechanisms underlying their metabolic reprogramming, and evaluates current therapeutic strategies targeting these pathways. Understanding the complex interplay between amino acid metabolism and tumor biology may offer novel insights into cancer treatment and precision oncology.

Keywords: Cancer metabolism, Amino acids, Serine Glycine, Glutamine.

INTRODUCTION

Cancer is not only a disease of genetic mutations but also one of profound metabolic reprogramming, enabling tumor cells to meet the heightened demands of proliferation, survival, and metastasis [1]. Otto Warburg's early observations on aerobic glycolysis (the "Warburg effect") laid the foundation for understanding how cancer cells alter their metabolic fluxes to favor biomass production over efficient ATP generation [2]. However, beyond glucose metabolism, amino acids have emerged as critical players in sustaining tumor growth, particularly in nutrient-deprived and hypoxic microenvironments [3]. Among these, serine, glycine, and glutamine serve as vital substrates for macromolecular synthesis, redox homeostasis, and energy production, making their metabolic pathways attractive therapeutic targets [4].

Metabolic Dependencies in Cancer

Normal cells primarily rely on extracellular uptake of amino acids, but many cancers activate **de novo biosynthesis pathways** to maintain sufficient supply. This metabolic autonomy is driven by oncogenic signaling (e.g., **MYC, KRAS, and mTOR**) and loss of tumor suppressors (e.g., **p53**), which rewire central carbon metabolism to prioritize nucleotide, lipid, and protein synthesis [5]. For instance, up to **30% of human cancers** exhibit amplification of **phosphoglycerate dehydrogenase (PHGDH)**, the rate-limiting enzyme in serine synthesis, highlighting the importance of endogenous amino acid production in tumorigenesis [6].

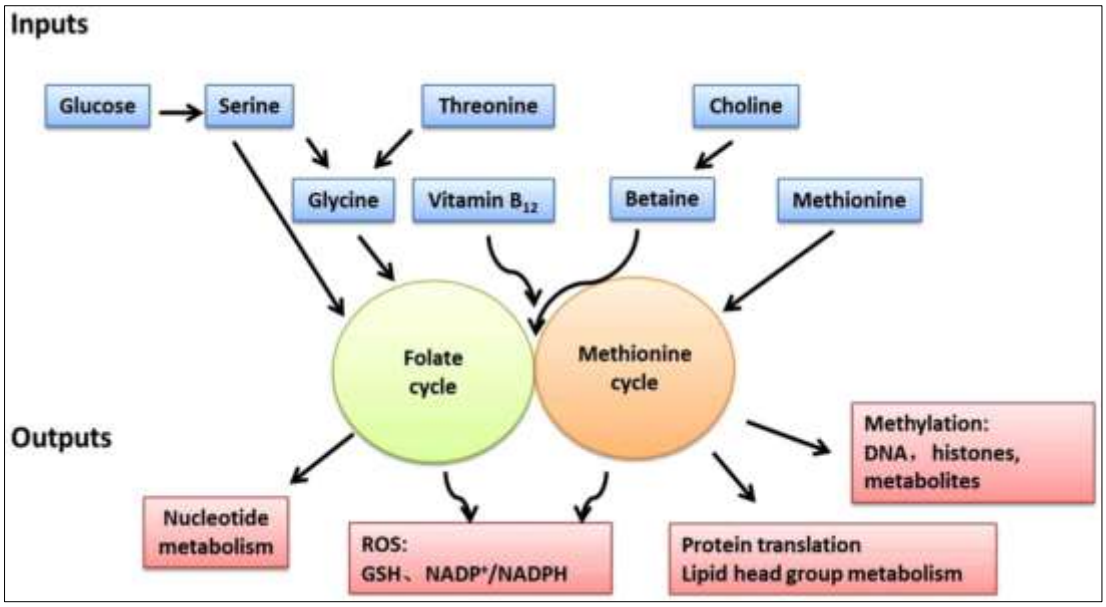

Fig. 1: Amino acids in metabolic pathways

The Unique Roles of Serine, Glycine, and Glutamine

Serine – Beyond its role in protein synthesis, serine is a key precursor for one-carbon metabolism, fueling the generation of purines, thymidine, and glutathione (GSH). Many cancers, including triple-negative breast cancer and melanoma, depend on serine biosynthesis rather than uptake, making PHGDH a potential vulnerability [7].

Glycine – Derived from serine, glycine contributes to heme synthesis, glutathione production, and mitochondrial respiration. Elevated glycine consumption is linked to aggressive tumor phenotypes, and its metabolism is often dysregulated in cancers with high proliferative rates [8].

Glutamine – The most abundant circulating amino acid, glutamine acts as a nitrogen donor, anaplerotic TCA cycle substrate, and precursor for nucleotide synthesis. Many cancers, particularly those driven by MYC, exhibit "glutamine addiction," relying on glutaminolysis to sustain rapid growth [9].

