

L-ARGININE METABOLISM IN CANCER: LINKING TUMOR INFLAMMATION, APOPTOSIS, AND ANGIOGENESIS

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L-arginine metabolism has emerged as a central regulatory axis in cancer biology, integrating metabolic reprogramming, immune modulation, and tumor microenvironment remodeling. Cancer cells frequently rewire arginine uptake, synthesis, and degradation pathways to sustain proliferation, evade immune surveillance, and adapt to metabolic stress conditions. This metabolic flexibility is enabled through coordinated regulation of key enzymatic nodes, including argininosuccinate synthase 1, argininosuccinate lyase, arginase isoforms (ARG1 and ARG2), and nitric oxide synthases, which collectively control intracellular arginine availability and its downstream signaling outputs. In the tumor microenvironment, arginine metabolism becomes a competitive interface between malignant cells and immune populations. Tumors exploit arginine depletion through increased arginase activity in myeloid-derived suppressor cells and tumor-associated macrophages, leading to impaired T-cell activation and suppression of anti-tumor immunity. In parallel, nitric oxide generated from arginine metabolism exerts concentration-dependent effects that can either promote tumor progression through angiogenesis and survival signaling or induce cytotoxic stress and apoptosis at higher levels. Additionally, polyamine biosynthesis derived from arginine catabolism further supports tumor growth, chromatin remodeling, and resistance to cell death. This review provides a comprehensive synthesis of L-arginine metabolic pathways in cancer, with a particular focus on their roles in tumor-associated inflammation, apoptotic regulation, and angiogenesis. We also discuss therapeutic strategies targeting arginine dependency, including arginine deprivation therapies, arginase inhibition approaches, and emerging combination immunometabolic strategies, as well as key resistance mechanisms such as argininosuccinate synthase 1 re-expression and metabolic rewiring. Collectively, L-arginine metabolism represents a multifunctional metabolic hub that connects tumor progression with immune regulation and offers multiple promising therapeutic entry points in oncology.

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Introduction. Cancer development is not solely driven by genetic mutations, but is also profoundly influenced by metabolic reprogramming that allows tumor cells to sustain uncontrolled proliferation, survive under hostile microenvironmental conditions, and evade immune destruction [1, 2]. Among the various metabolic adaptations observed in cancer, amino acid metabolism has gained increasing attention, with L-arginine emerging as a central metabolite that connects cellular metabolism with immune regulation and tumor biology [3, 4].

L-arginine is a semi-essential amino acid involved in multiple physiological processes, including protein synthesis, nitric oxide production, polyamine biosynthesis, creatine metabolism, and immune cell signaling [5]. Under normal physiological conditions, systemic arginine levels are tightly regulated through dietary intake and endogenous synthesis via the intestinal–renal axis. However, in cancer, this homeostatic balance is frequently disrupted, leading to either arginine dependency or pathological arginine depletion within the tumor microenvironment [6].

Major enzymes and metabolites involved in L-arginine metabolism and their roles in cancer

Component	Type	Biochemical Function	Relevance in Cancer
L-Arginine	amino acid	central substrate for nitric oxide synthesis, polyamine production, protein synthesis, and immune regulation	frequently depleted or highly utilized in tumors; regulates proliferation, immune responses, and angiogenesis [7, 8]
CAT-1 (SLC7A1)	transporter	mediates cellular uptake of extracellular L-arginine	often upregulated in cancer cells to support increased metabolic demands and proliferation [9]
ASS1 (Argininosuccinate Synthase 1)	enzyme	catalyzes the conversion of citrulline and aspartate to argininosuccinate	frequently downregulated in several cancers, leading to arginine auxotrophy and sensitivity to arginine deprivation therapy [10]
ASL (Argininosuccinate Lyase)	enzyme	converts argininosuccinate into arginine and fumarate	supports endogenous arginine synthesis and nitric oxide production through the citrulline–NO cycle [11, 12]
ARG1 (Arginase 1)	enzyme	hydrolyzes arginine to ornithine and urea	highly expressed in myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs); promotes immune suppression [8, 13]
ARG2 (Arginase 2)	enzyme	hydrolyzes arginine to ornithine and urea in extrahepatic tissues	supports tumor metabolism, adaptation to hypoxia, and polyamine biosynthesis [8, 13]
Ornithine	metabolite	product of arginase activity; precursor for polyamine synthesis	supports tumor growth and serves as a substrate for biosynthetic pathways [14, 15]
ODC (Ornithine Decarboxylase)	enzyme	converts ornithine into putrescine	rate-limiting enzyme in polyamine biosynthesis; frequently over-expressed in malignant tissues [16]
Putrescine	polyamine	the first polyamine produced from ornithine	promotes cell proliferation and tumor progression [17, 18]
Spermidine	polyamine	intermediate polyamine derived from putrescine	supports nucleic acid stability, protein synthesis, and cellular growth [17, 19]

