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Urea cycle dysregulation: a new frontier in cancer metabolism and immune evasion

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Abstract

Cancer cells experience metabolic reprogramming to enhance the synthesis of nitrogen and carbon, facilitating the production of macromolecules essential for tumor proliferation and growth. A central strategy in this process involves reducing catabolic activities and managing nitrogen, thereby improving the efficiency of nitrogen utilization. The urea cycle (UC), conventionally recognized for its role in detoxifying excess nitrogen in the liver, is pivotal in this metabolic transition. Beyond the hepatic environment, the differential expression of UC enzymes facilitates the utilization of nitrogen for the synthesis of metabolic intermediates, thereby addressing the cellular metabolic requirements, especially under conditions of nutrient scarcity. In oncogenic contexts, the expression and regulation of UC enzymes undergo substantial modification, promoting metabolic reprogramming to optimize nitrogen assimilation into cellular biomass. This reconfigured UC not only enhances tumor cell survival but also plays a pivotal role in the reorganization of the tumor microenvironment (TME), thereby aiding in immune evasion. This review examines the mechanistic underpinnings of urea cycle dysregulation (UCD) in cancer, highlighting its dynamic roles across various tumor types and stages, as well as the therapeutic implications of these alterations. Understanding how UC relaxation promotes metabolic flexibility and immune evasion may help develop novel therapeutic strategies that target tumor metabolism and enhance anti-cancer immunity.

Keywords Urea cycle, Cancer metabolism, Metabolic reprogramming, Tumor immunogenicity, Cancer treatment

Introduction

Cancer cells exhibit extensive metabolic reprogramming processes that facilitate cancer proliferation and survival in adverse tumor microenvironments (TME) [1–4]. Among the various metabolic alterations observed, dysregulation of the urea cycle (UCD) has emerged as a critical characteristic of numerous malignancies, exerting a significant impact on cancer cell metabolism and the TME [5, 6]. The urea cycle (UC) is indispensable for maintaining nitrogen homeostasis and promoting ammonia detoxification under typical physiological conditions [6, 7]. However, the UC has been reprogrammed in cancer cells, shifting from its detoxification role to supporting metabolic growth and immune escape [6–10]. A growing body of research provides evidence that the

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expression and activity of UC-associated enzymes are significantly altered across various cancer types [11]–[12]. These alterations result in the accumulation of intermediate metabolites, which are subsequently redirected to fuel biosynthetic pathways, thereby facilitating tumor progression [12–17].

In addition to facilitating anabolic processes, UCD significantly influences the immunological environment of tumors [4, 18]. The TME is a complex ecosystem comprising cancer cells, stromal cells, and immune cells, all of which participate in dynamic metabolic interactions [1–4]. Metabolites of the UCD, including arginine, ornithine, and citrulline, have significant immunomodulatory effects [18–21]. Arginine is a critical substrate for regulatory T-cells (Tregs) function, and its depletion in the TME—often due to argininosuccinate synthetase 1 (ASS1) downregulation—results in impaired Tregs proliferation and activation, thus weakening the antitumor immune response [1–3]. Additionally, the accumulation of ornithine and its downstream metabolites, such as polyamines, promotes the activity of immunosuppressive cells, including Tregs and myeloid-derived suppressor cells (MDSCs), further contributing to immune evasion [4–7].

The complex interplay between urea cycle dysregulation, metabolic reprogramming, and immune modulation poses both challenges and opportunities for therapeutic intervention. Targeting key enzymes in the urea cycle represents a promising strategy to disrupt the metabolic dependencies of cancer cells, while simultaneously modulating the immune TME to enhance antitumor immunity [8–11]. Recent research has emphasized the potential of therapeutic strategies, including arginine depletion via pegylated arginine deiminase (ADI-PEG20) and the integration of metabolic inhibitors with immune checkpoint inhibitors, to enhance the therapeutic effect [22–24]. Nonetheless, the plasticity of tumor metabolism and the presence of compensatory pathways present substantial challenges that need to be addressed to optimize the efficacy of these therapeutic interventions.

Herein, we highlight the adaptable roles of UC intermediates and byproducts in cancer, and the changes in UC components that drive this metabolic shift. This insight could lead to new therapies targeting weaknesses from UC deregulation in tumors.

UCD and its impact on Cancer metabolism

Overview of the UC

The contributions of Hans Krebs to the biochemistry field are incontrovertible, especially regarding the investigation of urea synthesis [25, 26]. In 1932, in collaboration with his colleague Kurt Henseleit, he elucidated that in the presence of ammonium salts, the introduction of ornithine to slices of animal liver tissue markedly increased urea production [25].

In this context, research on the UC has progressed substantially, elucidating the pivotal role of ammonia metabolism and excretion in maintaining nitrogen homeostasis within the body. The UC serves as the primary pathway for nitrogenous waste processing in mammals, and its proper functioning is crucial for preventing ammonia accumulation [17, 25, 26]. The metabolic activity of the UC is regulated at multiple levels to accommodate the organism's diverse physiological demands. At the transcriptional level, elevated ammonia levels can induce the expression of carbamoyl phosphate synthetase I (CPS1), ASS1, and ARG1 through C/EBP family transcription factors [27, 28]. Moreover, hormones such as glucagon and insulin influence the activity of UC enzymes by modulating the expression of their respective related genes [29–31]. Within the mitochondria, N-acetylglutamate (NAG), a vital activator of carboxy phosphate synthase 1 (CPS1), is synthesized in response to dietary protein intake and ammonia concentrations [32–35]. Additionally, post-transcriptional and post-translational regulatory mechanisms play a significant role in maintaining the dynamic equilibrium of the UC [36, 37]. For example, small RNAs, such as miRNA-23b, can downregulate ASS1 protein expression by targeting its mRNA, thereby reducing urea biosynthesis [27, 36]. These regulatory mechanisms play a collective role in ensuring the metabolic adaptability of the UC under both physiological and pathological conditions.

Disruption of UC functionality can result in excessive ammonia accumulation, leading to hyperammonemia, a condition closely linked to neurotoxicity, hepatic encephalopathy, and other pathological manifestations [10, 34]. Congenital UCDs are frequently caused by mutations in genes such as CPS1, ornithine transcarbamylase (OTC), ASS1, or argininosuccinate lyase (ASL), resulting in the abnormal accumulation of ammonia and intermediate metabolites [32, 38, 39]. Furthermore, defects in SLC25A13 (citrin) or ORNT1 can impair the transmembrane transport of intermediates, exacerbating metabolic imbalances [35, 40, 41]. In patients with chronic liver disease, the reduced metabolic capacity of the UC significantly increases the risk of hepatic encephalopathy and ammonia toxicity [39].