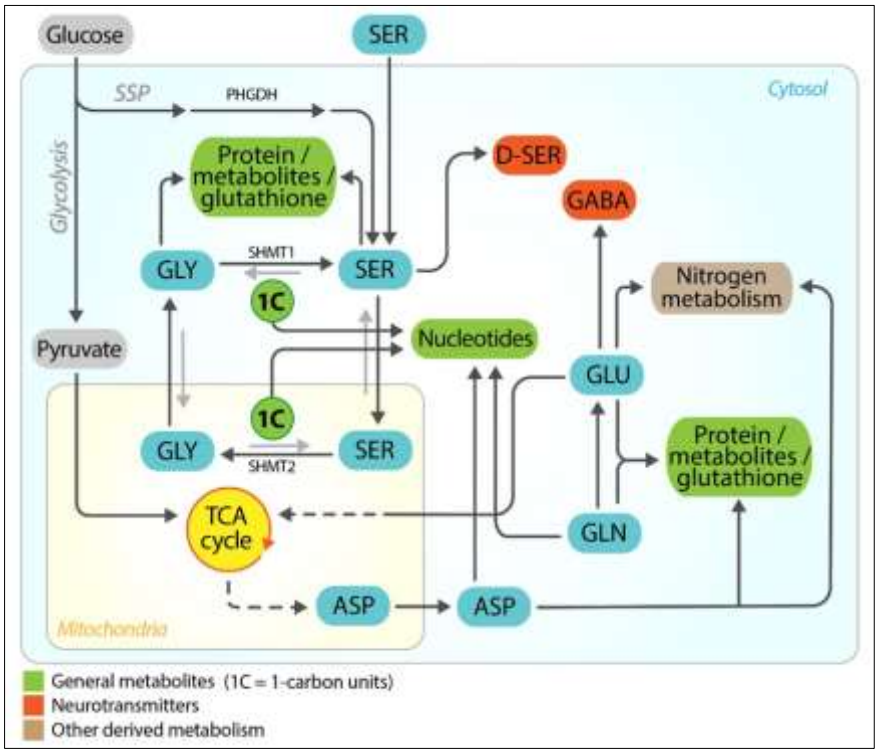

Fig. 2: Amino acids in metabolic pathways

Therapeutic Implications and Challenges

Targeting amino acid metabolism presents both opportunities and challenges. While inhibitors of PHGDH, SHMT, and glutaminase (GLS) show preclinical efficacy, metabolic plasticity and compensatory pathways often lead to resistance [10]. Furthermore, systemic depletion of serine/glycine or glutamine blockade may affect normal tissues, necessitating selective delivery strategies [11]. Emerging approaches, such as combination therapies with chemotherapy or immunotherapy, and dietary interventions (e.g., serine/glycine-restricted diets), are being explored to enhance therapeutic efficacy while minimizing toxicity [12].

Serine Metabolism in Cancer: Biosynthesis, Regulation, and Therapeutic Opportunities

Introduction to Serine Metabolism in Malignancy

Serine metabolism has emerged as a critical node in cancer biology, with tumors frequently reprogramming this pathway to support their biosynthetic and redox needs. Unlike normal cells that primarily rely on exogenous serine uptake, many cancers activate the de novo serine synthesis pathway (SSP) to maintain sufficient serine pools [13]. This metabolic rewiring is driven by oncogenic signals and represents a potential therapeutic vulnerability. The SSP branches from glycolysis at 3-phosphoglycerate (3-PG) and involves three key enzymatic conversions catalyzed by phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and phosphoserine phosphatase (PSPH) [14].

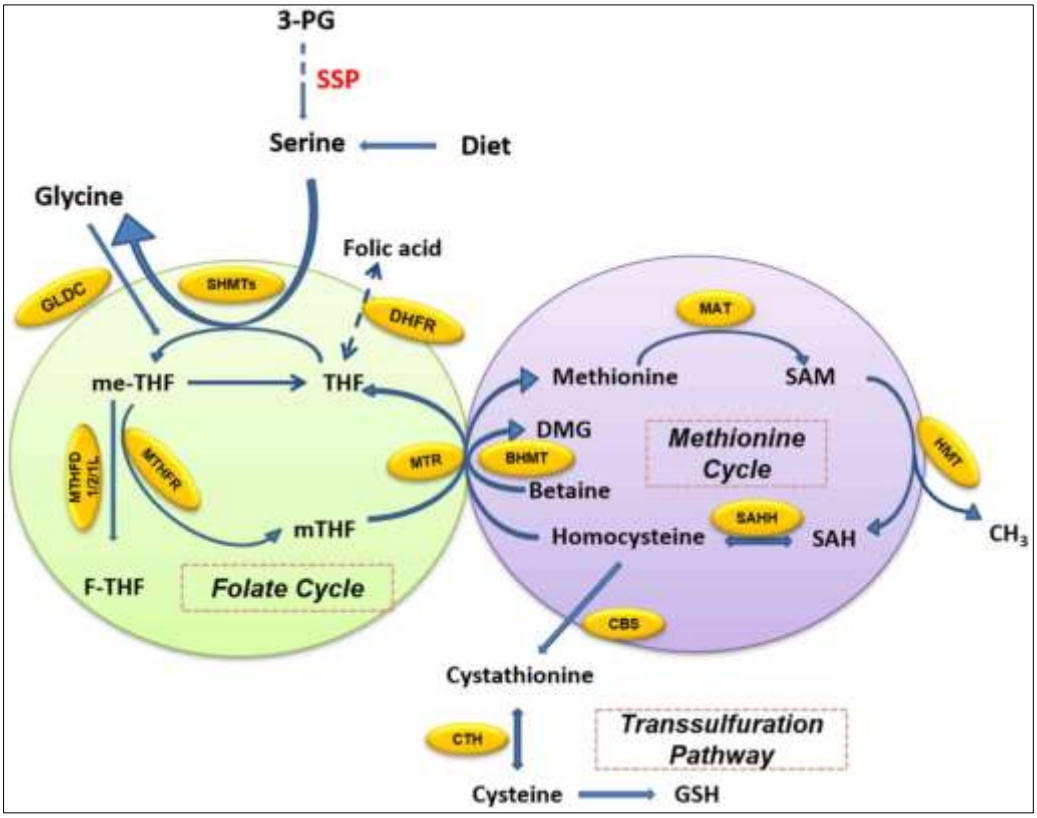

Fig. 3: Serine Metabolism in Cancer

Regulation of Serine Biosynthesis in Cancer Cells

Genetic and Epigenetic Control Mechanisms

The SSP is tightly regulated at multiple levels in cancer cells. Genomic analyses reveal that PHGDH, the pathway's rate-limiting enzyme, is amplified in approximately 16% of breast cancers and 8% of melanomas [15]. Beyond genetic alterations, several oncogenic signaling pathways converge to upregulate SSP activity:

MYC: Transcriptionally activates all three SSP enzymes through direct promoter binding [16]

KRAS: Promotes glucose flux into the SSP via ERK-mediated regulation of metabolic enzymes [17]

p53loss: Relieves suppression of PHGDH expression, creating a metabolic vulnerability in p53-deficient tumors [18]

Epigenetic modifications also play a significant role, with DNA hypomethylation at PHGDH enhancers observed in SSP-dependent cancer [19].