Spermine	polyamine	terminal polyamine in the biosynthetic pathway	regulates chromatin organization, cell survival, and proliferation [20, 21]
NOS (Nitric Oxide Synthases)	enzyme family	converts arginine into nitric oxide (NO) and citrulline	regulates angiogenesis, apoptosis, immune responses, and tumor progression [22–24]
iNOS (NOS2)	enzyme	produces high amounts of NO during inflammation	can mediate either tumoricidal effects or tumor promotion, depending on NO concentration [25]
eNOS (NOS3)	enzyme	produces NO in endothelial cells	supports angiogenesis, vascular remodeling, and tumor blood supply [26, 27]
NO (Nitric Oxide)	signaling molecule	regulates vascular function, cell signaling, and oxidative stress	low concentrations promote survival and angiogenesis, whereas high concentrations induce apoptosis and DNA damage [28]
Citrulline	metabolite	byproduct of NO synthesis and precursor for arginine regeneration	supports recycling of arginine through the ASS1/ASL pathway [29]
Fumarate	metabolite	product of ASL activity	connects arginine metabolism with the tricarboxylic acid (TCA) cycle and cellular bioenergetics [8]

Many tumors exhibit reduced expression of argininosuccinate synthase 1 (ASS1), rendering them unable to synthesize arginine from citrulline and thus dependent on extracellular arginine availability [3]. In parallel, increased expression of arginase enzymes and NO synthases (NOS) further reshapes arginine flux, diverting it into immunosuppressive and pro-tumorigenic pathways [30]. As a result, arginine metabolism becomes a central metabolic node linking tumor growth, immune escape, chronic inflammation, and angiogenesis, making it an attractive target for therapeutic intervention.

Study Area.

L-Arginine Metabolism in Cancer: Pathway Organization and Functional Complexity. L-arginine metabolism in mammalian cells is organized through a tightly interconnected network involving uptake, endogenous synthesis, and multiple catabolic branches [5, 31–33]. Arginine can be obtained either through dietary sources or synthesized endogenously via the intestinal–renal axis (Fig. 1). In this pathway, intestinal epithelial cells convert amino acid precursors such as glutamine, glutamate, and proline into citrulline, which is subsequently transported to the kidneys and converted into arginine. The enzymatic conversion of citrulline to arginine is catalyzed by ASS1 and argininosuccinate lyase (ASL) [29, 34]. ASS1 catalyzes the ATP-dependent condensation of citrulline and aspartate to form argininosuccinate, which is then cleaved by ASL to generate arginine and fumarate (see Table). This pathway represents the primary mechanism of endogenous arginine biosynthesis in mammalian tissues. However, in many cancer types, ASS1 expression is significantly downregulated or completely silenced, leading to arginine auxotrophy and increased tumor dependency on extracellular arginine supply [35, 36]. Arginine uptake is primarily mediated by cationic amino acid transporters, especially CAT-1 (SLC7A1), which is frequently upregulated in cancer cells (see Table). This increased transporter expression enhances arginine influx and supports the metabolic

demands of rapidly proliferating tumor cells, particularly under conditions of nutrient limitation [8].