The UC comprises five primary enzymes and at least two crucial transport proteins [8, 35] (Fig. 1). The process begins with CPS1 catalyzing the conversion of ammonia and bicarbonate into carbamoyl phosphate (CP) within the mitochondrial matrix. This reaction is activated by NAG, synthesized by N-acetylglutamate synthase (NAGS) [35, 42–44]. After that, OTC facilitates the reaction between CP and ornithine, resulting in the production of citrulline, which also occurs in the mitochondria

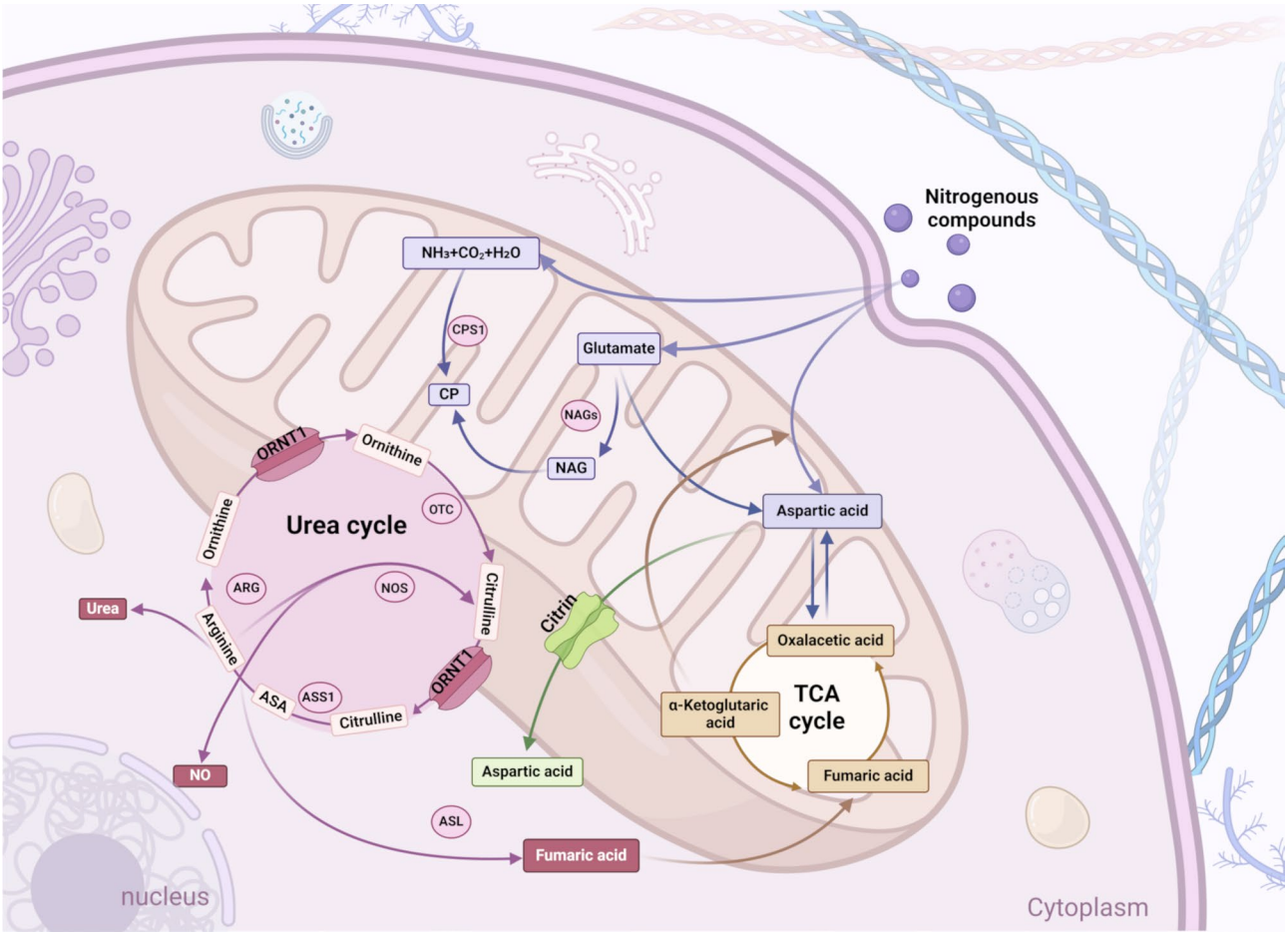

Fig. 1 Overview of the urea cycle. The urea cycle (UC) represents the principal biochemical pathway for nitrogen excretion. This process is initiated within the mitochondrial matrix, where carbamoyl phosphate synthetase I (CPS1) facilitates the synthesis of carbamoyl phosphate (CP) from ammonia, carbon dioxide, and water. Subsequently, ornithine transcarbamylase (OTC) catalyzes the conversion of CP and ornithine into citrulline, which is then translocated to the cytoplasm. Within the cytoplasmic compartment, argininosuccinate synthetase (ASS1) incorporates an additional nitrogen atom from aspartate to synthesize argininosuccinate. The enzyme argininosuccinate lyase (ASL) then cleaves argininosuccinate to yield fumarate and arginine. Finally, arginase (ARG) hydrolyzes arginine to generate urea and regenerate ornithine, thereby completing the cycle

[26]. In the cytosol, ASS1 mediates the ATP-dependent condensation of citrulline and aspartate, leading to the synthesis of argininosuccinate [14]. Subsequently, ASL catalyzes the cleavage of argininosuccinate into arginine and fumarate. The cycle concludes with arginase (ARG) hydrolyzing arginine to produce urea and ornithine [23, 24, 45]. The urea is excreted, while ornithine is transported back into the mitochondria for reuse [7].

In extrahepatic tissues, intermediates of the UC perform a variety of functions. The transporters citrin and ORNT1 play crucial roles in the translocation of citrulline and ornithine across the mitochondrial membrane [28, 34]. Citrin is a vital component of mitochondrial metabolism, facilitating the import of glutamate into the mitochondrial matrix and the export of aspartate into the cytosol. Conversely, ORNT1 is specifically responsible for the transport of ornithine [28, 34]. Arginine acts as a key precursor for nitric oxide synthesis, whereas ornithine is involved in polyamine biosynthesis, and citrulline can be converted back into arginine in some tissues, primarily the kidney [8, 17].

Tumor cells undergo metabolic reprogramming to adapt to the demands of rapid proliferation and microenvironmental regulation. Tumors retain arginine by suppressing ARG activity to support polyamine synthesis and protein translation [8, 28]. Concurrently, the downregulation of ASS1 inhibits the conversion of citrulline and aspartate, ensuring the availability of metabolites for NO synthesis and tumor angiogenesis [8]. This metabolic remodeling not only enhances tumor cell survival but also influences the tumor immune microenvironment by modulating immune cell function.

Furthermore, tumor-associated UC reprogramming, coupled with the tricarboxylic acid (TCA) cycle, enhances the metabolic adaptability of tumor cells [26, 29, 32]. For example, fumarate serves as a critical junction

between the UC and TCA cycle, not only supplying carbon backbones to tumor cells but also enhancing cellular adaptability by modulating the stability of HIF-1α [25, 29]. These mechanisms indicate that targeting the metabolic remodeling of the UC could represent an innovative strategy for anti-tumor therapy. Importantly, in tumor subtypes characterized by low ASS1 expression, therapeutic strategies involving the supplementation of citrulline or arginine to attenuate tumor progression show considerable promise.

Cancer-Specific reconfiguration of UC enzymes and metabolites

Metabolic roles of proximal UC enzymes and intermediates

The proximal enzymes of the UC are integral to the initial stages of pathways that contribute to broader metabolic processes. Notably, CPS1 and OTC, which are localized within the mitochondrial matrix, are pivotal in the regulation of ammonia and glutamine assimilation pathways [25]. CPS1 facilitates the accumulation of ammonia, which is subsequently utilized for the synthesis of glutamine. As a critical nitrogen donor, glutamine is indispensable for protein, nucleotide, lipid, and antioxidant biosynthesis, thereby fueling tumor proliferation [28, 33]. The reliance on glutamine for proliferation and growth is recognized as a hallmark of cancer cell metabolism [15, 29]. Tumor cells acquire glutamine from their environment through various mechanisms, including transport proteins, macropinocytosis, and extracellular vesicles [15, 29].

CPS1 facilitates cell survival by converting nitrogen from ammonia into pyrimidine metabolites; its downregulation can result in pyrimidine deficiency, DNA damage, and subsequent T-cell death [28, 33]. Research studies suggest that Liver kinase B1 (LKB1) inhibits CPS1 transcription via AMPK, but co-occurring KRAS mutation and LKB1 loss led to CPS1 overexpression, thereby upregulating the pyrimidine synthesis pathway and promoting tumor proliferation [28, 32, 39]. The expression of the NAGS and CPS1 genes is upregulated in glioblastoma, glioma, and stomach adenocarcinoma (STAD) [33–35, 44, 45]. High NAGS expression is linked to poor prognosis in glioblastoma patients, whereas low NAGS expression is associated with adverse outcomes in lung adenocarcinoma patients [34–36]. Nevertheless, even if NAGS is insufficient, CPS1 may continue to drive tumorigenesis through metabolic reprogramming [28, 36].

