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The Role of L-Arginine in Digestive System Cancers: From Metabolism to Therapy

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Abstract

L-arginine metabolic reprogramming is a critical metabolic hallmark of digestive system malignancies, exerting dual roles in tumorigenesis and disease progression through intricate regulatory networks. This review systematically summarizes recent advances in the L-arginine metabolic axis within digestive system tumors. It covers key steps along this axis, including transmembrane transport mediated by the Solute Carrier (SLC) family, intracellular flux partitioning through the arginase (ARG) and nitric oxide synthase (NOS) pathways, and downstream polyamine biosynthesis. Particular emphasis is placed on gastric cancer (GC), colorectal cancer (CRC), and hepatocellular carcinoma (HCC). Pancreatic cancer is also preliminarily discussed. Our synthesis reveals tissue-specific arginine metabolic profiles across different digestive system tumors. In GC, systemic disturbances in arginine-derived metabolites are observed. CRC exhibits a high dependency on exogenous arginine uptake mediated by SLC3A2. HCC displays aberrant arginine accumulation, and the non-enzymatic functions of metabolic enzymes further contribute to tumor promotion in this context. Furthermore, this review elucidates that L-arginine, acting through upstream signaling nodes of the mTORC1 pathway, exerts bidirectional regulatory effects on both tumor growth promotion and antitumor immune response modulation. Metabolic imbalance not only promotes tumor progression via epigenetic modifications but also remodels the immune microenvironment to facilitate immune evasion. In light of this regulatory network, arginine deprivation therapy, arginase inhibitors, and immuno-metabolic combination strategies have emerged as promising therapeutic avenues. Nevertheless, tumor heterogeneity, compensatory metabolic activation, and the complexity of metabolic-immune crosstalk pose substantial challenges to clinical translation. To date, arginine-targeted strategies have not been estab-

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lished as standard-of-care regimens in digestive system malignancies. The majority of evidence derives from preclinical models and early-phase exploratory trials, and thus their efficacy and safety await validation in large-scale studies. Looking forward, the integration of multi-omics technologies, gene editing, and organoid models may offer a viable roadmap for advancing clinical translation. Such biomarker-guided, personalized combination regimens could facilitate the implementation of L-arginine metabolism-targeted therapies in precision oncology for digestive system malignancies.

Keywords

L-Arginine, Digestive System Malignancies, Metabolic Reprogramming, SLC Transporters, Arginine Deprivation Therapy, Biomarkers

1. Introduction

Digestive system malignancies, including gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), and pancreatic cancer, are leading causes of cancer-related mortality worldwide [1] [2]. Their initiation and progression are closely linked to metabolic reprogramming. L-arginine, a conditionally essential amino acid, plays a pivotal role in nitrogen metabolism, protein synthesis, and immune regulation [3]. The aberrant remodeling of its metabolic pathways during tumorigenesis and progression has increasingly become a focus of research.

In recent years, substantial attention has been directed toward the dysregulation of L-arginine metabolism in digestive system tumors. This metabolic imbalance not only affects tumor cell proliferation, survival, and susceptibility to ferroptosis [4], but also profoundly reshapes immune responses within the tumor microenvironment (TME) by inducing T-cell dysfunction [5] [6]. Notably, the metabolic profiles of L-arginine exhibit considerable heterogeneity across different digestive system malignancies [1] [2] [7], and this diversity may directly account for their differential responses to arginine-targeted therapeutic strategies. Moreover, arginine metabolism engages in intricate crosstalk with key signaling pathways such as mTOR, the tumor immune microenvironment, and epigenetic modifications [8]. The activation of compensatory metabolic circuits and the emergence of therapeutic resistance further impede the translation of these findings into clinical practice. Therefore, a comprehensive understanding of the central role of the L-arginine metabolic network in the initiation, progression, and immune evasion of digestive system malignancies holds substantial theoretical and clinical value for the development of targeted therapeutic approaches [5] [9].

Against this backdrop, the present review focuses on GC, CRC, and HCC, with a preliminary discussion on pancreatic cancer. Esophageal cancer and cholangiocarcinoma are not extensively covered, owing to the paucity of mechanistic studies, and await systematic review in future work. This review focuses on the meta-

bolic characteristics, regulatory mechanisms, and therapeutic targeting of L-arginine, while underscoring the clinical relevance of metabolic heterogeneity across different digestive system tumors. Additionally, we discuss key challenges and future directions in current research, aiming to provide a theoretical framework for the development of arginine metabolism-targeted antitumor strategies.

2. Core Molecular Mechanisms of L-Arginine Metabolism

The biological effects of L-arginine in digestive system malignancies are not mediated by a single pathway. Instead, they depend on the complete metabolic axis that encompasses transmembrane transport, intracellular flux partitioning, and downstream conversion (Figure 1). Aberrations affecting key molecular nodes within this axis provide the metabolic foundation for tumor survival and progression.