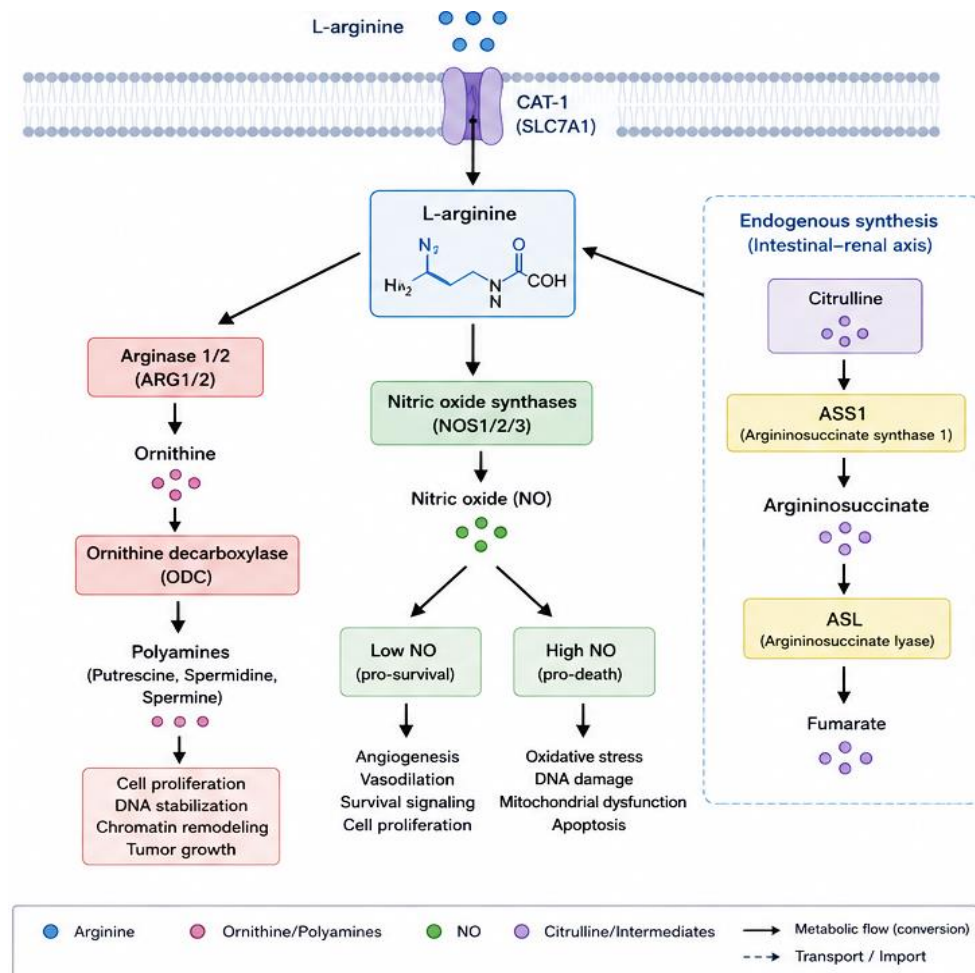


Fig. 1. L-arginine metabolic network in cancer. L-arginine is obtained through extracellular uptake via CAT-1 or synthesized endogenously from citrulline by ASS1 and ASL (see Table). Arginine is metabolized by arginases to ornithine and polyamines, by NOS enzymes to NO and citrulline, or recycled to sustain endogenous synthesis. These pathways regulate tumor cell proliferation, survival, apoptosis, and angiogenesis.

Once inside the cell, arginine is metabolized through several competing enzymatic pathways. One major route is catalyzed by arginase enzymes, ARG1 and ARG2, which hydrolyze arginine into ornithine and urea [37, 38]. Ornithine serves as a precursor for polyamine biosynthesis, generating putrescine, spermidine, and spermine through ornithine decarboxylase (ODC) (see Table). These polyamines are essential for DNA stabilization, chromatin structure regulation, RNA processing, and cell cycle progression [18]. Their accumulation is strongly associated with tumor proliferation, metastatic potential, and resistance to apoptosis.

Another major metabolic branch involves NOS, including endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) isoforms [39–41]. These enzymes

convert arginine into NO and citrulline. NO functions as a pleiotropic signaling molecule with highly context-dependent effects in cancer. At low concentrations, NO promotes angiogenesis, vascular permeability, and pro-survival signaling pathways such as PI3K/AKT [42, 43]. In contrast, at higher concentrations, NO induces oxidative stress, mitochondrial dysfunction, DNA damage, and apoptosis.