CPS1 expression and function in cancer are influenced by multiple factors. Studies have shown that CPS1 may be affected by KRAS and LKB1 gene mutations in non-small cell lung cancer (NSCLC) [28]. In cells with simultaneous mutations in KRAS and LKB1, CPS1 expression is negatively correlated with LKB1 [28]. LKB1 inhibits CPS1 transcription through AMPK, and the silencing of CPS1 leads to cell death and reduced tumor growth [28]. This suggests that CPS1 may be a metabolic vulnerability in certain aggressive subtypes of NSCLC.

Additionally, in STAD, elevated expression levels of NAGS, CPS1, and Citrin facilitate tumor cell proliferation by augmenting the production and supply of NAG and aspartate [33, 35]. However, throughout the Correa cascade of gastric carcinogenesis, CPS1 expression is progressively downregulated, with a pronounced reduction observed in intestinal-type gastric cancer. This diminished CPS1 expression is closely correlated with tumor progression, increased invasion depth, and poorer overall survival, indicating that CPS1 may serve as a potential prognostic biomarker for patients with gastric cancer [33]. Furthermore, CPS1 expression is significantly reduced in small intestine adenocarcinoma and hepatocellular carcinoma (HCC), likely due to hypermethylation of its promoter region [35, 39, 42]. Treatment with demethylating agent 5-nitrocytidine can restore CPS1 expression in HCC cells. This suggests that DNA methylation is a key mechanism for inhibiting CPS1 expression in HCC, and high methylation of the CPS1 gene may become a potential biomarker for HCC [46]. Additionally, CPS1 downregulation is associated with adverse clinical outcomes, including lymphatic infiltration and decreased survival [39, 44]. In CPS1-deficient HCC, the disruption of the UC leads to the activation of fatty acid oxidation (FAO), which provides energy for tumor cells, enhances their proliferation, and confers resistance to chemotherapy [43]. During the recurrence and metastasis of HCC, CPS1 expression was further downregulated, while CAD expression was upregulated in recurrent tumors [39, 42, 44]. The differential expression pattern of CPS1 and CAD has been identified as an independent prognostic marker, suggesting that targeting pyrimidine synthesis may provide a novel therapeutic strategy for HCC.

These findings highlight the context-dependent regulation of CPS1 in cancer. While CPS1 downregulation in gastric and liver tumors is linked to deeper invasion and poor prognosis, its upregulation in early-stage or metabolically active cancers may support proliferation through enhanced nitrogen metabolism and nucleotide synthesis. This dual behavior suggests CPS1 functions as an adaptable metabolic node, responding to tumor stage, microenvironment, and metabolic demand. CPS1 may be upregulated to meet biosynthetic needs during rapid growth, but downregulated under hypoxia or nutrient stress to reduce metabolic load or shift nitrogen toward alternative pathways, such as fatty acid oxidation or glutamine metabolism [47]. Oncogenic signals like β-catenin may further shape its expression pattern [15]. Viewing CPS1 as a metabolic switch, rather than a fixed marker,

may better reflect its role in tumor adaptation and offer new directions for targeted therapy.

Effects of distal UC enzymes and their metabolites

Regulation of aspartate and ASS1 Aspartate serves as an essential nitrogen and carbon donor for nucleotide biosynthesis, playing a crucial role in cellular proliferation [40]. The uptake of aspartate is mediated by the transporter SLC1A3, while additional sources of aspartate include protein catabolism, glutamine degradation, and de novo synthesis of oxaloacetate [41]. Citrin, an aspartate-glutamate carrier predominantly expressed in hepatic tissue, facilitates the intercellular exchange of metabolites. Notably, citrin is overexpressed in HCC, breast cancer, and esophageal cancer, and its expression correlates with poor prognosis in colorectal cancer [7, 11].

The upregulation of Citrin enhances the cytosolic availability of aspartate, whereas the downregulation of ASS1 facilitates aspartate metabolism in tumors, thereby promoting pyrimidine synthesis [40]. Inhibition of Citrin has been proved to inhibit tumor growth in ASS1-deficient tumors [40, 43]. ASS1, an enzyme responsible for catalyzing the argininosuccinate synthesis, is upregulated by p53 and regulated by the transcription factor SP4 in various cancers [14]. Reduced expression of ASS1 is related to the progress of drug resistance and lung metastasis [48, 49]. Studies indicate that ASS1 expression is frequently downregulated in multiple cancers, including malignant melanoma and renal cell carcinoma [50–53]. The loss of ASS1 results in the accumulation of citrulline, which is subsequently utilized for arginine synthesis, thereby promoting tumor growth and providing a survival advantage in arginine-depleted environments [22, 23].

Availability of arginine and fumarate Alterations in the expression of ASL and ARG can significantly affect the availability of arginine, ornithine, and other metabolites essential for tumor cell proliferation [23, 48, 51]. Arginine, a pivotal intermediate in the UC, plays a vital role in numerous metabolic pathways, functioning both as a substrate for urea production and as a precursor for nitric oxide (NO) synthesis [8, 23]. The metabolism of arginine is competitively regulated by ARG and nitric oxide synthase (NOS) [23]. Elevated ARG activity promotes urea production and the ornithine cycle, whereas NOS preferentially converts arginine into NO, which is crucial for vasodilation, immune modulation, and neurotransmission [23, 25]. The regulation of ASL expression directly influences the efficiency of arginine synthesis, thereby impacting the balance of broader metabolic networks [23, 48]. Differential expression of these enzymes enables tumor cells to adapt to the TME, optimize nutrient utilization, and enhance their proliferative capacity. This metabolic reprogramming endows tumor cells with remarkable flexibility, enabling them to survive and thrive in diverse environmental conditions.

The role of ornithine in cell proliferation In oncological contexts, ornithine undergoes conversion to putrescine via the catalytic activity of ornithine decarboxylase (ODC) [54, 55]. Subsequently, putrescine is transformed into spermidine and spermine through additional enzymatic reactions, which play a crucial role in modulating cellular proliferation and transcription by facilitating the hypusination of eukaryotic initiation factor 5 A (eIF5A) [50, 56]. The excessive production of these polyamines is strongly linked to tumor cell proliferation, survival, and metastasis [50]. As a result, the dysregulated activation of the ornithine metabolism pathway is regarded as a vital aspect of tumor metabolic reprogramming [56, 57]. OTC mediates the transfer of CP to ornithine, resulting in the formation of citrulline, which subsequently participates in the UC [56]. OTC is predominantly expressed in the liver and small intestine of mammals and is essential for maintaining amino acid homeostasis, particularly concerning L-glutamine and L-arginine [56]. In tumorigenic conditions, OTC expression is often suppressed. Reduced expression of OTC has been documented in various cancers, including colorectal cancer, HCC, and glioblastoma [50–53, 58].

In particular, reduced expression of OTC in HCC is correlated with larger tumor size and higher tumor grade. OTC silencing shifts nitrogen metabolism from the UC's excretory route to anabolic pathways, promoting nucleotide, amino acid, and polyamine biosynthesis, thereby driving tumor proliferation [56, 57]. This metabolic reprogramming enhances the tumor's reliance on exogenous arginine [23]. Consequently, depleting arginine or pharmacologically limiting its availability may represent a viable strategy for cancer therapy.

Nevertheless, some studies suggest that OTC expression can be upregulated by tumor suppressor genes such as p53 in certain cancer cell lines, indicating that OTC may have differential regulatory roles in specific cancer subtypes [50, 59, 60].