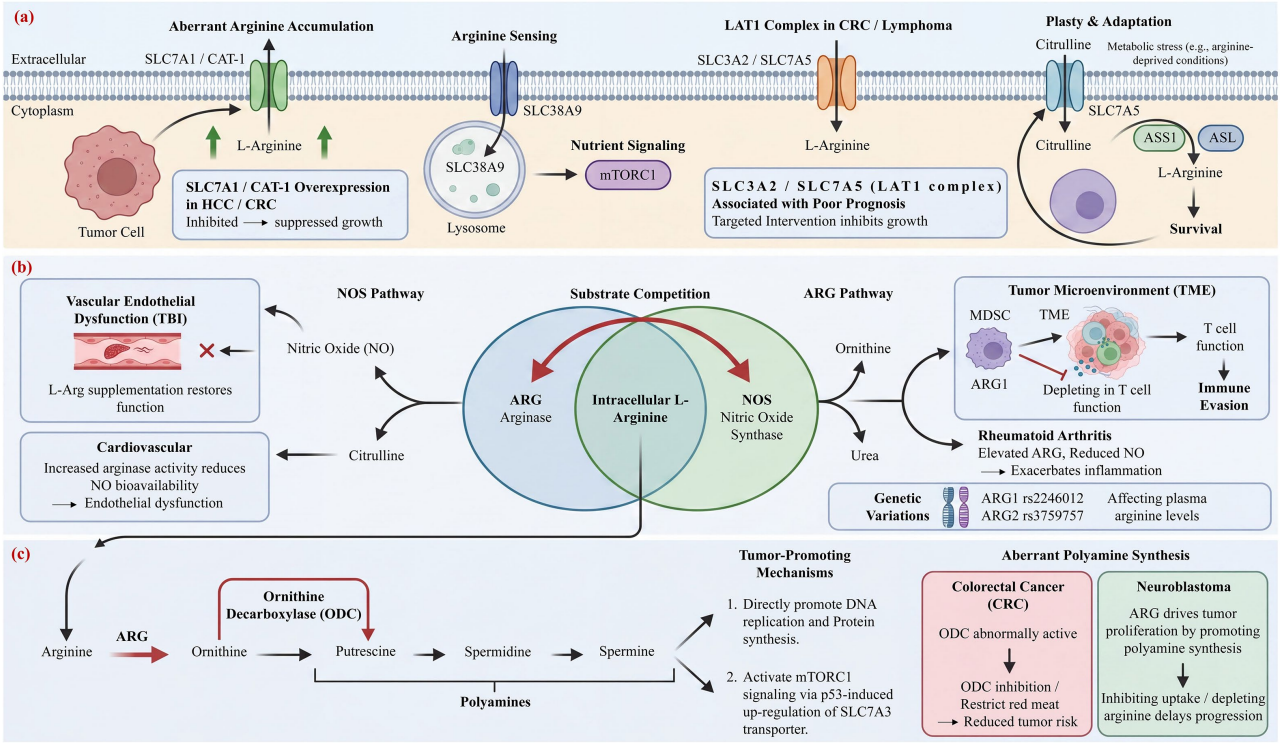

Figure 1. Core molecular mechanisms of L-arginine metabolism in cancer. (a) Transmembrane transport: arginine uptake mediated by the SLC family. (b) Intracellular partitioning: substrate competition and functional imbalance. (c) Downstream conversion: tumor-promoting effects of polyamine synthesis.

2.1. Transmembrane Transport: Solute Carrier (SLC) Family-Mediated Arginine Uptake

The intracellular bioavailability of L-arginine is a prerequisite for its biological functions and is governed by transmembrane uptake mediated by the SLC transporter family. In digestive system malignancies, multiple SLC family members are specifically overexpressed to meet the metabolic dependency of tumor cells on arginine (Figure 1(a)). For example, the cationic amino acid transporter SLC7A1

(also known as CAT-1) is overexpressed in both HCC and CRC. Its overexpression promotes aberrant arginine accumulation [2] [10]. In addition, inhibition of SLC7A1 significantly suppresses HCC growth both *in vitro* and *in vivo* [10]. Beyond mediating transmembrane arginine uptake, certain SLC members also participate in intracellular arginine sensing and signal transduction. For example, SLC38A9, located on the lysosomal membrane, is involved in sensing intracellular arginine and subsequently regulates nutrient signaling [2]. In addition, SLC3A2 and SLC7A5 form the LAT1 heterodimeric complex. In this complex, SLC7A5 mediates the transmembrane transport of substrates. SLC3A2 serves as an accessory subunit. It is essential for complex stability and membrane localization. Aberrant arginine uptake mediated by this complex in CRC is closely associated with poor prognosis, and targeted intervention significantly inhibits tumor growth [2] [11] [12]. Of note, the substrate specificity of these transporters for arginine varies among individual molecules. The direct evidence for their roles in digestive system tumors also differs. These distinctions should be taken into account when interpreting relevant studies. Furthermore, the plasticity of the SLC transport system represents a critical basis for tumor cells to adapt to metabolic stress and evade arginine-targeted therapies. Under arginine-deprived conditions, tumor cells can take up citrulline via the SLC7A5 transporter and convert it to arginine through intracellular argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL), thereby sustaining survival. Accordingly, inhibition of SLC7A5 may effectively block the growth of various cancer cell lines [13]. Furthermore, genetic variants can affect transporter function; for instance, the rs2720574 polymorphism in the SLC7A2 gene has been significantly associated with an increased risk of colorectal adenoma (OR = 1.36 − 1.73) [14].

It should be noted, however, that the aforementioned findings are predominantly derived from *in vitro* cell lines and xenograft tumor models. The former cannot fully recapitulate the metabolic competition among different cell types within the TME, while the latter may compromise the accuracy of arginine metabolic regulation owing to species differences. Moreover, genetic association studies, such as those on rs2720574, suggest potential pathogenic mechanisms. However, the effect sizes remain modest (OR < 2), and functional validation is still insufficient. Their clinical significance therefore warrants further elucidation. Therefore, despite the centrality of the SLC transporter family in modulating arginine bioavailability and therapeutic outcomes, the inherent limitations of the currently employed model systems substantially mitigate the translational relevance of existing evidence.

2.2. Intracellular Flux Partitioning: Substrate Competition and Functional Imbalance between the ARG and NOS Pathways

Once inside the cell, L-arginine is primarily channeled into two core pathways, namely arginase (ARG) and nitric oxide synthase (NOS), which engage in complex substrate competition (**Figure 1(b)**). Studies have shown that L-arginine de-

pletion resulting from elevated ARG activity, followed by reduced NO synthesis, represents a common mechanism of tissue damage across various disease states. However, when L-arginine supply is sufficient, substrate competition between the two pathways is not pronounced. Under such conditions, the activity of L-arginine transporters and the regulation of NOS by protein synthesis pathways become more critical determinants [15]. Within the TME, ARG1 is highly expressed in myeloid-derived suppressor cells (MDSCs), where it suppresses T-cell function through L-arginine depletion, thereby mediating immune evasion [5] [16]. Although this mechanism carries significant pathological implications, it should be noted that part of the supporting evidence derives from non-digestive disease models, including rheumatoid arthritis [17], traumatic brain injury [18], and cardiovascular diseases [19] [20]. The precise regulatory details may differ in digestive system tumors and thus warrant further validation. Genetic studies have indicated that polymorphisms in the ARG1 gene (rs2246012) and ARG2 gene (rs3759757) can influence plasma arginine levels [21], suggesting that genetic variants may endogenously modulate the balance of metabolic pathways. Nevertheless, their functional relevance in digestive system malignancies remains to be elucidated.

2.3. Downstream Conversion: Pro-Tumor Effects of the Polyamine Synthesis Pathway

ARG catalyzes the hydrolysis of L-arginine to L-ornithine, whereby this key precursor for polyamine biosynthesis is subsequently converted to putrescine by ornithine decarboxylase (ODC), and further to spermidine and spermine (**Figure 1(c)**) [22]. The ODC-catalyzed reaction represents the rate-limiting step of the polyamine synthesis pathway. As critical regulators of cell growth, polyamines drive tumor progression through a dual mechanism: they directly promote DNA replication and protein synthesis [23], while also activating mTORC1 signaling via p53-induced expression of the arginine transporter Slc3a7, thereby enhancing cancer cell survival under metabolic stress (**Figure 1(c)**) [24]. Aberrant polyamine synthesis carries significant pathological implications in digestive system tumors. In CRC, ODC-mediated polyamine synthesis is excessively active, and clinical evidence has demonstrated that ODC inhibition or restricted red meat intake significantly reduces tumor risk [2]. Animal studies further reveal that oral L-arginine administration markedly elevates total plasma polyamine levels, accompanied by altered arginine decarboxylase expression in the small intestine and liver [25]. These findings suggest that exogenous arginine supplementation directly fuels polyamine production. Cross-cancer analyses reinforce this association. In neuroblastoma, ARG2 drives tumor proliferation by promoting polyamine synthesis, whereas blockade of arginine uptake or direct arginine depletion retards tumor progression [26]. These findings provide experimental support for arginine deprivation therapy. Collectively, these findings indicate that targeting the arginase-polyamine synthesis axis holds potential as an anti-metabolic therapeutic strategy in digestive system malignancies.