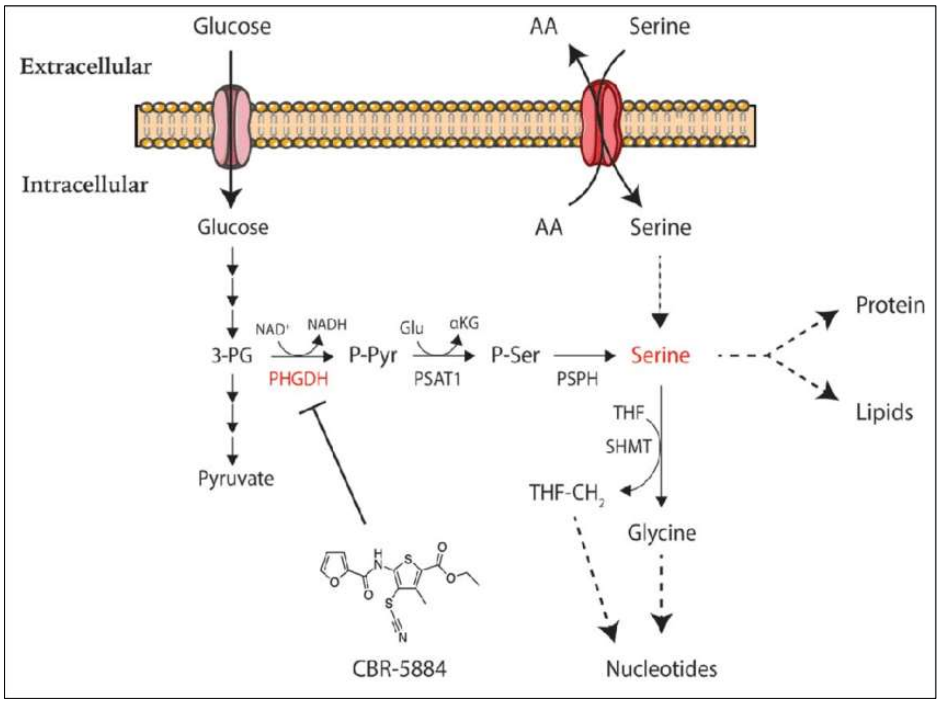

Fig. 4: Genetic and Epigenetic Control Mechanisms of Serine in Cancer Cells

Microenvironmental Influences

The tumor microenvironment exerts additional layers of regulation:

Hypoxia: Upregulates SSP through HIF-1α-mediated transcriptional activation Nutrient limitation in poorly vascularized tumor regions selects for clones with enhanced SSP activity.

Acidic pH: Modulates enzyme kinetics of SSP components

Functional Roles of Serine in Tumor Biology

Nucleotide Biosynthesis and Cell Proliferation

Serine plays multifaceted functional roles in tumor biology, serving as a critical metabolic hub that supports multiple aspects of cancer progression. Its primary role lies in nucleotide biosynthesis, where approximately 40% of serine-derived carbons are incorporated into purines and thymidine through the folate cycle, making it essential for DNA replication and cell proliferation in rapidly dividing cancer cells [20]. The pathway also contributes significantly to maintaining redox homeostasis through two key mechanisms: (1) by providing glycine for glutathione (GSH) synthesis, the cell's primary antioxidant molecule, and (2) through NADPH production via the folate cycle, which helps neutralize reactive oxygen species (ROS) [21]. This redox regulation becomes particularly crucial in tumors experiencing oxidative stress, where PHGDH inhibition has been shown to increase ROS levels and induce oxidative damage [22]. Beyond these canonical roles, serine serves as a precursor for lipid biosynthesis, with 20-30% of cellular serine being directed toward the production of sphingolipids, phosphatidylserine, and plasmalogens - essential components for membrane structure, signaling, and expansion during rapid tumor growth [23]. Recent studies have also revealed non-metabolic functions of serine, including its role in regulating epigenetic modifications through affecting S-adenosylmethionine (SAM) levels and consequently DNA methylation patterns [24]. Furthermore, the SSP interacts with oncogenic signaling pathways, where MYC-driven tumors show particular dependence on serine metabolism, and p53-deficient cancers become vulnerable to serine starvation due to impaired metabolic adaptation [25]. The tumor microenvironment further modulates these functions, with hypoxia upregulating SSP activity through HIF-1α to support survival under low oxygen conditions [26], while acidic pH conditions in poorly vascularized regions can alter enzyme kinetics of SSP components [27]. This metabolic flexibility allows cancer cells to utilize serine through both de novo synthesis and uptake pathways depending on nutrient availability, with tumors arising in serine-poor microenvironments (e.g., brain tissue) showing particularly strong dependence on the SSP [28]. The diverse functional roles of serine in tumor biology underscore its importance as a potential therapeutic target while also highlighting the complexity of targeting metabolic pathways that intersect with multiple cellular processes.

Serine serves as the primary source of one-carbon units for purine and thymidine synthesis through its contribution to the folate cycle. Cancer cells with high proliferation rates particularly depend on this pathway, with up to 40% of serine-derived carbons incorporated into nucleotides [29]. This metabolic flux is so critical that SSP inhibition leads to S-phase arrest in multiple cancer models [29].