Effects of UCD on other metabolic pathways

UCD not only impairs ammonia processing but also induces alterations in other metabolic pathways. Enzymes of the UC are intricately associated with gluconeogenesis and lipid metabolism [32, 61–63]. Both the UC and gluconeogenesis are dependent on amino acid metabolism [63]. During the process of deamination, amino acids liberate ammonia, whereas the resultant carbon skeletons are capable of entering the gluconeogenesis pathway [63].

In hepatic tissues, glutamine undergoes deamination, resulting in the release of ammonia, which subsequently participates in the UC [64]. Concurrently, the carbon skeleton of glutamine is channeled into gluconeogenesis, thereby establishing a biochemical link between the UC and gluconeogenic pathways [64]. Similarly, aspartate, an essential intermediate of the UC, contributes to gluconeogenesis by being converted into oxaloacetate. This oxaloacetate can then be transformed into phosphoenolpyruvate (PEP), facilitating its incorporation into the gluconeogenic pathway [65, 66]. The synthesis of fatty acids necessitates NADPH as a reducing agent, and certain steps within the UC require ATP consumption, which may influence NADPH production. Consequently, UCD may impact energy metabolism, indirectly affecting NADPH availability and, by extension, fatty acid synthesis [67]. Moreover, oxaloacetate serves as a pivotal intermediate in both gluconeogenesis and lipid metabolism, playing a dual role by participating in gluconeogenesis and contributing to lipid metabolism via the citric acid cycle [2, 61]. Aspartate produced by the UC can be converted into oxaloacetate, thereby linking the UC with both gluconeogenesis and lipid metabolism [47].

Finally, UCD influences amino acid metabolism and availability, with certain amino acids, such as glutamate, being integral to lipid metabolism [2, 63]. Specifically, glutamate serves as a significant source of acetyl-CoA, a crucial precursor in lipid synthesis [30, 60].

Effect of UCD on tumor immunogenicity

Immune evasion has become a classic characteristic in the field of oncology. Initially, tumor cells are subject to surveillance and recognition by the immune system; however, as immune editing advances, these cells progressively attain an immune evasion state, thereby expediting the metastatic process [68, 69]. This evasion constitutes a significant barrier to enhancing the effectiveness of cancer therapies [69]. The mechanisms underlying tumor immune evasion are intricate and can be broadly categorized into two main aspects (Fig. 2). Firstly, tumor cells facilitate immune evasion by downregulating major histocompatibility complex (MHC) expression, diminishing immunogenicity, or inhibiting genes responsible for antigen presentation [18–20]. Secondly, alterations within the host immune system contribute to this evasion, including the inability to detect low levels of tumor antigens in the early stages, as well as increased antigen tolerance and dysfunction of Tregs induced by MDSCs and Tregs themselves [70, 71].

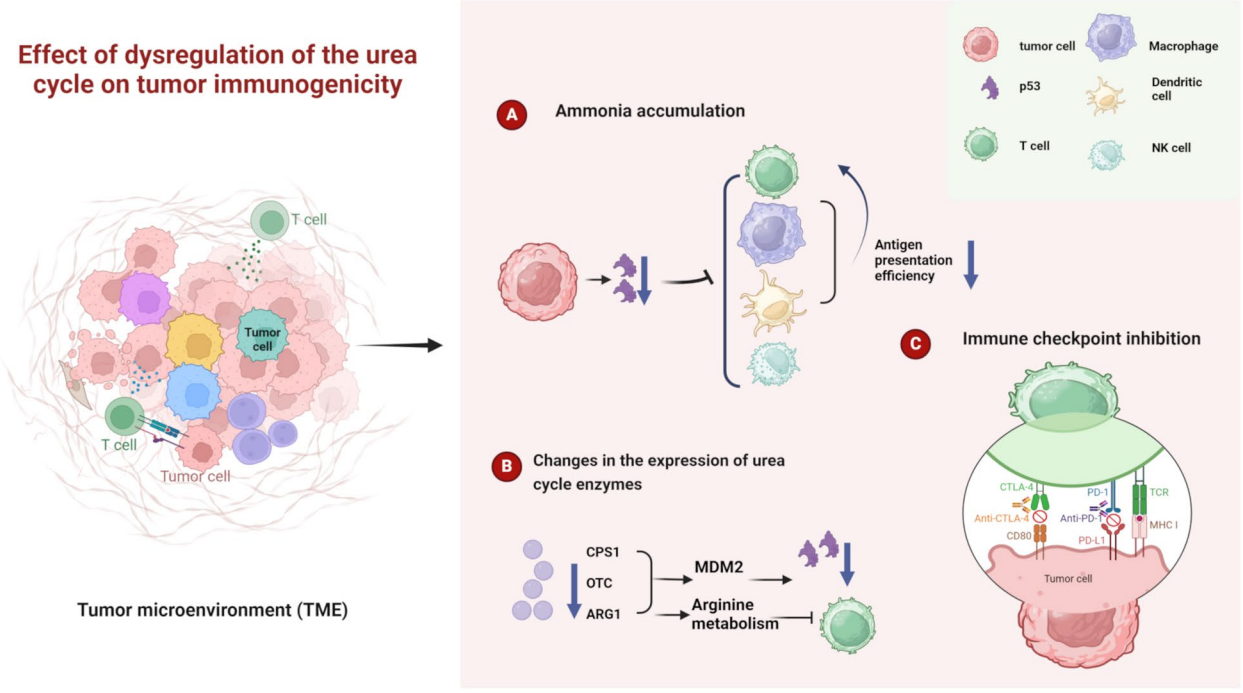

Fig. 2 Effect of dysregulation of the urea cycle on tumor immunogenicity. The dysregulation of the urea cycle (UCD) within the tumor microenvironment (TME) significantly impacts immune responses and facilitates immune evasion. (**A**) The accumulation of ammonia, resulting from impaired nitrogen metabolism, diminishes the efficiency of antigen presentation, thereby weakening immune surveillance. (**B**) Alterations in the expression of urea cycle enzymes, such as CPS1, OTC, and ARG1, affect MDM2 activity and arginine metabolism, further modulating immune responses. (**C**) The inhibition of immune checkpoints is intensified as dysregulated nitrogen metabolism enhances PD-L1 and CTLA-4 mediated T cell suppression, thereby promoting immune escape. Collectively, these metabolic alterations contribute to tumor progression by fostering an immunosuppressive microenvironment

Metabolic alterations resulting from UCD significantly contribute to the establishment of a highly immunosuppressive TME [29, 70, 71]. The depletion of arginine, coupled with the accumulation of ornithine and polyamines, synergistically suppresses key components of the anti-tumor immune response [72, 73]. Diminished arginine availability adversely affects T-cell receptor (TCR) signaling, resulting in T-cell anergy and exhaustion, which is characterized by reduced effector functions and a decreased proliferative capacity in response to antigen stimulation [70, 73]. Furthermore, the accumulation of polyamines promotes an increase in MDSCs and Tregs, which further inhibit effective anti-tumor immunity through the secretion of immunosuppressive cytokines and interference with effector T-cell activity [74–76].

Macrophages within the TME are influenced by UCD, frequently undergoing polarization towards the alternatively activated macrophages (M2 macrophages) phenotype, which is linked to tissue repair and tumor-promoting activities [74–76]. It is known that M2 macrophages can secrete anti-inflammatory cytokines, promote angiogenesis, and facilitate tumor cell invasion and metastasis [76]. The imbalance between classically activated macrophages (M1 macrophages) (characterized by pro-inflammatory and anti-tumor functions) and M2 macrophages (characterized by immunosuppressive and pro-tumor functions) is a defining feature of the immunosuppressive TME [76–79]. UCD plays a pivotal role in sustaining this imbalance and promoting tumor progression.