3. Arginine Metabolic Features in Digestive System Tumors

Digestive system malignancies exhibit distinctive arginine metabolic reprogramming that is tissue-specific across tumor types and directly impacts tumor progression, microenvironment remodeling, and therapeutic responses (Figure 2).

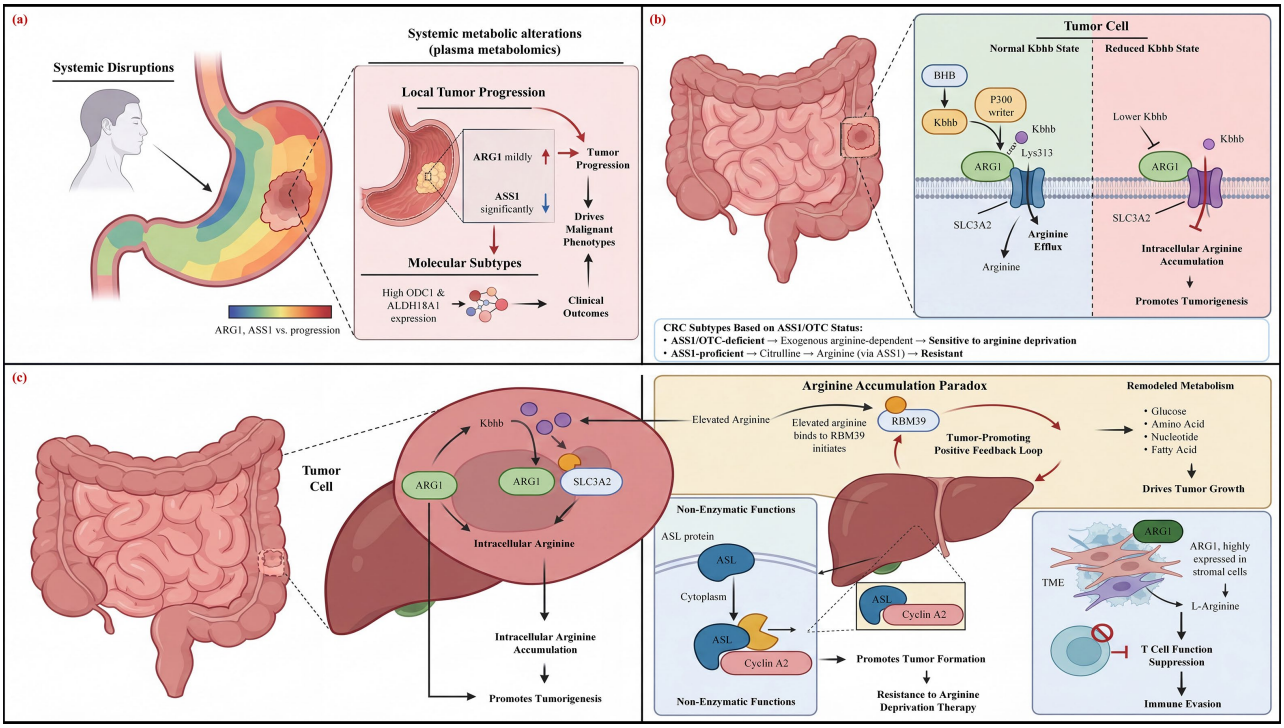

Figure 2. Metabolic characteristics of arginine in digestive system malignancies. (a) Gastric cancer: systemic arginine metabolic disturbances. (b) Colorectal cancer: dependence on SLC3A2-mediated arginine uptake. (c) Hepatocellular carcinoma: arginine accumulation and non-enzymatic functions of metabolic enzymes.

3.1. Gastric Cancer: Systemic Arginine Metabolic Disturbances

Patients with GC exhibit systemic disturbances in arginine metabolism (Figure 2(a)). Plasma metabolomic analyses show significantly reduced arginine, citrulline, and ornithine levels, with more pronounced depletion of citrulline and ornithine in metastatic GC [7]. These metabolites may thus serve as markers of disease progression. At the tissue level, ARG1 expression is mildly upregulated, whereas ASS1 is markedly downregulated, particularly in metastatic and cardia-subtype gastric cancers, and its expression level correlates negatively with local tumor progression [7]. Based on the expression profiles of arginine metabolism-related genes, GC can be classified into distinct molecular subtypes, among which high expression of genes such as ODC1 and Δ1-pyrroline-5-carboxylate synthase (ALDH18A1) drives the malignant phenotype [27] [28]. Clinical correlation analyses further indicate that patients with higher pretreatment plasma arginine levels or elevated ASS1 expression tend to have longer overall survival [29]. However, changes in plasma metabolites are not equivalent to local arginine availability within the tumor microenvironment. The true metabolic status of arginine in GC

tissues and its impact on T cell function still require direct validation using techniques such as tissue microdialysis, in situ metabolomics, or single-cell metabolic analysis. Notably, current research on arginine metabolism in GC relies predominantly on plasma metabolomics and tissue transcriptomics. The former is susceptible to confounding factors such as diet and gut microbiota. The latter, in contrast, cannot adequately capture the metabolic heterogeneity or intercellular interactions among different cell subsets within the tumor microenvironment. These subsets include tumor cells, immune cells, and stromal cells. Future studies should integrate single-cell metabolomics and spatial metabolomics to more precisely delineate the cell-type-specific features of arginine metabolism in GC tissues.