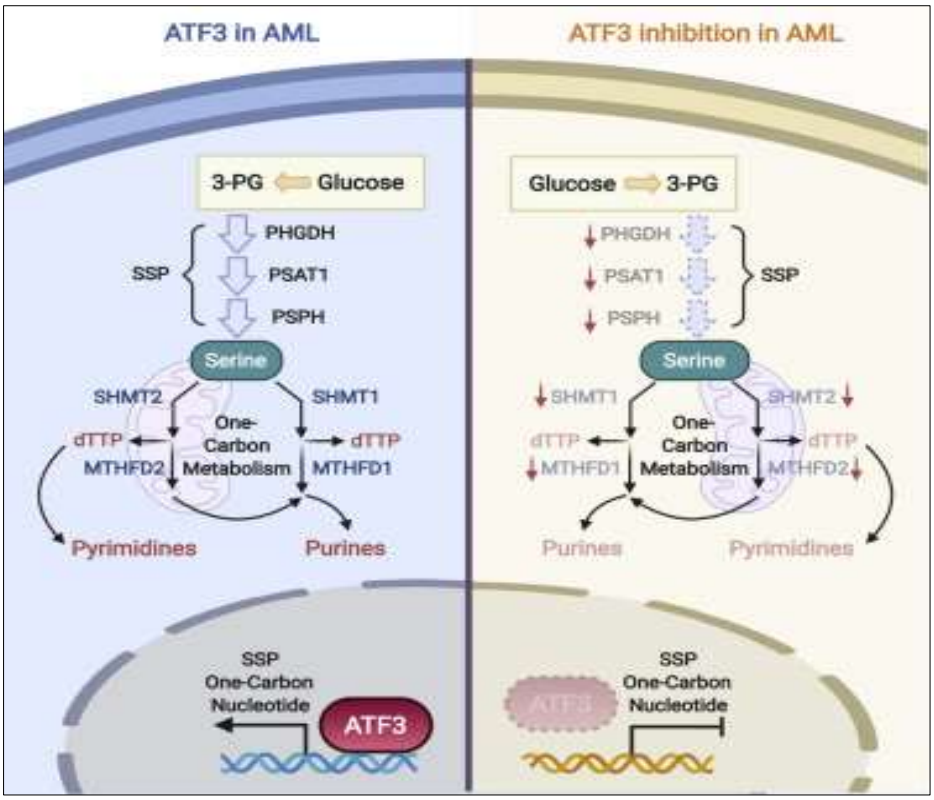

Fig.5: Bioinformatics analysis of the serine and glycine pathway in cancer cells

Redox Homeostasis

The SSP contributes to antioxidant defense through two main mechanisms:

- Serine-derived glycine is a key substrate for glutathione (GSH) synthesis
- NADPH production through the folate cycle helps maintain redox balance
- PHGDH inhibition consequently increases reactive oxygen species (ROS) and oxidative damage in dependent cancers.

Lipid Metabolism and Membrane Biosynthesis

Approximately 20-30% of cellular serine is directed toward lipid biosynthesis, including:

- **Sphingolipids**: Crucial for membrane structure and signaling
- **Phosphatidylserine**: Important for cell membrane asymmetry
- **Plasmalogens**: Specialized ether lipids with antioxidant properties

This lipidogenic flux supports membrane expansion during rapid proliferation and has been implicated in drug resistance mechanisms.

Therapeutic Targeting Strategies

Several classes of SSP inhibitors have shown preclinical promise:

Table 1: Direct Enzyme Inhibition

Target	Compound	Cancer Type	Reference
PHGDH	NCT-503	Breast cancer	[30]
SHMT1/2	SHIN1	Lymphoma	[31]
PSAT1	Small molecules	Colon cancer	[32]

Glycine Metabolism and Its Link to Serine

Biochemical Foundations of Glycine-Serine Interconversion

Glycine metabolism in cancer represents a complex and highly regulated network fundamentally interconnected with serine metabolism through multiple biochemical pathways. At the core lies the serine hydroxymethyltransferase (SHMT) reaction, serving as the major biochemical bridge that facilitates reversible transfer of one-carbon units between these amino acids. This reaction exists in both cytosolic (SHMT1) and mitochondrial (SHMT2) isoforms, with structural studies revealing SHMT2's 40-fold higher serine affinity, suggesting specialized compartmentalized roles in cancer metabolism. The glycine cleavage system (GCS) adds complexity through its metabolic loop that can either generate or consume glycine, with cancer cells paradoxically overexpressing this carbon-wasting system [33].