In conclusion, the immunomodulatory effects of UCD contribute to the formation of a TME that supports tumor growth and resists immune-mediated destruction. By altering the availability of critical metabolites, cancer cells can effectively suppress anti-tumor immunity, promote immune evasion, and enhance tumor survival.

Arginine depletion caused by UCD and its immunosuppressive effects

Alterations in UC metabolites significantly influence the TME, resulting in modifications to immune cell activation, polarization, and function. The depletion of arginine, frequently due to the downregulation of ASS1, leads to an arginine-deficient milieu that hinders the activation and proliferation of effector Tregs, thereby compromising anti-tumor immunity [53, 80–83].

Furthermore, diminished arginine availability constrains the efficacy of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, both critical for effective immune-mediated tumor control [53, 83–87]. In cancer patients receiving immune checkpoint inhibitor (ICI) therapy, low arginine levels have been significantly correlated with clinical benefit, indicating that arginine concentrations may serve as a predictive biomarker for ICI responsiveness [81, 83, 84].

Within the TME, cancer cells deplete arginine, consequently limiting T-cell proliferation [79]. Studies have shown that the lack of arginine inhibits T-cell activation and proliferation through multiple mechanisms. For instance, arginine deprivation disrupts intracellular signaling pathways in T-cells, thereby impairing cytokine production and cell cycle progression [86, 87]. Besides, Arginine methylation plays a crucial role in T-cell signaling by modulating the signal transduction intensity of the common cytokine receptor γ-chain (γc) and the kinase JAK3 [73]. This post-translational modification is facilitated by protein arginine methyltransferases (PRMTs), which are essential for the maintenance and function of various T-cell subsets, including invariant natural killer T cells (iNKT cells), CD4 + T cells, and CD8 + T cells [88]. The deletion of PRMT5, a key arginine methyltransferase, leads to a marked reduction in signaling via γc-family cytokines and a substantial loss of thymic iNKT cells, as well as a decreased number of peripheral CD4 + and CD8 + T cells [70, 88].

Moreover, PRMT1, another critical arginine methyltransferase, has been shown to regulate T-cell responses by influencing the recruitment of transcription factors such as STAT3 and STAT5 [88, 89]. PRMT1-dependent modification of histones is required to stabilize the stimulatory STAT3 and displace the inhibitory STAT5 at the IL-17 locus, thereby activating IL-17 gene expression and promoting Th17 cell differentiation [88]. This regulation is crucial for the balance between Th17 cells and regulatory T cells, impacting autoimmune responses [89].

Furthermore, arginine methylation is implicated in the regulation of immune responses through its effect on cytokine signaling [85, 86]. The methylation of arginine residues in proteins modulates the strength of γc-family cytokine signaling, which is essential for T-cell maintenance and activation. This modification facilitates the expression of signal-transducing components, thereby influencing the overall immune response [69, 85, 86].

Under arginine-deprived conditions, T-cells exhibit reduced CD3 chain expression, which is closely linked to the functionality of the T-cell receptor (TCR) [90–92]. Furthermore, arginine deficiency induces autophagy, a protective cellular mechanism activated in response to endogenous stress [91]. In such conditions, Tregs experience endoplasmic reticulum (ER) stress, leading to cell cycle arrest at the G0/G1 phase without triggering apoptosis [7, 91].

Overall, in the TME, arginine deprivation is considered a key mechanism of tumor immune evasion. Tumor cells and certain immune cells, such as MDSCs, suppress the activity of anti-tumor Tregs by depleting arginine [82, 93]. Consequently, targeting arginine metabolism may

represent a potential strategy to enhance T-cell-mediated immune responses.

UCD and the imbalance of macrophage polarization

Research studies indicate that UCD not only disrupts nitrogen metabolism but also affects macrophage polarization and function by altering metabolic pathways [76]– [, 89]. For example, UCD can induce specific gene expression changes, leading to metabolic reprogramming in macrophages, which may influence their transition to the M1 or M2 phenotype [73, 76]. M1 macrophages typically exhibit enhanced glycolysis and reduced oxidative phosphorylation, whereas M2 macrophages rely predominantly on effective oxidative phosphorylation to maintain their function [74, 75].

Moreover, UCD may result in the accumulation of ammonia and other metabolic intermediates, which could alter macrophage function by impacting their metabolic state [73]. For instance, studies have identified a link between UCD and metabolic changes in hepatic macrophages, potentially affecting systemic metabolism and immune responses [76]. Under chronic inflammatory conditions, macrophage polarization is closely tied to their metabolic pathways, and UCD may drive a shift toward the pro-inflammatory M1 phenotype, exacerbating inflammatory responses [73, 74, 77].

Finally, macrophage metabolic reprogramming is intricately linked to their functional roles in different pathological contexts. For example, M1 macrophages require a rapid energy supply to respond to pathogens, a demand that may be modulated by UC regulation [73, 74]. Understanding the interplay between UCD, macrophage metabolism and polarization offers valuable insights for targeting macrophage-driven processes in cancer and other diseases.

Regulation of immune checkpoint molecules by UCD

In the TME, effector T-cell exhibit reduced cytokine expression, diminished effector functionality, and impaired reactivation capacity—a state known as "T-cell exhaustion" [79]. Exhausted T-cell express high levels of various inhibitory receptors, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and ITIM domain (TIGIT) [79, 94–97]. These receptors, often known as immune checkpoints, can effectively inhibit T-cell activation [71, 79, 90].

PD-1 is a central immune checkpoint regulated through transcriptional activation, distinct from the regulatory mechanism of CTLA-4 [91, 92]. PD-1 contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM), which recruit the inhibitory phosphatase SHP-2 [93, 94]. This interaction directly suppresses the TCR-CD28 signaling pathways, including ZAP70, Ras-MAPK, and PI3K, thereby attenuating T-cell activation [91–93]. Additionally, PD-1 promotes T-cell migration within tissues, reducing the time spent recognizing peptide-MHC complexes. Furthermore, PD-1 upregulates the transcription factor BATF, which weakens T-cell proliferation and cytokine secretion [93].

The ligands for PD-1, PD-L1, and PD-L2, are primarily expressed in tumor cells and tumor-infiltrating immune cells [92]. These ligands promote tumor immune escape and lead to T-cell inhibition through their interaction with PD-1 [92, 93]. UCD may influence the expression of immune checkpoint molecules such as PD-L1 through metabolic reprogramming and enable tumor cells to evade immune attack via checkpoint pathways [92]. For instance, the accumulation of ammonia and other metabolic byproducts can upregulate PD-L1 expression through signaling pathways, suppressing T-cell activity and aiding tumor cells in escaping immune surveillance [20, 93]. This metabolic regulatory mechanism provides novel insights into tumor immune evasion and identifies potential therapeutic targets for overcoming immune checkpoint-mediated suppression.

Therapeutic potential of targeting UCD for cancer treatment

Targeting UCD in cancer represents a promising therapeutic approach, particularly in overcoming the metabolic adaptations that promote tumor growth and immune evasion (Fig. 3). To inhibit tumor metabolism and restore effective anti-tumor immunity, several strategies have been proposed to target key components of the UC. The following sections discuss therapeutic interventions for UC enzymes, the potential synergistic effects with existing immunotherapies, and the challenges associated with implementing these strategies in the clinical environment.

Targeting of the UC enzymes

Arginine-deprivation therapy

One promising therapeutic approach involves directly inhibiting dysregulated UC enzymes, such as ASS1 and CPS1. In ASS1-downregulated cancers, treatment strategies focus on exploiting this metabolic vulnerability [94, 95]. Tumors lacking ASS1 promote cell proliferation by enhancing pyrimidine synthesis, a process involving the activation of the CAD complex (comprising carbamoyl phosphate synthetase 2, aspartate transcarbamoylase, and dihydroorotase) [39, 96, 97].