3.2. Colorectal Cancer: SLC3A2 Mediated Dependency on Arginine Uptake

CRC is metabolically characterized by a pronounced dependence on exogenous arginine. Notably, CRC exhibits marked intertumoral heterogeneity: a subset of cases harbors ornithine transcarbamylase (OTC) deficiency or loss of ASS1 expression, resulting in an arginine-auxotrophic phenotype. Consequently, these tumor cells are incapable of de novo arginine synthesis and become critically dependent on transporter-mediated uptake, primarily via SLC3A2, for arginine acquisition and survival (**Figure 2(b)**) [30]. Emerging evidence indicates that β-hydroxybutyrylation (Kbhb) of ARG1 plays an important regulatory role in CRC. Reduced Kbhb levels of ARG1 weaken its binding to SLC3A2, inhibit arginine efflux, result in intracellular arginine accumulation, and ultimately promote tumorigenesis [11]. Histone acetyltransferase p300, which functions as a "writer" of Kbhb, can be activated by β-hydroxybutyrate to enhance Kbhb modification of ARG1 at the Lys313 site, thereby facilitating arginine efflux [11]. Based on this metabolic dependency, arginine deprivation exhibits unique potential in ASS1/OTC-deficient CRC. It can not only induce CRC cells into a reversible quiescent state but also increase their susceptibility to ferroptosis. Combined treatment with ferroptosis inducers significantly potentiates the antitumor efficacy *in vivo* [4]. But it should be noted that the sensitivity to arginine deprivation depends on the ASS1/OTC status of CRC cells. For CRC subtypes that retain ASS1 expression, they can uptake citrulline and utilize endogenous ASS1 to synthesize arginine, thereby exhibiting intrinsic resistance to arginine deprivation therapy. Nevertheless, the current evidence is derived predominantly from *in vitro* cell lines and xenograft tumor models. A major limitation is that these systems cannot fully recapitulate the complexity of metabolic crosstalk within the TME or the intricacies of human arginine regulatory networks. Moreover, treatment responses may vary across different genetic backgrounds and tumor stages, and the underlying mechanisms of resistance warrant further investigation.

3.3. Hepatocellular Carcinoma: Arginine Accumulation and Non-Enzymatic Functions of Metabolic Enzymes

HCC exhibits a paradoxical arginine metabolic profile: despite reduced expression

of ASS1, a key enzyme in arginine biosynthesis, intracellular arginine levels are markedly elevated [1]. This aberrant state may arise from a dual mechanism involving enhanced uptake (e.g., upregulation of SLC7A [13]) and reduced consumption (impaired downstream polyamine conversion [1]) (**Figure 2(c)**). High levels of arginine bind to RNA-binding motif protein 39 (RBM39), initiating a pro-tumorigenic positive feedback loop that rewires glucose, amino acid, nucleotide, and fatty acid metabolism to drive tumor growth (**Figure 2(c)**) [1]. Beyond its canonical metabolic functions, the non-enzymatic activities of arginine metabolic enzymes are particularly prominent in HCC. ASL promotes tumorigenesis and confers resistance to arginine deprivation therapy through cytoplasmic interaction with cyclin A2 [31]. Meanwhile, high ARG1 expression within the TME depletes L-arginine and suppresses T-cell function, thereby mediating immune evasion (**Figure 2(c)**) [32]. In addition, one study found that ARG2-specific $CD8^+$ T cells are capable of recognizing and targeting ARG2-expressing regulatory T cells (Tregs) [16], suggesting that ARG2 may serve as a potential immunotherapeutic target. However, this finding directly pertains to Tregs rather than cancer cells, and its direct cytotoxic effect on $ARG2^+$ cancer cells remains to be further investigated. Collectively, these features lay the foundation for exploring arginine depletion therapies (e.g., arginine deiminase, arginase) in HCC. However, the causal relationship between arginine accumulation and low ASS1 expression in HCC remains unclear, and its directionality requires elucidation through temporal experimental models. Furthermore, whether the role of RBM39 as an arginine effector is restricted to HCC or also applies to other digestive system tumors awaits further validation.

3.4. Summary

In summary, GC, CRC, and HCC all exhibit L-arginine metabolic network dysregulation, yet adopt markedly different adaptive strategies. These include systemic arginine depletion in GC, exogenous uptake dependency in CRC, and arginine accumulation synergistically driven by non-enzymatic enzyme functions in HCC. These distinct patterns essentially reflect different metabolic dependencies evolved by tumor cells to withstand metabolic stress. However, these seemingly disparate phenotypes are not isolated; instead, they arise from extensive crosstalk between arginine metabolism, signaling pathways, epigenetics, and the immune microenvironment. This interactive network serves as the core regulatory hub that orchestrates tumor progression and immune evasion.

4. Key Regulatory Networks in Pathogenesis

To decipher how the above metabolic phenotypes drive malignant progression, it is essential to dissect the underlying regulatory network. Arginine metabolism is intimately integrated with signaling pathways, the immune microenvironment, and epigenetic modifications, constituting a complex hub that orchestrates tumor growth and immune evasion (**Figure 3**). This section systematically examines how

L-arginine, acting as a signaling molecule, modulates tumor cell proliferation, survival, and immune evasion.

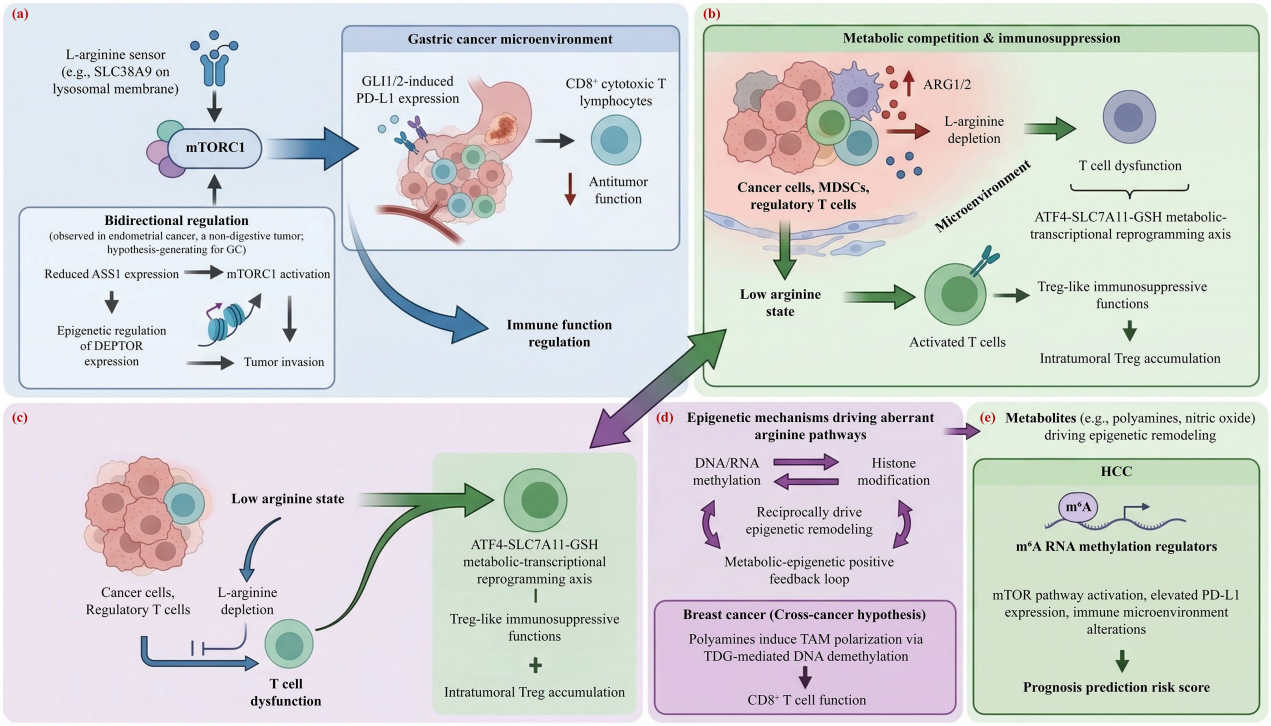

Figure 3. L-Arginine regulatory networks in the pathogenesis of digestive system malignancies. (a) mTOR signaling pathway and arginine sensing mechanisms. (b) Crosstalk between arginine metabolism and the tumor immune microenvironment. (c) Mechanisms of arginine deficiency in the tumor immune microenvironment. (d) Epigenetic mechanisms driving aberrant arginine metabolic pathways. (e) Regulatory pathways of m^{6}A RNA methylation in HCC.