Together, these interconnected metabolic pathways establish arginine as a central hub metabolite that integrates nutrient availability, redox balance, immune regulation, and tumor progression.

L-Arginine Metabolism and Tumor-Associated Inflammation. One of the most critical roles of arginine metabolism in cancer lies in its regulation of tumor-associated inflammation and immune escape [8, 44]. The tumor microenvironment is characterized by chronic inflammatory signaling combined with profound immune dysfunction, both of which are tightly controlled by arginine availability and its metabolic fate.

Within the innate immune compartment, macrophages exhibit functional plasticity that is strongly influenced by arginine metabolism. Classically activated M1 macrophages utilize iNOS to convert arginine into nitric oxide, which exerts cytotoxic effects on tumor cells and supports pro-inflammatory immune responses [37, 45]. In contrast, alternatively activated tumor-associated macrophages (TAMs) upregulate arginase 1 (ARG1), which diverts arginine metabolism toward ornithine and polyamine production while simultaneously depleting extracellular arginine. This metabolic shift suppresses T-cell activation and promotes tumor progression through immune evasion and tissue remodeling.

Myeloid-derived suppressor cells (MDSCs), which accumulate in many tumor types, further intensify this immunosuppressive environment. These cells express high levels of ARG1 and generate reactive oxygen species, both of which contribute to T-cell dysfunction [36, 46, 47]. A key mechanism underlying immune suppression is the depletion of extracellular arginine, which leads to downregulation of the CD3 ζ chain of the T-cell receptor complex, thereby impairing antigen recognition and T-cell activation.

In adaptive immunity, CD8⁺ cytotoxic T-cells are highly dependent on arginine for metabolic reprogramming, proliferation, and effector function. Arginine deprivation within the tumor microenvironment results in reduced mTOR signaling, impaired cytokine production, decreased interferon- γ secretion, and eventual T-cell exhaustion [34]. This metabolic restriction is further reinforced by immune-suppressive cytokines such as IL-10 and TGF- β , which are secreted by tumor-associated immune and stromal cells [48, 49]. Together, these mechanisms establish a metabolically enforced immune escape state that allows tumors to persist despite immune infiltration.

L-Arginine Metabolism and Apoptosis in Cancer. Arginine metabolism is also tightly linked to the regulation of programmed cell death pathways in cancer [12, 36, 37, 50]. Tumors that exhibit ASS1 deficiency are particularly vulnerable to arginine deprivation, which induces severe metabolic stress and triggers apoptosis (Fig. 2).

One of the primary mechanisms of arginine starvation-induced cell death involves mitochondrial dysfunction. Arginine depletion leads to impaired mitochondrial respiration and excessive production of reactive oxygen species, which in

turn cause oxidative damage to proteins, lipids, and DNA. This stress culminates in the loss of mitochondrial membrane integrity and the release of cytochrome c into the cytoplasm, initiating the intrinsic apoptotic pathway. Subsequent activation of caspase-9 and executioner caspases such as caspase-3 and caspase-7 leads to chromatin condensation, DNA fragmentation, and irreversible cell death [51].