Studies have shown that cancer cells with low levels of ASS1 and/or ASL exhibit increased sensitivity to arginine deprivation therapy (ADT), leading to reduced survival under nutrient-limited conditions [94, 95]. Moreover, ASS1 downregulation facilitates tumor growth and

Inhibitor Type	Mechanism of Action	Advantages	Challenges
ADI-PEG20	• Catalyzes the degradation of arginine into citrulline and ammonia, Depriving tumors of extracellular arginine	• Clinically advanced, long half-life, low toxicity	• Potential immunogenicity leading to immune rejection
PEG-rhARG1	• Degrades arginine into ornithine and urea via recombinant human arginase 1, targeting extracellular arginine	• Humanized design, reduced immunogenicity; PEGylation extends half-life; effective in ASS1-deficient tumors	• Tumor resistance via ASS1 re-expression or metabolic reprogramming; possible impact on T-cell function
Arginase	• Converts arginine into ornithine and urea, reducing available extracellular arginine	• Efficient depletion of arginine; modulates the tumor microenvironment	• Requires optimization of half-life and immunogenicity
Epigenetic Modulators	• Downregulates ASS1 expression through epigenetic regulation, reducing tumor adaptability to arginine depletion	• Can reduce resistance when combined with ADI therapy	• Toxicity of epigenetic drugs needs further evaluation
Combined Metabolic Blockers	• Disrupts compensatory pathways by inhibiting citrulline or glutamine metabolism	• Multi-target blockade enhances therapeutic efficacy	• Dosage optimization and safety of combination therapies still require refinement
Ornithine Transcarbamylase (OTC) Inhibitors	• Inhibits OTC, preventing ornithine from converting back to arginine, disrupting the urea cycle	• Specific inhibition of urea cycle, reducing resistance likelihood	• Potential metabolic adaptability and resistance
Arginine Transport Inhibitors	• Inhibits arginine uptake via transporters like SLC7A1, reducing extracellular arginine levels	• Targets extracellular arginine intake, depriving tumors of essential nutrients	• May affect normal cell metabolism
Arginyl-tRNA Synthetase (ArgRS) Inhibitors	• Inhibits ArgRS, decreasing arginine involvement in protein synthesis	• Directly targets the arginine biosynthesis pathway	• In the early stages of research, clinical application still needs further exploration
mTOR Pathway Inhibitors	• Inhibits mTOR signaling, which is involved in arginine-related metabolic pathways	• Combines arginine deprivation with mTOR inhibition, enhancing anti-tumor effects	• Lack of specificity may affect normal cells, requiring precise targeting

Fig. 3 Targeting the Urea Cycle for Cancer Therapy

invasiveness by rewiring metabolic pathways, whereas restoring ASS1 expression suppresses tumor cell proliferation and enhances sensitivity to metabolic stress [94, 97]. Another study revealed that ASS1 deficiency in lung fibrosis inhibited fibroblast proliferation, migration, and invasion, further underscoring the critical role of ASS1 in cell survival [95]. Similarly, cells with low ASL levels demonstrate higher mortality under metabolic stress, likely due to the enzyme's vital role in amino acid metabolism [98, 99]. These findings suggest that targeting ASS1 and ASL could provide novel therapeutic opportunities, particularly for tumors with markedly reduced expression of these enzymes.

ADI-PEG 20 is a novel anti-cancer drug that depletes circulating arginine by converting it into citrulline and ammonia, thereby inhibiting cancer cell growth [94, 100]. Phase I and II clinical trials have highlighted the tolerability and potential efficacy of ADI-PEG 20 in HCC and melanoma [94, 100–102]. The effectiveness of this strategy is partly attributed to its selective action on ASS1-negative tumors, which are highly sensitive to ADI-PEG 20 due to their dependence on external arginine sources [102, 103]. In a Phase I/II study involving patients with advanced melanoma, ADI-PEG 20 was well-tolerated and achieved transient yet effective arginine depletion, resulting in notable disease control rates in some uveal melanoma patients [100]. Additionally, a separate Phase I trial demonstrated that combining ADI-PEG 20 with cisplatin showed promising anti-tumor activity in patients with ASS1-deficient melanoma or metastatic solid tumors [102]. A randomized Phase II trial (ADAM) revealed that ADI-PEG 20 provided significant overall survival benefits in over 75% of ASS1-deficient tumors compared to best supportive care [94, 99]. Furthermore, ADI-PEG 20 monotherapy demonstrated efficacy in a Phase II trial targeting refractory and relapsed cancers [101, 102].

Beyond its direct anti-tumor effects, ADI-PEG 20 modulates the tumor immune microenvironment by reducing Tregs accumulation, inducing tumor T-cell infiltration, and influencing immune checkpoint expression [94, 103, 104]. The combination of metabolic inhibitors and immune checkpoint inhibitors (ICIs) can produce synergistic effects—metabolic interventions reduce immunosuppressive barriers in the TME, while ICIs fully activate immune responses—ultimately leading to significant improvements in cancer treatment outcomes [85, 104].

However, it is worth noting that tumor cells can develop resistance to arginine deprivation therapy (ADT) through various mechanisms [105–108] (Fig. 4). Tumor recurrence after ADT is partially attributed to the presence of neutralizing antibodies that restore plasma arginine and citrulline levels to pre-treatment levels within eight weeks [108, 109]. Intracellular resistance mechanisms include ASS1 overexpression, which increases endogenous arginine production, and the activation of transcriptional programs such as MYC and STAT5, although the precise molecular mechanisms that bypass arginine deprivation remain unclear [107, 108].