4.1. mTOR Signaling Pathway and Arginine Sensing Mechanisms

L-Arginine not only serves as a metabolic substrate but also functions as a critical signaling molecule for the mTOR pathway, directly participating in the regulation of cellular metabolism and growth [33]. The molecular mechanisms by which L-arginine activates mTORC1 involve multiple levels of regulation. First, arginine binds to transporters such as SLC38A9 on the lysosomal membrane, altering the lysosomal membrane potential [34] [35]. Second, it can directly act on the Ragulator complex of mTORC1 to promote nucleotide exchange on Rag GTPases [35]-[37]. Third, in the absence of arginine, the CASTOR1 and GATOR1/2 complexes serve as sensors and exert inhibitory functions [38] [39]. This sensing mechanism is often constitutively activated in tumors due to aberrant expression of metabolic enzymes, and may exhibit tumor-type-specific differences, thereby providing diverse entry points for targeted intervention.

Within the TME, aberrant activation of mTOR signaling exerts multiple protumorigenic effects. In GC, the mTOR signaling pathway mediates GLI1/2-induced PD-L1 expression, thereby suppressing the antitumor function of CD8$^+$ cytotoxic T lymphocytes (**Figure 3(a)**). Conversely, the mTOR inhibitor rapamycin

can effectively reverse this immunosuppressive state [40]. Notably, the metabolic status of arginine and mTORC1 activity exhibit a bidirectional regulatory relationship. Reduced ASS1 expression activates mTORC1 signaling and promotes tumor invasion through epigenetic regulation of DEPTOR expression in endometrial cancer, a non-digestive system malignancy (**Figure 3(a)**) [41]. However, this finding is mainly from endometrial cancer models. Its applicability to gastric, colorectal, and hepatocellular cancers needs validation through digestive system tumor-specific studies. Here, we regard it as a valuable cross-cancer regulatory hypothesis that may point toward potential research directions. At the immune cell level, $CD8^+$ TIL effector function depends on the leucine-RagD-mTORC1 axis, wherein amino acid deprivation reduces mTORC1 activity and suppresses T-cell proliferation and cytokine secretion [42]. Collectively, these findings indicate that L-arginine, through the mTORC1 sensing machinery, simultaneously regulates tumor cell proliferation and T-cell function, constituting a central node in the metabolic-immune crosstalk network.

However, the differential responses of mTORC1 in tumor cells versus immune cells remain poorly understood. Direct validation is still needed to determine whether constitutive tumor mTORC1 activation depletes TME arginine through metabolic competition, thereby impairing T-cell mTORC1 signaling, using co-culture systems or in situ models. Furthermore, whether the regulatory pattern observed in endometrial cancer is generalizable to GC, CRC, and HCC awaits further substantiation by additional digestive system tumor-specific evidence.

4.2. Crosstalk between Arginine Metabolism and the Tumor Immune Microenvironment

Metabolic imbalance of arginine within the TME is a key driver of immunosuppression. Cancer cells, MDSCs, and Tregs highly express ARG1/2, depleting L-arginine in the microenvironment through metabolic competition and thereby inducing T-cell dysfunction (**Figure 3(b)**) [16] [32] [43]. Mechanistic studies have revealed that this low-arginine state drives activated T cells to acquire Treg-like immunosuppressive functions via the ATF4-SLC7A11-GSH metabolic-transcriptional reprogramming axis, which is positively correlated with intratumoral Treg accumulation (**Figure 3(b)** and **Figure 3(c)**) [44]. Based on the expression profiles of key arginine metabolic enzymes, tumors can be classified into two types: ARG1-positive tumors that are dependent on exogenous L-arginine, and those with high ASS1 expression that are capable of autonomous arginine synthesis. These two types exhibit markedly different immunomodulatory responses to arginine deprivation therapy [32]. CRC tissues exhibit a non-auxotrophic phenotype owing to ASS1 expression. However, clinical studies have shown that L-arginine supplementation neither reduces MDSC frequency nor ameliorates immunosuppression [45]. These observations underscore the value of metabolic subtyping in guiding immunotherapeutic strategies.

However, the causal link between low arginine and Treg-like functional acqui-

sition remains unconfirmed, as most current evidence comes from *in vitro* assays. Its physiological relevance within the TME therefore requires further validation using *in vivo* lineage-tracing or conditional knockout models. Moreover, systematic clinical evidence is still lacking regarding how arginine metabolic heterogeneity affects immune cell function in human tumors, as most studies are based on animal models. Thus, translating arginine-targeted interventions into clinical practice as immunotherapy enhancers will necessitate careful evaluation of their applicability and safety across distinct tumor metabolic subtypes.

4.3. Epigenetic Regulation of Metabolic Pathways

Epigenetic mechanisms are deeply involved in the aberrant regulation of arginine metabolic pathways, while metabolic products can in turn drive epigenetic remodeling, forming a metabolic-epigenetic positive feedback loop (**Figure 3(d)** and **Figure 3(e)**). In endometrial cancer (a non-digestive system tumor), reduced ASS1 expression activates mTORC1 signaling and promotes tumor migration and invasion through epigenetic regulation of DEPTOR expression (**Figure 3(a)**) [41]. Although this finding originates from a non-digestive system tumor, it suggests a regulatory paradigm that may be broadly conserved across cancer types. In this paradigm, altered metabolic enzymes drive signaling pathway aberrations via epigenetic reprogramming. Metabolites derived from arginine metabolism, including polyamines and NO, can directly participate in epigenetic modifications. In breast cancer (a non-digestive system tumor), polyamines induce tumor-associated macrophage polarization toward a pro-tumorigenic phenotype through TDG-mediated DNA demethylation, thereby suppressing $CD8^+$ T cell function (**Figure 3(d)**) [46]. This further supports the cross-cancer relevance of metabolite-driven epigenetic regulation. The above findings from breast and endometrial cancers suggest a potential mode of crosstalk between metabolites and epigenetic modifications. Nevertheless, direct corroborative evidence in digestive system malignancies is scarce. Therefore, dedicated investigations are required. These should target GC, CRC, and HCC specifically. In HCC, the expression of m^6A RNA methylation regulators is closely associated with mTOR pathway activation, elevated PD-L1 expression, and alterations in the immune microenvironment. A risk score based on these factors effectively predicts patient prognosis (**Figure 3(e)**) [47], suggesting that RNA epigenetic modifications may also participate in the regulation of arginine metabolism-related pathways.