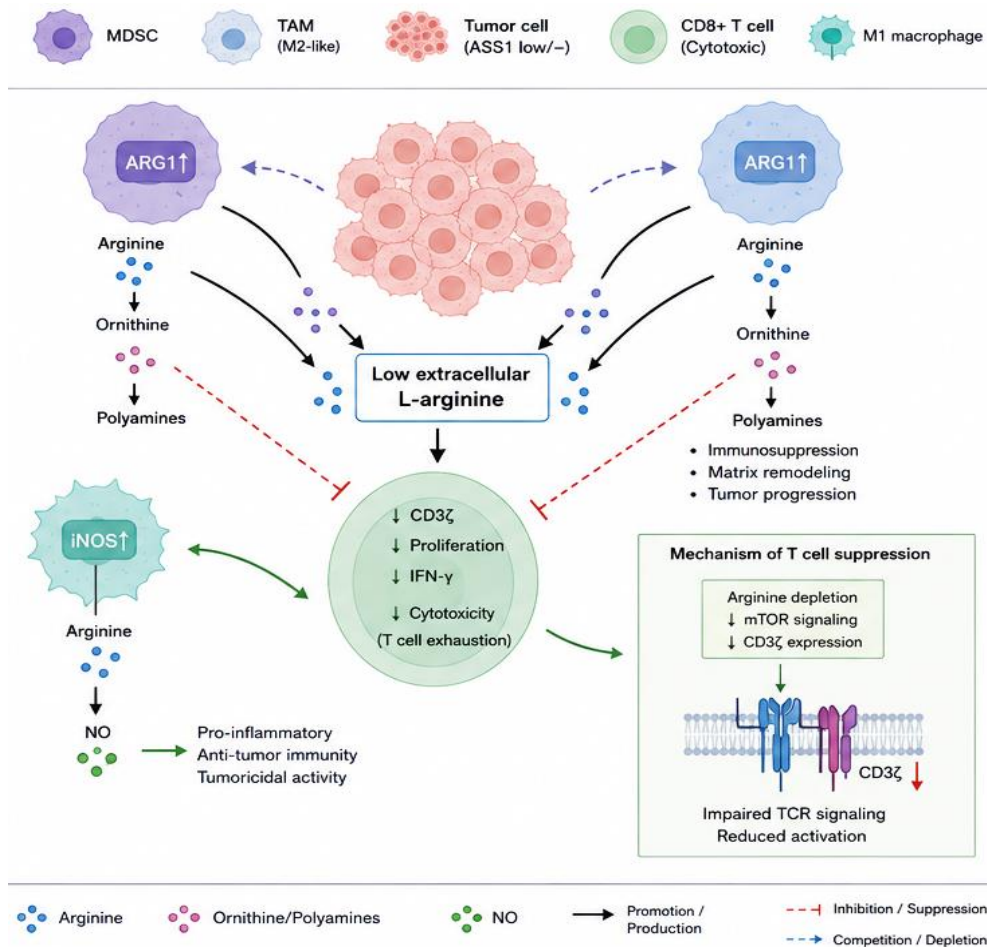


Fig. 2. Arginine competition in the tumor microenvironment. Arginase-expressing MDSCs and TAMs deplete extracellular arginine, leading to reduced availability for cytotoxic T-cells. This results in impaired TCR signaling, decreased proliferation, reduced cytokine production, and T-cell exhaustion. In contrast, iNOS-expressing M1 macrophages produce NO and support anti-tumor immunity. Tumor cells compete for arginine and adapt to low arginine conditions, promoting immune evasion and tumor progression.

In addition to caspase-dependent apoptosis, arginine deprivation can also activate caspase-independent cell death pathways. In this context, mitochondrial proteins such as apoptosis-inducing factor and endonuclease G translocate to the nucleus and induce DNA fragmentation independently of caspase activation. This dual mechanism of apoptosis ensures that arginine-dependent tumor cells are efficiently eliminated under conditions of metabolic stress.

Prolonged arginine deprivation may also trigger autophagic cell death and necroptosis, further expanding the spectrum of cell death mechanisms associated with arginine metabolism disruption. Collectively, these processes highlight the critical role of arginine availability in maintaining tumor cell survival and underscore its therapeutic potential.

L-Arginine Metabolism and Angiogenesis. Angiogenesis is essential for tumor growth, progression, and metastasis, and L-arginine metabolism plays a central role in regulating vascular biology within the tumor microenvironment. NO produced from arginine via NOS is a major mediator of endothelial function and vascular remodeling [52–55].

At physiological concentrations, NO promotes endothelial cell proliferation, vasodilation, and vascular permeability, thereby supporting the formation of new blood vessels. In cancer, this process is frequently co-opted by tumor cells to facilitate nutrient delivery and oxygen supply. NO also enhances vascular endothelial growth factor signaling, which further amplifies angiogenic responses and promotes tumor vascularization [56, 57].

Under hypoxic conditions, which are commonly present in rapidly growing tumors, arginine metabolism is often upregulated, leading to increase NO production and enhanced angiogenic signaling [58, 59]. However, the biological effects of NO remain highly context dependent, as excessive levels may induce cytotoxicity and inhibit tumor growth.