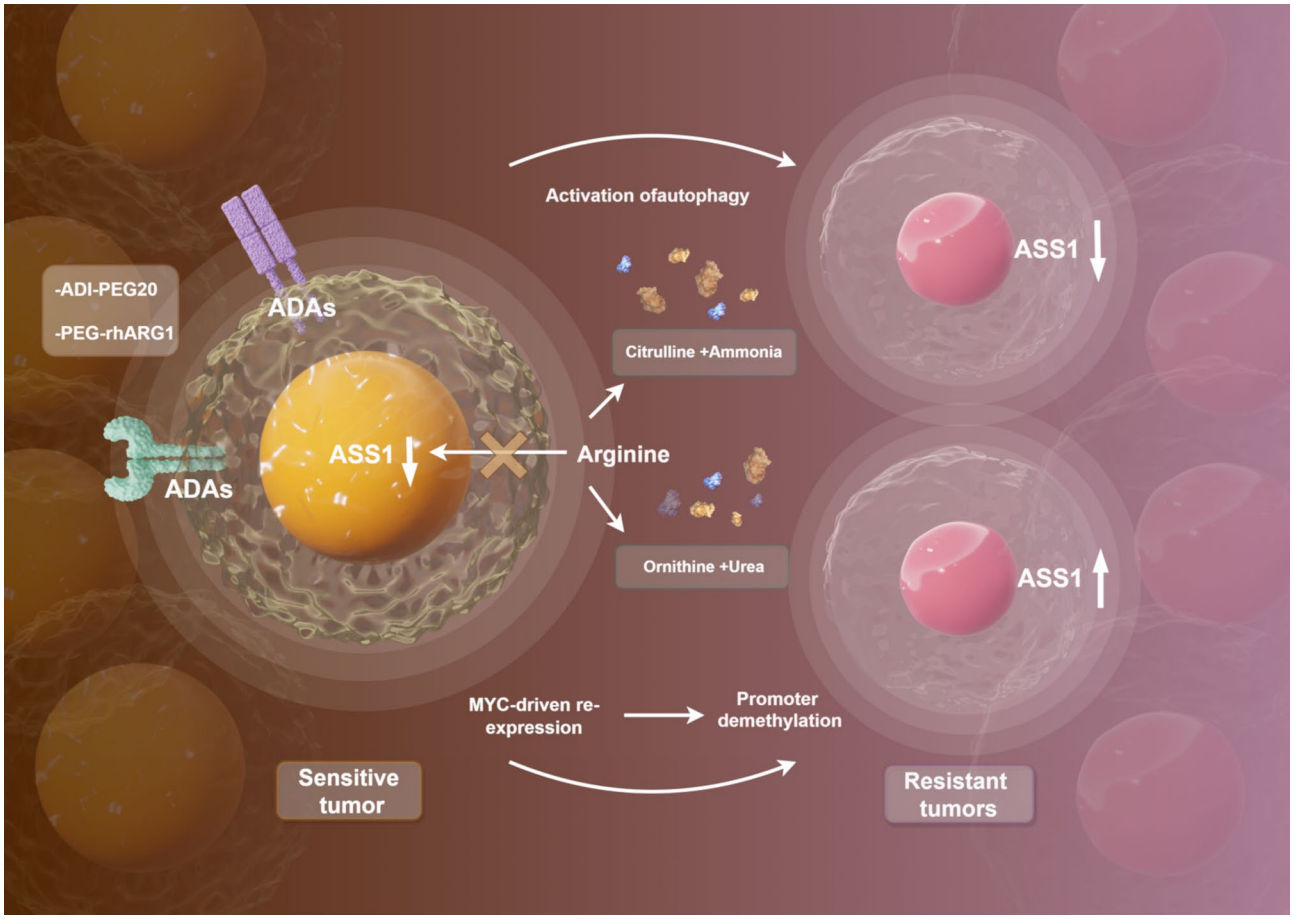

Fig. 4 Arginine Deprivation and ASS1 Re-expression in Tumor Resistance. Modulating arginine metabolism elicits varied responses in tumors. Arginine-depleting agents, such as ADI-PEG20 and PEG-rhARG1, cause arginine deprivation in tumors deficient in argininosuccinate synthetase 1 (ASS1), leading to metabolic stress, activation of autophagy, and subsequent tumor cell death in susceptible tumors. Conversely, resistant tumors may re-express ASS1 via MYC-mediated promoter demethylation, thereby facilitating the biosynthesis of arginine from citrulline and ammonia

Additionally, changes in the expression of specific transporters may enable tumor cells to more effectively scavenge arginine from the surrounding environment or neighboring cells, further complicating the therapeutic landscape [109, 110]. Tumor heterogeneity can lead to the emergence of inherently resistant subclones with unique genetic mutations or epigenetic modifications that confer survival advantages under arginine-deprived conditions [110, 111]. The persistence of resistant tumor cell populations can result in more aggressive and refractory disease following initial treatment [108].

Understanding these resistance mechanisms is crucial for developing effective strategies to enhance the efficacy of ADT. Combining ADT with immunotherapy or targeted therapies may help overcome resistance and improve patient outcomes. This combination strategy counteracts tumor cell adaptation, mitigates resistance, and harnesses both enhanced immune activation and targeted inhibition to achieve more effective tumor elimination, ultimately improving treatment efficacy and patient survival.

An inhibitor of CPS1

CPS1 is frequently upregulated to support nucleotide biosynthesis, making it another promising therapeutic target [112]. Inhibiting CPS1's activity disrupts the production of CP, thereby limiting the availability of pyrimidines necessary for DNA and RNA synthesis [39, 112]. This strategy aims to interfere with cancer cell proliferation by restricting nucleotide synthesis, ultimately impairing tumor growth [109].

The integration of metabolic pathways in cancer cells is critical for their survival and proliferation. For instance, the mechanistic target of rapamycin complex 1 (mTORC1) has been shown to couple nucleotide synthesis with cellular demands, creating a targetable metabolic vulnerability in cancer therapy [109]. Additionally, phosphoribosyl pyrophosphate synthetase 2 plays a pivotal role in linking protein and nucleotide biosynthesis,

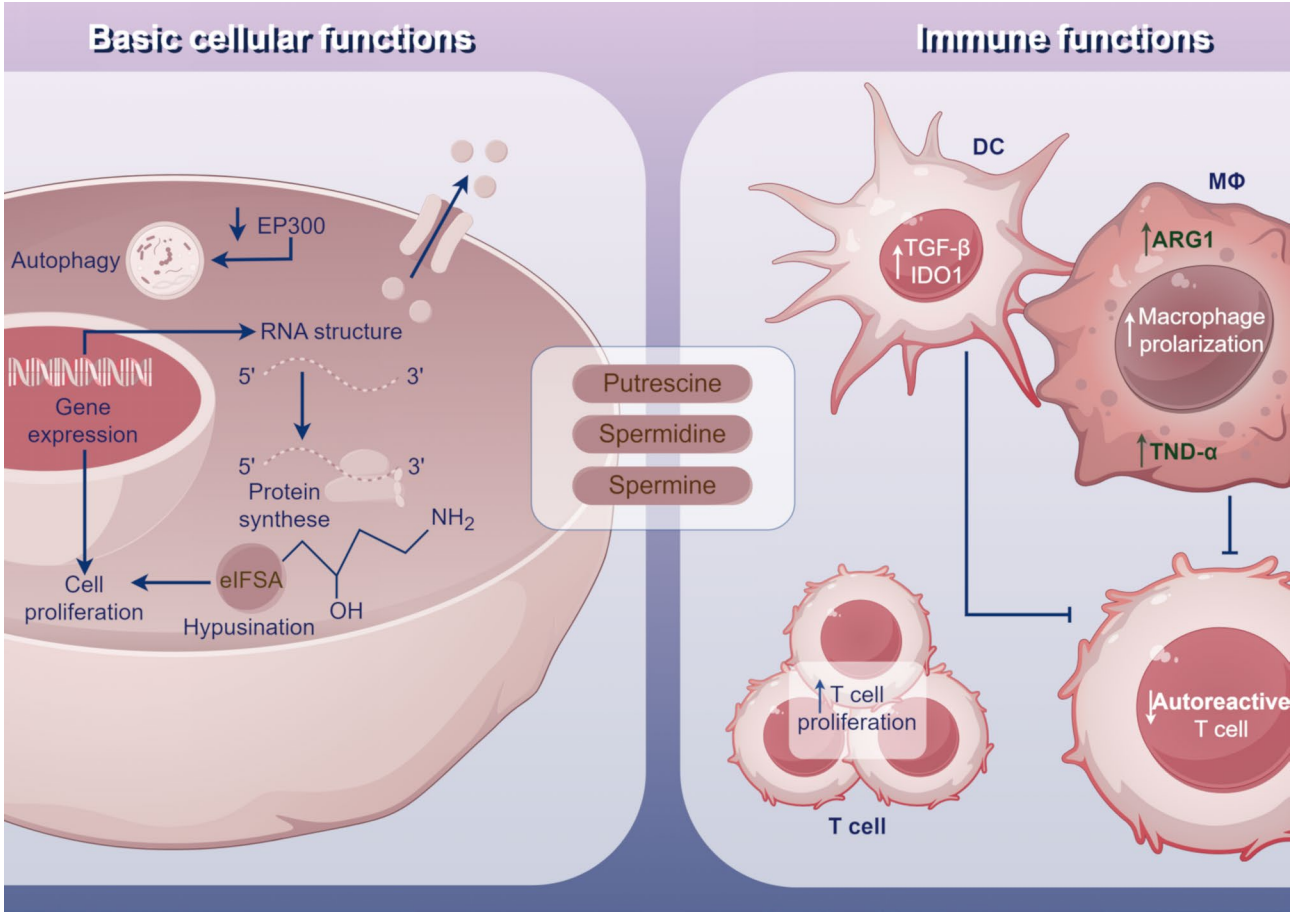

Fig. 5 Polyamines in Cellular and Immune Functions. Polyamines (putrescine, spermidine, spermine) regulate gene expression, RNA structure, protein synthesis, and cell proliferation. They influence autophagy via EP300 and support the hyphenation of eIF5A. In the immune system, polyamines modulate dendritic cell (DC) and macrophage (MΦ) polarization, increasing TGF-β, IDO1, and ARG1 expression

underscoring the interconnection of these pathways in cancer cells [110]. Furthermore, the serine synthesis pathway, particularly through the enzyme phosphoglycerate dehydrogenase, has been identified as an essential pathway in aggressive breast cancer, suggesting that targeting metabolic enzymes can yield significant therapeutic benefits [111].