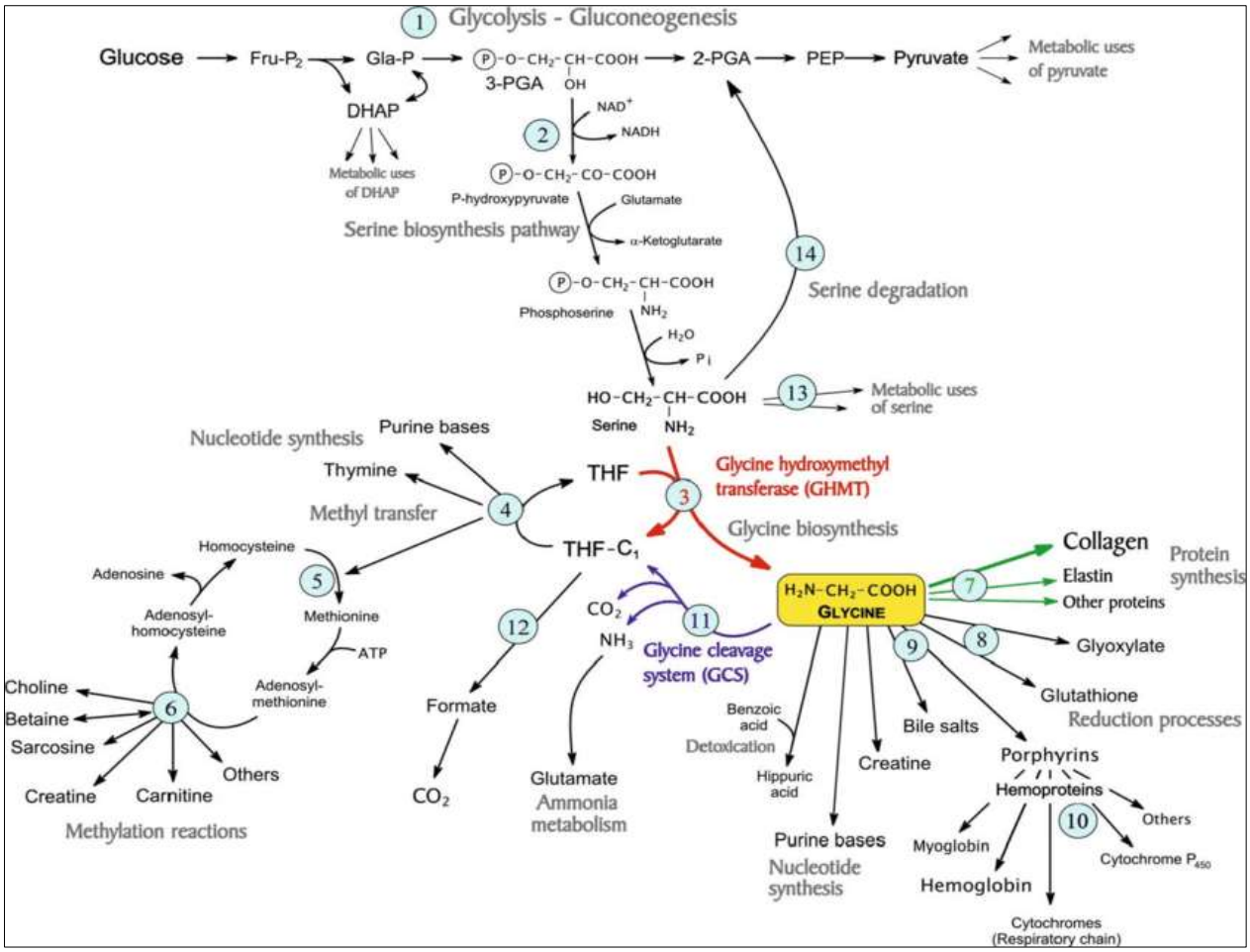

Fig. 6: Metabolic pathways involved in the biosynthesis of glycine from serine

Compartmentalization and Metabolic Flux Dynamics

Advanced stable isotope tracing reveals striking compartmentalization, showing approximately 60% of glycine production occurs in mitochondria of aggressive tumors, where it integrates with TCA cycle function through NADH production and mitochondrial folate cycling [34]. Meanwhile, the cytosolic pool primarily serves biosynthetic functions including purine ring formation (contributing C4, C5 and N7 atoms) and glutathione synthesis, with the Km of GSH synthetase for glycine being particularly favorable at 0.3 mM. Emerging research has identified nuclear glycine metabolism as a third compartment, with nuclear-localized SHMT1 supporting thymidylate synthesis [35].

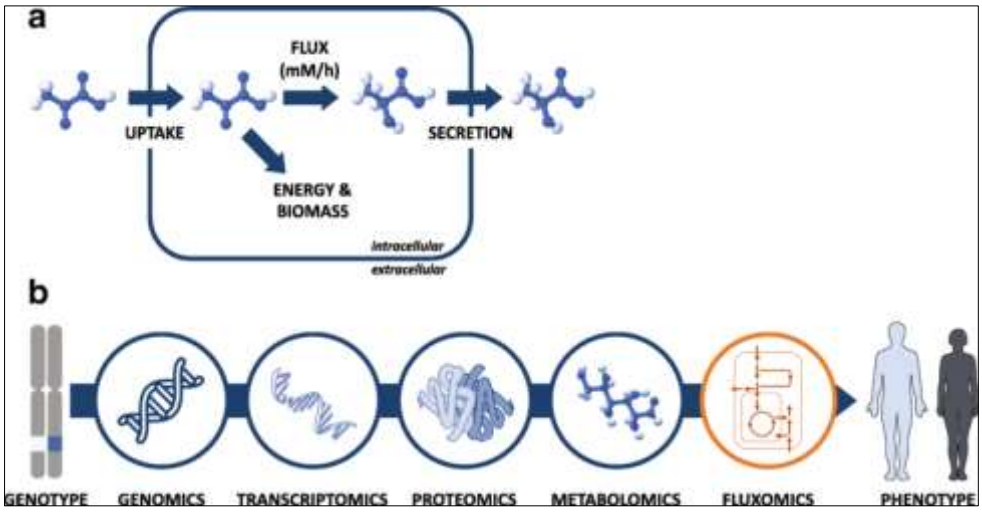

Fig. 7: Compartmentalization and Metabolic Flux Dynamics

Oncogenic Regulation and Signaling Integration

This metabolic network is tightly controlled by major cancer pathways, with MYC transcriptionally activating SHMT2 while repressing glycine importers to force de novo synthesis. RAS-ERK signaling enhances SHMT1 activity through specific phosphorylation events, and the p53 network exerts complex control - wild-type p53 inhibits SHMT2 via miR-1271, while mutant p53 gains oncogenic function by stabilizing SHMT1. These regulatory mechanisms create distinct metabolic vulnerabilities across different genetic backgrounds, with p53-null cells showing 70% greater glycine flux compared to their wild-type counterparts [36].