Collectively, these findings indicate that metabolites arising from arginine metabolic dysregulation promote tumor immune evasion by driving both metabolic reprogramming and epigenetic modifications, including DNA/RNA methylation and histone modifications [9]. However, the current evidence regarding the causal links between metabolites and epigenetic alterations is largely derived from correlative analyses or *in vitro* intervention studies. The precise molecular channels through which metabolites traverse cellular and nuclear membranes to directly modulate epigenetic enzyme activity remain poorly defined. Moreover, whether the mechanistic insights obtained from non-digestive system tumors can be reca-

pitulated in GC, CRC, and HCC awaits validation by digestive system tumor-specific studies. Future investigations should systematically delineate the complete signaling cascade connecting metabolites, epigenetic modifications, and tumor phenotypes, which is a prerequisite for translating this regulatory network into actionable therapeutic targets.

5. Targeted Therapeutic Strategies

L-arginine metabolic reprogramming represents a unique therapeutic vulnerability in digestive system malignancies. Arginine deprivation, enzyme activity modulation, and immuno-metabolic combination strategies have shown efficacy in preclinical and early-phase clinical studies. Nevertheless, tumor heterogeneity, compensatory metabolic activation, and drug resistance remain the principal obstacles to clinical translation (Table 1).

Table 1. Therapeutic strategies targeting L-arginine metabolism.

Therapeuti Strategy	Mechanism of Action	Representative Agents/ Interventions	Clinical Advantages & Evidence	Key Challenges & Limitations	References
Arginine deprivation therapy	Degrades extracellular arginine, selectively killing arginine-auxotrophic tumor cells (ASS1/OTC deficient)	Pegylated arginine deiminase (ADI-PEG20), recombinant human arginase	1) Significantly prolongs progression-free survival in ASS1-deficient malignant mesothelioma (3.2 months vs. 2.0 months). 2) Exhibits anti-tumor activity against pancreatic cancer and other tumors.	1) Compensatory metabolic activation (e.g., ASS1 re-expression, activation of endogenous synthesis pathways). 2) Colorectal cancer responds poorly due to ability to synthesize arginine from citrulline. 3) Resistance is common.	[48]-[54]
Arginase inhibitors	Inhibit ARG1 activity, restore arginine levels in the TME, reverse immunosuppression, enhance chemosensitivity	CB1158, L-Norvaline, dual-target inhibitor OATD-02	1) Promotes T cell infiltration and prolongs survival of tumor-bearing mice. 2) Suppresses pro-survival signaling in multiple myeloma. 3) Synergizes with chemotherapeutic agents (e.g., oxaliplatin).	1) May antagonize the efficacy of certain chemotherapies (e.g., 5-FU). 2) Double-edged sword effect of autophagy increases complexity of regulation. 3) Requires precise assessment of tumor metabolic characteristics.	[5] [30] [57] [58] [60]
Immune checkpoint combination strategies	Enhances efficacy of immune checkpoint blockade through metabolic intervention, modulates the tumor immune microenvironment	L-Norvaline + ADI-PEG20; OATD-02 + PD-1/PD-L1 inhibitors	1) Significantly increases $CD8^+$ T cell infiltration and reduces immunosuppressive cells. 2) Enhances efficacy of PD-1 blockade in colon cancer models.	1) Arginine levels exert dual effects on immune cells: excessive deprivation suppresses T cell function, while high ARG1 expression in MDSCs exacerbates immunosuppression. 2) Requires individualized design of combination regimens.	[5] [53] [58] [59] [61] [62]

5.1. Clinical Translation of Arginine Deprivation Therapy and Compensatory Mechanisms

Arginine deprivation therapy primarily targets tumors that exhibit arginine auxotrophy due to deficiency of ASS1 or OTC expression. Clinical-grade agents, including pegylated arginine deiminase (ADI-PEG20) and recombinant human arginase, have demonstrated safety and antitumor activity in clinical trials by degrading extracellular arginine to selectively eliminate arginine-auxotrophic tumor cells [48] [49]. In pancreatic cancer, PEG-BCT-100 (a pegylated recombinant human arginase) combined with canavanine synergistically induces apoptosis in arginine biosynthesis enzyme-deficient pancreatic cancer cells. Patients with ASS1/OTC deficiency are more sensitive to this therapy [50]. Furthermore, a phase II trial in ASS1-deficient malignant pleural mesothelioma showed that ADI-PEG20 significantly extended median progression-free survival versus control (3.2 vs. 2.0 months; HR = 0.56, P = 0.03) [51].

However, the efficacy of arginine deprivation therapy is often constrained by compensatory metabolic pathway activation in tumor cells. Different tumor types exhibit distinct resistance mechanisms. In pancreatic ductal adenocarcinoma, microenvironmental arginine deficiency induces tumor cells to upregulate endogenous arginine biosynthesis pathways, maintaining intracellular arginine levels to evade elimination [52]. In HCC, aberrant arginine accumulation, through binding to RBM39, forms a pro-tumorigenic positive feedback loop that attenuates the effectiveness of deprivation therapy [1]. In CRC, arginine deprivation activates the AMPK-p53-p21 pathway to induce cell cycle arrest and, under certain conditions, sensitizes cells to ferroptosis, with synergistic antitumor effects when combined with ferroptosis inducers in CRC models [4]. Nevertheless, this metabolic stress response itself underpins tumor resistance. Clinically, re-expression of ASS1 following ADI-PEG20 treatment has been observed, further compromising sustained efficacy [53]. Moreover, as mentioned above, the response of CRC to arginine deprivation therapy is subtype-specific. It depends on the expression status of ASS1/OTC [30] [54]. This suggests that tissue-specific metabolic differences are a key factor that must be emphasized in clinical translation.

Notably, arginine supplementation and deprivation have fundamentally distinct indications. L-arginine supplementation enhances T-cell function and improves immune checkpoint blockade efficacy [55] [56], whereas deprivation therapy kills ASS1-deficient tumor cells metabolically [50] [51]. This differential efficacy essentially reflects the opposing effects of arginine on tumor cells versus immune cells. Therefore, supplementation and deprivation are applicable to distinct metabolic subtypes and treatment phases, and clinical decision-making should comprehensively evaluate both the tumor arginine nutritional phenotype and the immune microenvironment status. Furthermore, current clinical evidence is largely derived from small-scale or early-phase studies, and the efficacy of ADI-PEG20 in digestive system malignancies warrants confirmation in large-scale prospective trials.