In summary, the role of CPS1 in nucleotide biosynthesis aligns with a broader understanding of how manipulating metabolic pathways can be leveraged for cancer treatment, highlighting the potential of targeting metabolic enzymes as a viable strategy in oncology. Although direct CPS1 inhibitors are still in early stages of development, targeting pathways that regulate CPS1 expression or activity may provide an indirect means of disrupting its function.

ODC inhibitor

Inhibiting ornithine decarboxylase (ODC), the enzyme responsible for synthesizing polyamines from ornithine has been proven to significantly regulate various cellular processes [113]. For instance, studies have demonstrated that targeting ODC can suppress cancer cell proliferation, including in esophageal squamous cell carcinoma [113, 114]. Using difluoromethylornithine (DFMO) to inhibit ODC not only reduces polyamine levels but also induces apoptosis in cancer cells, highlighting the therapeutic potential of ODC inhibitors in cancer treatment [113, 114].

Regulating polyamine levels is critical for maintaining intracellular homeostasis and functionality. Polyamines such as putrescine, spermidine, and spermine play essential roles in cell growth, differentiation, and apoptosis [112, 113] (Fig. 5). The balance of these metabolites is tightly controlled by ODC and its regulatory proteins, including antizyme [112]. ODC inhibition reduces polyamine production, leading to cell cycle arrest and increased differentiation across various cancer cell lines [113–115]. Moreover, an interaction between polyamines and the circadian clock has been observed, with polyamine levels oscillating in a daily rhythm and influencing circadian regulation [114]. This suggests that controlling

polyamine levels through ODC inhibition may have broader implications beyond cancer therapy, potentially affecting metabolic processes and circadian rhythm regulation.

In the context of immune responses, T-cell depend on polyamines for proliferation and functionality. Inhibiting ODC in T-cell impairs their ability to mount effective immune responses, underscoring the critical role of polyamine levels in immune cell function [115]. Thus, strategically reducing polyamines via ODC inhibition provides a multifaceted approach to modulating cellular behavior in both cancer and the immune environment [115, 116].

In summary, inhibiting ODC to lower polyamine levels has profound implications for cancer therapy, immune function, and circadian rhythm regulation, making it a promising therapeutic target for diverse interventions.

Combined strategies to strengthen immunotherapy

The immunosuppressive effects of UCD provide a robust theoretical foundation for combining metabolic interventions with immunotherapy. Immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized cancer treatment [116–118]. In clinical trials, dual immune checkpoint inhibition strategies (such as the combination of anti-PD-1/PD-L1 and anti-CTLA-4) have shown significant survival advantages in patients with melanoma and non-small cell lung cancer [118]. However, their efficacy is often limited by the immunosuppressive TME [116, 117].

Targeting UC enzymes to modulate metabolite availability offers an opportunity to reprogram the TME, making it more conducive to effective immune responses [79, 119]. For instance, strategies to supplement arginine or enhance arginine cycling within the TME can alleviate T-cell suppression and improve the efficacy of ICIs [120, 121]. Conversely, reducing polyamine levels by inhibiting ODC synthesis can diminish the activity of T-cell and MDSCs, thereby enhancing anti-tumor immunity. Studies have shown that in glioblastoma, polyamines promote the survival of myeloid suppressor cells by buffering the pH value within cells, leading to immune suppression [122, 123]. By using DFMO, the specific polyamine levels in tumors can be reduced, thereby enhancing the effectiveness of immunotherapy or radiation therapy, thus improving animal survival rates [123].

In addition, in the study of ovarian cancer, the combination of DFMO and 5-azacytidine significantly increased the proportion of M1 macrophages in the TME while reducing the number of immune suppressor cells [124]. This combined therapy not only reduced the tumor burden but also extended the survival period of mice, indicating that regulating macrophage polarization can enhance anti-tumor immune [124].

MDSCs in the TME consume L-arginine by overexpressing arginase 1 (Arg1), thereby inhibiting T-cell anti-tumor responses [125]. By suppressing Arg1 activity, the levels of L-arginine can be restored, thus improving the anti-tumor immune response. This strategy has also demonstrated certain safety and immunogenicity in clinical trials, indicating that targeting Arg1 can enhance anti-tumor immunity [125].

In summary, the combined use of metabolic inhibitors and immune checkpoint blockade has shown potential synergistic effects in both preclinical and clinical studies, offering new ideas and directions for future cancer treatment. Further research and clinical trials are expected to optimize the application of this combination therapy, thereby improving patient outcomes and survival rates.

Conclusion

Complex interactions among urea cycle disorder, metabolic reprogramming, and immune regulation in cancers provide key insights into tumor biology and treatment opportunities. Alterations in the UC not only support tumor growth by enhancing nucleotide and polyamine biosynthesis but also create an immunosuppressive microenvironment that promotes immune evasion. This dual role underscores the importance of understanding metabolic adaptations in cancer and how these changes can be targeted for therapeutic benefit.

Recent advancements in understanding UCD have highlighted the potential of metabolic interventions to complement existing cancer therapies, particularly immunotherapies. Targeting key enzymes such as ASS1 and CPS1 offers promising approaches to exploit the metabolic vulnerabilities of cancer cells, while combination strategies involving immune checkpoint inhibitors and metabolic modulators have shown encouraging preclinical results. These approaches aim to inhibit tumor growth and remodel the TME to enhance immune-mediated cancer cell destruction.

However, there are still major challenges in translating these findings into effective clinical treatment. The metabolic plasticity of cancer cells enables them to adapt to targeted interventions, often through the activation of compensatory pathways to maintain metabolic homeostasis. A deeper understanding of the metabolic networks and regulatory mechanisms involved in UCD is essential for identifying new targets and developing strategies to prevent therapeutic resistance. Moreover, tumor heterogeneity among patients and within individual tumors complicates the identification of reliable biomarkers of patients' choice and treatment response.

Future research should focus on several important areas to overcome these challenges. First, comprehensive metabolic profiling of tumors to identify specific vulnerabilities associated with UCD can guide the development

of more personalized treatment approaches. Second, elucidating the mechanistic links between UC metabolites and immune cell function can provide new insights on how metabolic interventions can enhance anti-tumor immunity. Finally, integrating metabolic therapies with emerging immunotherapy approaches, such as adoptive T-cell transfer and cancer vaccines, holds the potential to improve therapeutic efficacy and the durability of responses.

In conclusion, UCD is a pivotal aspect of cancer metabolism with profound implications for tumor growth and immune regulation. Targeting the metabolic dependencies and immunological consequences of UC alterations provides a promising approach for cancer therapy. Continued research in this field, with a focus on overcoming metabolic plasticity and leveraging combination strategies, will be critical for translating these insights into more effective treatments and ultimately improving outcomes for cancer patients.

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Author contributions
Y.S. conceptualized the review, conducted the literature search, and wrote the majority of the manuscript. R.L. contributed to the manuscript revisions and provided critical feedback on the analysis and discussion sections. H.S., H.Z., and Y.L. offered guidance on the structure and content, as well as provided funding support. K.X., X.C., L.H., and Y.Z. assisted in reviewing the manuscript and contributed to the refinement of key sections. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Conflict of interest
The authors declare that they have no competing interests.

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