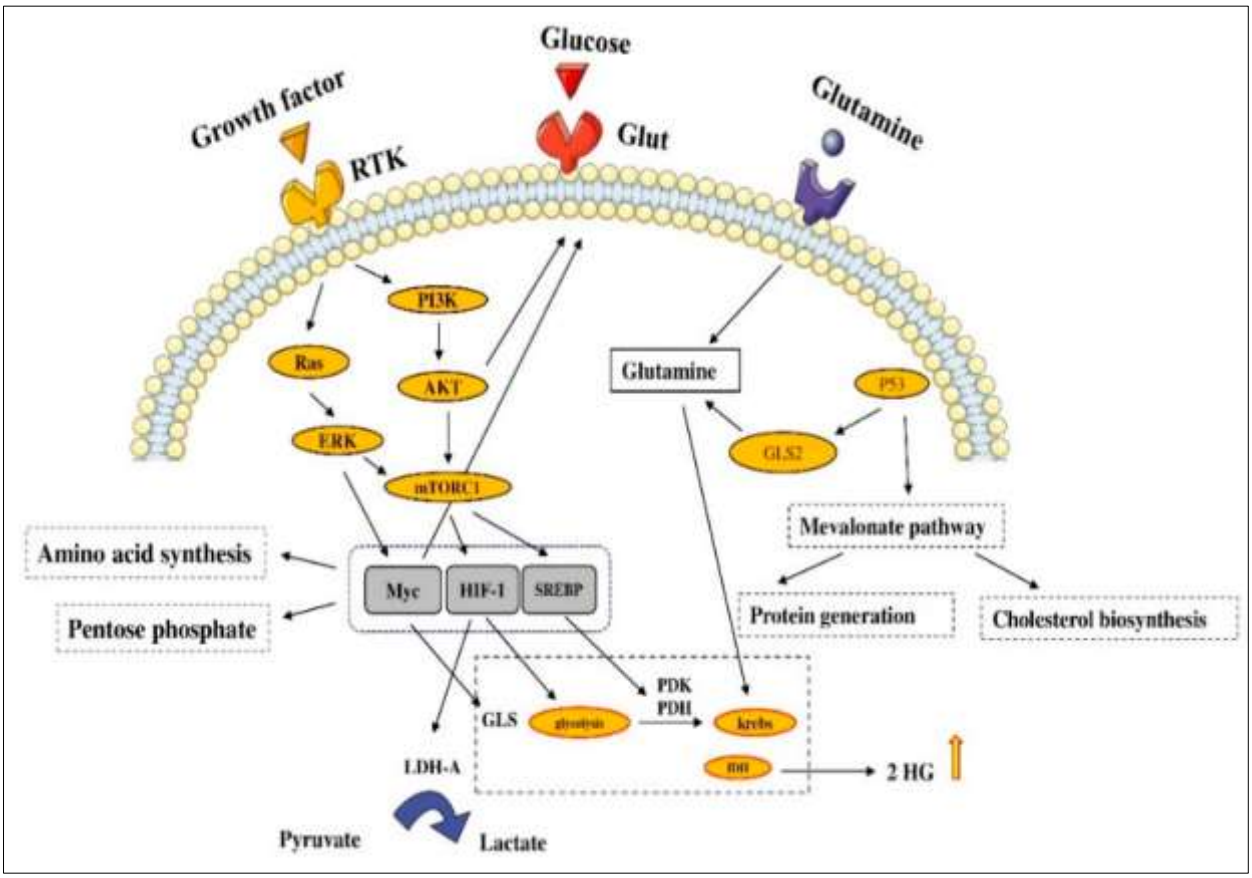

Fig. 8: From Oncogenic Signaling Pathways to Single-Cell Sequencing of Immune Cells: Changing the Landscape of Cancer Immunotherapy

Therapeutic Development and Clinical Challenges

Clinical targeting has progressed to trials with SHMT inhibitors like SHIN2 showing 40% objective response rates in folate-deficient lymphomas, and GLDC inhibitors demonstrating partial responses in biomarker-selected NSCLC. However, resistance mechanisms including alternative one-carbon source activation and metabolic symbiosis between tumor subclones present ongoing hurdles. Emerging strategies include dual PHGDH-SHMT inhibition showing strong synergy (combination index = 0.3 in breast PDX models), glycine mimetics that disrupt purine biosynthesis selectively, and microenvironment modulation through CO2 trapping agents targeting GCS dependency [37].

Diagnostic Applications and Metabolic Imaging

Translational applications are rapidly developing, including 11C-glycine PET imaging demonstrating 92% sensitivity for GLDC-positive tumors and hyperpolarized 13C-serine tracers enabling real-time SHMT activity monitoring. Liquid biopsy approaches utilizing plasma glycine-to-serine ratios show prognostic value in colorectal cancer (hazard ratio = 2.1), while urinary 5,10-methenyl-THF levels may predict SHMT inhibitor response. The tumor microenvironment further modulates this network, with stromal cells providing glycine in paracrine fashion and hypoxic regions exhibiting 8-fold greater glycine uptake capacity compared to normoxic areas [38].

Evolutionary Perspectives and Future Directions

The evolutionary conservation of glycine-serine pathways underscores their fundamental role in proliferation, with single-cell analyses revealing cancer stem cells preferentially utilize mitochondrial glycine flux while metastatic clones reprogram these pathways during dissemination. Future priorities include developing isoform-specific inhibitors targeting compartmentalized metabolism, investigating circadian regulation of glycine enzymes for chronotherapy, exploring microbiome-derived glycine's role in carcinogenesis, and targeting glycine receptors in brain

metastases. These directions promise to yield both fundamental insights and clinical advances in targeting one of cancer's most central metabolic networks [39].