5.2. Arginase Inhibitors and Combination Therapeutic Strategies

Unlike deprivation therapy, arginase inhibitors restore L-arginine levels within the TME, thereby reversing arginine depletion-induced immunosuppression and enhancing chemosensitivity. In colon cancer models, the dual-target inhibitor OATD-02 reduces polyamine levels and promotes T-cell infiltration, significantly prolonging survival in tumor-bearing mice [5]. In addition, in multiple myeloma (a non-digestive system malignancy), the arginase inhibitor CB1158 reverses arginine deficiency-induced pro-survival effects by inhibiting the mTORC2-AKT pathway and reducing intratumoral AKT phosphorylation [57]. This finding suggests that arginase inhibitors may have direct anti-tumor effects beyond immunomodulation. However, their applicability in digestive system tumors requires further validation. Furthermore, combination of the arginase inhibitor L-Norvaline with ADI-PEG20 markedly potentiates antitumor immune responses [58]. However, optimization of combination strategies must take into account tumor metabolic heterogeneity and activation of compensatory pathways [59]. Preclinical studies have shown that ADI-PEG20 acts synergistically with oxaliplatin in ASS1-negative CRC cells, whereas arginase inhibition may antagonize the efficacy of oxaliplatin and 5-fluorouracil [30]. Although ASS1-deficient tumors are sensitive to arginine deprivation, they can be rescued by uptake of L-citrulline, indicating a partial arginine prototrophic phenotype [60]. Therefore, the design of combination regimens should be guided by precise assessment of tumor metabolic characteristics.

5.3. Metabolic Modulation Strategies for Immune Checkpoint Blockade

The profound crosstalk between arginine metabolism and the tumor immune microenvironment provides a theoretical basis for combination immunotherapy. In colon cancer models, OATD-02 enhances T-cell activation through metabolic reprogramming and significantly potentiates the efficacy of PD-1/PD-L1 blockade [5]. L-Norvaline combined with ADI-PEG20 increases tumor-infiltrating $CD8^+$ T cells and $CCR7^+$ dendritic cells while reducing immunosuppressive monocytes and macrophages, and this synergistic effect is dependent on an intact immune system [58]. Moreover, studies based on small cell lung cancer models (a non-digestive system tumor) suggest that arginine deprivation therapy combined with PD-1/PD-L1 inhibitors may improve clinical outcomes [61]. However, the efficacy and safety of this strategy in digestive system tumors require further validation. With respect to nutrient supplementation strategies, L-arginine supplementation increases the proportion of tumor-peptide-specific $CD8^+$ T cells in tumor-draining lymph nodes and potentiates the efficacy of cyclophosphamide combined with anti-PD-1 antibody [55]. When delivery efficiency is enhanced via nanocarrier systems, combination with anti-PD-L1 therapy significantly remodels the TME. This is reflected by increased tumor-infiltrating T cells, reduced MDSCs, and M1-type macrophage polarization, which ultimately prolongs

survival in tumor-bearing mice [56]. Collectively, these findings indicate that arginine-targeted interventions, whether through deprivation, enzyme inhibition, or nutritional supplementation, hold synergistic potential with immune checkpoint blockade.

The impact of arginine on immune cell function is dual-edged. On one hand, MDSCs suppress T-cell function by depleting microenvironmental arginine via ARG1, and arginine deprivation therapy may exacerbate this state [53] [59]. On the other hand, immune-mediated tumor killing also relies on adequate arginine supply [62]. Therefore, combination strategies should be tailored to tumor arginine dependence. In ARG1-high immunosuppressive tumors, arginase inhibitors plus immune checkpoint blockade may be preferred. In ASS1-deficient tumors, however, the potential immunosuppressive effects of arginine deprivation warrant careful evaluation. However, these individualized strategies face multiple obstacles. Current evidence is largely derived from animal models, and clinical trials of OATD-02 are still ongoing. Its efficacy in patients with digestive system malignancies therefore remains to be confirmed. Arginine plays essential physiological roles in vascular endothelial maintenance, immune homeostasis, and nitrogen metabolism [3]. Systemic depletion may exert off-target effects on the cardiovascular, nervous, and immune systems [3], but these non-target toxicities have not been systematically assessed. Furthermore, published studies may be subject to positive outcome bias. Therefore, clinical translation will require comprehensive evaluation of metabolic subtypes, safety profiles, and levels of evidence on an individualized basis, in order to define the appropriate patient population and the benefit-risk ratio.

6. Challenges and Perspectives

6.1. Current Core Challenges

Despite the promising prospects of arginine-targeted therapeutic strategies in digestive system malignancies, multiple challenges remain. First, tissue-specific metabolic differences complicate intervention: HCC with arginine accumulation and pro-tumorigenic reprogramming [1]; CRC with transporter overexpression and polyamine synthesis [2]; and GC with systemic metabolite disturbances [7]. This metabolic heterogeneity argues against a one-size-fits-all therapeutic strategy, necessitating individualized regimens based on tumor metabolic profiles. Second, activation of compensatory metabolic pathways represents a core mechanism of resistance to arginine deprivation therapy. When arginine is depleted, tumor cells sustain homeostasis via endogenous synthesis [52], transporter upregulation [13], and metabolic reprogramming [1], or may enter reversible quiescence to resist treatment [4]. Third, the complexity of metabolic-immune crosstalk remains to be fully elucidated. Arginine deprivation exerts dual effects on immune cells; autophagy in this context can either promote tumor cell death or mediate immune evasion and therapeutic resistance [60], and potential drug antagonism may exist in combination regimens [30]. More fundamentally, a translational gap

exists between preclinical models and human tumors, as cell lines and xenograft models cannot fully recapitulate the human TME, potentially leading to overestimation of therapeutic efficacy. Clinical trials of OATD-02 are still ongoing [5], and its true efficacy awaits confirmation. Addressing these challenges will require deeper mechanistic investigations and large-scale randomized controlled trials.

6.2. Multi-Omics Integration and Precision Subtyping

A comprehensive understanding of the complexity of the arginine metabolic network will require systematic integration of multi-omics technologies. Combined metabolomic and transcriptomic analyses have already been applied to identify diagnostic metabolites and molecular subtype-related gene expression profiles in GC [7]. However, current studies are largely based on bulk tissue analyses, which cannot resolve the metabolic heterogeneity among distinct cell subsets within the TME. This limitation is critical, as tumor, immune, and stromal cells may differ fundamentally in arginine uptake, utilization, and metabolic competition, and these interactions may profoundly affect therapeutic responses. Future efforts should incorporate single-cell metabolomics to generate high-resolution maps for targeted metabolic interventions. In addition, the role of epigenetic modifications in regulating arginine metabolism warrants further exploration. Previous studies have preliminarily revealed associations between m^6A modifications and both the mTOR pathway and the immune microenvironment in HCC [63]; however, their specific functions in arginine metabolic regulation remain unclear. Future investigations should integrate epitranscriptomics with metabolic flux analysis to systematically elucidate how RNA modifications participate in the dynamic remodeling of metabolic networks. Concurrently, the potential roles of non-coding RNAs in regulating metabolic enzymes and transporters require further elucidation through epigenomic approaches [64]. The integration of these multi-omics data will facilitate the construction of a dynamic regulatory atlas of arginine metabolism and provide a theoretical foundation for the identification of precision therapeutic targets.