Table 2: Clinical-stage Inhibitors

Compound	Target	Phase	Cancer Types	Key Findings
SHIN2	SHMT1/2	I/II	Lymphoma, CRC	40% ORR in folate-deficient tumors
GCS-100	GLDC	I	NSCLC	3/12 PRs in GLDC+ patients
SGR-2921	GlyT1	II	Glioma	Improved PFS when combined with TMZ

Glutamine Addiction in Proliferating Tumors: Metabolic Rewiring and Therapeutic Opportunities

Glutamine addiction represents a hallmark metabolic vulnerability across diverse cancer types, characterized by tumor cells' increased dependence on glutamine to fuel anabolic growth and maintain redox homeostasis. This metabolic reprogramming arises from oncogene-driven alterations in glutamine uptake and utilization, with cancer cells consuming glutamine at rates 10-100 times higher than their normal counterparts [40]. The molecular basis of glutamine addiction involves multiple intersecting pathways: (1) enhanced expression of glutamine transporters (particularly ASCT2/SLC1A5 and SN2/SLC38A5), (2) elevated activity of glutaminase (GLS) converting glutamine to glutamate, and (3) redirected flux through aminotransferases that incorporate glutamine-derived nitrogen into nucleotides, amino acids, and hexosamines [41]. Notably, MYC-driven tumors demonstrate particularly strong glutamine dependence, with MYC directly transactivating genes encoding glutamine transporters and metabolic enzymes while simultaneously suppressing miR-23a/b to relieve inhibition of mitochondrial glutaminase [42]. Similarly, KRAS-mutant cancers rewire glutamine metabolism to generate α-ketoglutarate (αKG) for maintaining TCA cycle intermediates (anaplerosis), with KRAS promoting the non-canonical utilization of glutamine through aspartate transamination [43].

The metabolic fates of glutamine in cancer cells reveal sophisticated compartmentalization and pathway diversification. Approximately 60-70% of intracellular glutamine is processed in mitochondria through glutaminase-mediated conversion to glutamate, which is subsequently transformed to αKG either via glutamate dehydrogenase (GLUD1) or aminotransferase reactions [44]. This mitochondrial αKG serves critical roles in: (1) replenishing TCA cycle intermediates lost to biosynthetic reactions (particularly citrate for lipid synthesis), (2) generating NADPH through isocitrate dehydrogenase (IDH)-mediated reductive carboxylation in hypoxic conditions, and (3) providing substrates for histone and DNA demethylases that regulate epigenetic state [45]. The remaining glutamine flux is partitioned between cytoplasmic pathways including: (1) nucleotide synthesis via CAD protein-mediated incorporation into purine and pyrimidine rings, (2) hexosamine pathway supporting protein glycosylation and O-GlcNAcylation, and (3) glutathione synthesis for antioxidant defense [46]. Recent single-cell metabolomics studies have revealed remarkable heterogeneity in glutamine utilization patterns, with tumor-initiating cells preferentially routing glutamine into nucleotide synthesis while bulk tumor cells favor TCA cycle replenishment [47].

Therapeutic targeting of glutamine metabolism has progressed through several generations of drug development. First-generation glutaminase inhibitors (e.g., BPTES and CB-839) demonstrated proof-of-concept in preclinical models but showed limited clinical efficacy due to metabolic plasticity and compensatory mechanisms [48]. Current strategies focus on: (1) combination therapies pairing glutaminase inhibition with drugs targeting parallel pathways (e.g., mTOR inhibitors to block adaptive mTORC1 activation), (2) dual targeting of glutamine uptake and utilization (e.g., ASCT2 inhibitors with GLS blockers), and (3) exploiting synthetic lethal interactions (e.g., glutaminase inhibition in KRAS-mutant tumors with MEK inhibitors) [49]. Emerging approaches include: (1) glutamine antagonist prodrugs (e.g., JHU-083 that selectively targets tumor glutamine metabolism), (2) inhibitors of glutamine-derived oncometabolites (e.g., D-2HG in IDH-mutant cancers), and (3) engineered enzymes to deplete circulating glutamine (e.g., PEGylated glutaminase) [50]. Clinical challenges persist, including: (1) identifying reliable predictive biomarkers (e.g., GLS expression levels, 13C-glutamine PET imaging), (2) managing systemic toxicity from glutamine depletion, and (3) overcoming microenvironmental compensation where stromal cells provide alternative nutrients.

The tumor microenvironment profoundly influences glutamine addiction through multiple mechanisms. Hypoxic regions exhibit increased glutamine uptake and reductive carboxylation, while nutrient-poor areas develop scavenging mechanisms including macropinocytosis of extracellular proteins. Cancer-associated fibroblasts (CAFs) engage in metabolic symbiosis, exporting glutamine-derived metabolites (e.g., ammonia, aspartate) that adjacent tumor cells repurpose, creating therapeutic resistance. Immune cells compete with tumor cells for glutamine in the microenvironment, with glutamine blockade potentially having dual effects on both tumor proliferation and anti-tumor immunity. Recent studies highlight circadian regulation of glutamine metabolism,

with tumor glutamine utilization peaking during rest phases in animal models, suggesting chronotherapeutic opportunities.

Glutamine Addiction in Proliferating Tumors: Metabolic Reprogramming and Therapeutic Vulnerabilities

Glutamine addiction has emerged as a defining metabolic feature of many aggressive cancers, reflecting tumor cells' remarkable ability to rewire nitrogen and carbon metabolism to support rapid proliferation. This phenomenon extends beyond mere increased glutamine consumption to encompass fundamental restructuring of cellular biochemistry, with glutamine serving as: (1) the primary nitrogen donor for nucleotide and amino acid biosynthesis, (2) a critical anaplerotic substrate for TCA cycle replenishment, and (3) a key regulator of redox homeostasis through glutathione production. The molecular drivers of this addiction involve coordinated upregulation of glutamine transporters (SLC1A5, SLC38A5), mitochondrial import proteins (SLC25A11, SLC25A12), and metabolic enzymes (glutaminase, glutamate dehydrogenase), creating a metabolic pipeline that can consume up to 30% of circulating glutamine in cancer patients. Oncogenic transcription factors like MYC and HIF-1α orchestrate this program through direct transcriptional activation of glutamine metabolic genes while simultaneously suppressing microRNAs (e.g., miR-23a/b) that normally constrain glutaminase expression. The resulting metabolic flux creates dependencies that differ fundamentally from normal cells, with tumor mitochondria often running "backward" TCA cycles that use reductive carboxylation of α-ketoglutarate to generate citrate for lipid synthesis.

The clinical manifestations of glutamine addiction reveal striking tissue-specific patterns. Hematologic malignancies frequently exhibit extreme glutamine dependence for asparagine synthesis, while solid tumors like triple-negative breast cancer and glioblastoma rely more heavily on glutamine's anaplerotic role [51]. KRAS-driven tumors display unique metabolic flexibility, capable of utilizing glutamine through both canonical (glutaminase-dependent) and non-canonical (transaminase-mediated) pathways [52]. Recent single-cell metabolomics has uncovered metabolic heterogeneity within tumors, with stem-like subpopulations showing preferential routing of glutamine into nucleotide synthesis while differentiated tumor cells favor glutathione production [53]. This metabolic compartmentalization extends to the tumor microenvironment, where cancer-associated fibroblasts (CAFs) engage in metabolic symbiosis by exporting ammonia and other glutamine-derived metabolites that adjacent tumor cells repurpose [54]. The resulting metabolic ecosystem creates both challenges and opportunities for therapeutic intervention, as different cellular compartments may require distinct targeting strategies.

Current therapeutic approaches to exploit glutamine addiction have evolved through three generations of development. First-generation glutaminase inhibitors like BPTES demonstrated proof-of-concept but suffered from poor pharmacokinetics [55]. Second-generation compounds like CB-839 showed improved bioavailability but revealed limitations due to metabolic plasticity and compensatory activation of alternative pathways [56]. Emerging third-generation strategies employ: (1) dual targeting of glutamine uptake and metabolism (e.g., SLC1A5 inhibitors with glutaminase blockers), (2) tissue-specific prodrugs (e.g., brain-penetrant DON analogs), and (3) synthetic lethal combinations with pathway inhibitors (e.g., PARP inhibitors in BRCA-mutant models) [57]. Clinical challenges remain significant, particularly in identifying reliable biomarkers for patient stratification and managing the complex systemic effects of glutamine modulation [58]. However, innovative approaches combining glutamine metabolism inhibitors with immunotherapy or tumor-specific metabolic probes (hyperpolarized 13C-glutamine MRI) are showing promise in early clinical trials [59].

The future of targeting glutamine addiction lies in understanding its integration with other metabolic and signaling networks. Key frontiers include: (1) elucidating circadian regulation of glutamine metabolism and its implications for chronotherapy, (2) exploring microbiome influences on systemic glutamine availability, and (3) developing nanotechnologies for tumor-selective glutamine depletion [60]. Fundamental questions remain about why certain tumors become "addicted" to glutamine while others maintain metabolic flexibility, and how the tumor microenvironment shapes these dependencies during progression and metastasis. As our understanding of cancer-specific glutamine metabolism deepens, so too does the potential for precision interventions that exploit this metabolic vulnerability while sparing normal tissues.

Therapeutic Implications and Challenges in Targeting Glutamine Addiction

Current Therapeutic Landscape

The development of glutamine metabolism inhibitors has progressed through several generations, each addressing limitations of prior approaches. First-generation glutaminase inhibitors like BPTES demonstrated proof-of-concept in preclinical models but were hampered by poor pharmacokinetic properties and limited tissue penetration. Second-generation compounds such as CB-839 (telaglenastat) showed improved bioavailability and entered clinical trials, revealing both promise and challenges - while demonstrating single-agent activity in subsets of renal cell carcinomas and triple-negative breast cancers, broader efficacy was constrained by adaptive metabolic rewiring in tumors . This experience highlighted the need for combination strategies and better patient stratification biomarkers.

Innovative Combination Approaches

Current clinical efforts focus on rational combinations to overcome resistance mechanisms:

- **Dual metabolic targeting**: Pairing glutaminase inhibitors with drugs blocking compensatory pathways like fatty acid oxidation (e.g., etomoxir) or glycolysis inhibitors (e.g., 2-deoxyglucose)
- **Synthetic lethality strategies**: Combining glutamine blockade with PARP inhibitors in BRCA-deficient models or MEK inhibitors in KRAS-mutant tumors
- **Immunometabolic combinations**: Leveraging glutamine restriction to enhance checkpoint inhibitor efficacy by reducing immunosuppressive myeloid cell populations Emerging preclinical approaches include:
- **Tissue-specific prodrugs**: Modified versions of historical glutamine antagonists (e.g., JHU-083 for CNS malignancies) designed to limit systemic toxicity
- **Nanoparticle delivery systems**: Encapsulating glutamine analogs in tumor-targeted carriers to improve therapeutic index
- **Microenvironment modulation**: Targeting stromal contributions to glutamine metabolism with TGF-β inhibitors or FAK inhibitors.

CONCLUSION

The intricate interplay between serine, glycine, and glutamine metabolism in cancer cells reveals both the remarkable adaptability of tumors and their inherent metabolic vulnerabilities. As this review has highlighted, these amino acids serve as critical nodes in a rewired metabolic network that supports nucleotide biosynthesis, redox homeostasis, and energy production in proliferating tumors. The molecular drivers of this reprogramming from oncogene-mediated upregulation of biosynthetic enzymes to tumor suppressor loss enabling metabolic flexibility present compelling targets for therapeutic intervention.

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