6.3. Gene Editing and Organoid Modeling Strategies

To elucidate the regulatory mechanisms of key molecules in L-arginine metabolism, it is necessary to establish more precise gene editing models and organoid platforms. Key priorities include using CRISPR-Cas9 to knock out/overexpress arginine metabolic enzymes (ASS1, ASL, ODC1) and transporters (SLC3A2, SLC6A14), and validating their roles in tumorigenesis, metastasis, and drug resistance in digestive cancers [2] [27] [31]. For instance, it is essential to recapitulate in animal models the ASL overexpression-induced resistance phenotype to arginine deprivation therapy [31], and to explore the impact of RBM39 mutations on arginine-mediated metabolic reprogramming [1]. However, animal models cannot fully reproduce the heterogeneity and microenvironmental features of human tumors, a limitation that compromises the predictive validity of preclinical

findings for clinical translation. The establishment of organoid models offers a valuable tool to address this critical issue. Organoids preserve the heterogeneity, cellular composition, and partial microenvironmental features of original tumors, enabling dynamic monitoring of tumor cell adaptation to arginine-targeted interventions. Future efforts should focus on developing organoid platforms that recapitulate the molecular subtypes of GC [27] and ferroptosis sensitivity in CRC [4]. Such platforms would facilitate evaluation of gene editing and drug efficacy, and provide novel experimental systems to overcome therapeutic resistance.

6.4. Personalized Metabolic Intervention and Combination Therapeutic Strategies

Given the heterogeneity of arginine metabolism across tumors, future efforts should develop biomarker-guided individualized intervention strategies. First, patients should be stratified by ASS1 expression: ASS1-deficient tumors are candidates for arginine deprivation (e.g., ADI-PEG20) [48] [65] [66], whereas ASS1-proficient tumors may benefit from L-arginine supplementation plus immunomodulation [32] [62]. This metabolism-based stratification strategy holds promise for improving therapeutic efficacy while minimizing unnecessary toxicity. Second, combination regimens should be designed by integrating multi-omics data, such as arginine deprivation combined with ferroptosis inducers in CRC [4], or dual-target arginase inhibitors plus immune checkpoint blockade [5]. Optimization of combination strategies should not rely solely on single-agent activity, but must be grounded in a systematic understanding of tumor metabolic profiles, compensatory pathways, and cellular stress responses. Specifically, three dimensions should be comprehensively evaluated, namely metabolic dependency, compensatory plasticity, and drug-drug interaction profiles. Metabolic dependency refers to the determination of sensitivity to deprivation therapy by ASS1 expression status [48] [65] [66]; compensatory plasticity involves the activation of the citrulline salvage pathway and autophagic stress responses [60]; and drug-drug interaction profiles concern the context-dependent balance between synergy and antagonism [30].

6.5. Industrial Prospects and Clinical Translation

The industrial prospects of arginine metabolism-targeted therapies should focus on the development of novel agents and the optimization of delivery systems. Notably, the phase I/II clinical trial of OATD-02 (NCT05759923) is currently ongoing [5], marking a transition of arginine-targeted therapy from proof-of-concept to clinical evaluation. In addition, nanocarrier technologies offer significant potential to enhance therapeutic precision. For example, calcium peroxide nanoparticles loaded with L-arginine enable controlled nitric oxide release and ferroptosis induction [67], while functionalized L-arginine derivatives, via self-assembling carriers, enable efficient delivery of therapeutic proteins and exhibit potent growth-inhibitory effects in cancer cell lines [68]. The development of such ad-

vanced delivery systems may overcome the limitations of conventional administration and improve the therapeutic index.

Preclinical evidence has further expanded the potential applications of arginine-targeted therapies. Systemic arginine depletion mediated by pegylated arginase (pegzilarginase) not only directly suppresses tumor growth but also promotes $CD8^+$ T-cell infiltration and enhances immune responses [69]. Moreover, arginine deprivation enhances radiosensitivity in ASS1-deficient pancreatic cancer [70], suggesting that combination of arginine metabolism-targeted intervention with radiotherapy warrants further investigation. However, sensitivity to arginine deprivation varies across tumor subtypes, and arginase inhibition may antagonize the efficacy of chemotherapeutic agents such as 5-FU [30]. Future large-scale clinical trials are needed to validate the feasibility of combination strategies and to establish biomarker-based patient stratification models (e.g., based on ASS1 expression) to optimize therapeutic outcomes. Concurrently, the potential impact of arginine metabolism-targeted interventions on normal tissues should be carefully monitored to ensure treatment safety.

7. Conclusions

In summary, L-arginine metabolism plays a central regulatory role in the development, progression, and immune evasion of digestive system malignancies. However, the current therapeutic evidence in this field is largely derived from preclinical models and early-phase exploratory trials, and no standard treatment regimen has yet been established for digestive system malignancies. Existing studies indicate that GC, CRC, and HCC exhibit distinctly different adaptive patterns of arginine metabolism. This tissue-specific heterogeneity means that arginine-targeted strategies require biomarker-guided patient stratification, such as ASS1/OTC status, for effective individualized therapy. Notably, a significant gap remains between current research advances in arginine metabolism and their clinical translation. On one hand, the efficacy data from preclinical models need to be validated in digestive system tumor-specific clinical trials. On the other hand, many regulatory hypotheses proposed in non-digestive system tumors (e.g., findings from endometrial and breast cancers) still require confirmation or refinement through digestive system tumor-specific studies. Therefore, the path from proof-of-concept to clinical practice for arginine metabolism-targeted therapy requires systematic translational research.

Looking ahead, multi-omics integration will enable deeper analysis of arginine metabolic heterogeneity specific to digestive system tumors. Gene editing approaches and organoid models will enable functional validation of key molecular targets. These efforts will support the development of biomarker-guided personalized combination strategies. Collectively, these advances are expected to drive the scientific and prudent clinical translation of arginine metabolism-targeted therapies. Progress in this field will deepen our understanding of tumor metabolic reprogramming. It may also offer novel therapeutic avenues for patients with di-

gestive system cancers. Nevertheless, the ultimate clinical utility of these strategies remains to be established through large-scale, rigorously designed clinical trials.

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Author's Note

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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