In addition to NO, polyamines derived from arginine metabolism contribute to angiogenesis by promoting endothelial cell proliferation and extracellular matrix remodeling [24, 25, 60]. Thus, arginine metabolism serves as a dual regulator of both tumor vascularization and structural adaptation of the tumor microenvironment.

Therapeutic Targeting of L-Arginine Metabolism in Cancer. Given its central role in tumor biology, L-arginine metabolism has emerged as a promising therapeutic target in oncology. One of the most extensively studied strategies is arginine deprivation therapy, which exploits the metabolic vulnerability of ASS1-deficient tumors [34]. The most well-characterized agent in this category is pegargiminase (ADI-PEG20), a pegylated form of arginine deiminase that enzymatically degrades arginine into citrulline and ammonia. PEGylation extends its half-life and reduces immunogenicity, enabling sustained systemic arginine depletion.

Clinical studies have demonstrated that ADI-PEG20 rapidly reduces plasma arginine levels, thereby leading to metabolic stress and inhibiting tumor growth in susceptible cancers. However, therapeutic resistance frequently develops through restoration of ASS1 expression, allowing tumor cells to regain endogenous arginine synthesis and escape arginine dependency. In addition, immune-mediated neutralization of the enzyme may further limit long-term efficacy.

To overcome these limitations, combination therapies involving chemotherapy, radiotherapy, and immune checkpoint inhibitors are currently being investigated.

An alternative therapeutic strategy focuses on the inhibition of arginase enzymes to restore arginine availability within the tumor microenvironment and enhance T-cell function. Agents such as CB-1158 (numidargistat), which selectively inhibit ARG1, have been shown to increase systemic arginine levels and improve

anti-tumor immune responses. More recently, dual inhibitors such as OATD-02 targeting both ARG1 and ARG2 have shown promise in preclinical studies by remodeling the tumor microenvironment, reducing polyamine accumulation, and enhancing immune activation [61, 62]. However, clinical efficacy remains modest when used as monotherapy, emphasizing the importance of combination approaches. Overall, targeting arginine metabolism represents a rapidly evolving field with significant translational potential. Future strategies will likely depend on biomarker-driven patient selection, identification of resistance mechanisms, and rational combination with immunotherapeutic approaches.

Conclusion. L-arginine metabolism represents a central metabolic and immunological hub in cancer, integrating nutrient sensing, immune regulation, cell death pathways, and vascular remodeling. Cancer cells exploit this pathway to support proliferation, evade immune surveillance, and adapt to metabolic stress conditions, while simultaneously reshaping the tumor microenvironment into an immunosuppressive and pro-angiogenic niche.

Therapeutic interventions targeting arginine metabolism have demonstrated strong preclinical and early clinical promise, particularly in tumors with ASS1 deficiency. However, metabolic plasticity and adaptive resistance mechanisms remain major challenges that limit long-term efficacy. The future of arginine-targeted therapies will depend on a deeper understanding of tumor metabolic heterogeneity and the development of combination strategies that integrate metabolic targeting with immunotherapy and conventional anticancer treatments.

Collectively, L-arginine metabolism represents a highly dynamic and therapeutically relevant axis in cancer biology, offering multiple opportunities for translational exploitation and precision oncology approaches.

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**L-ԱՐԳԻՆԻՆԻ ՄԵՏԱԲՈԼԻԶՄԸ ՔԱՂՑԿԵՂԻ ԺԱՄԱՆԱԿ.
ՌԻՌՈՒՑՔԱՅԻՆ ԲՈՐԲՈՔՄԱՆ, ԱՊՈԴՏՈՉԻ ԵՎ ԱՆԳԻՈԳԵՆԵԶԻ
ՓՈԽԿԱՊԱԿՑՎԱԾ ՌԻԹՅՈՒՆԸ**

L-արգինինի մետաբոլիզմը դիտարկվում է որպես քաղցկեղի կենսաբանության կենտրոնական կարգավորիչ առանցք, որը միավորում է մետաբոլիկ վերածրագրավորումը, իմունային մոդուլյացիան և ուռուցքային միկրոմիջավայրի վերաձևավորումը: Քաղցկեղային բջիջները հաճախ վերածրագրավորվում են արգինինի կլանման, սինթեզի և քայքայման ուղիները՝ պրոլիֆերացիան պահպանելու, իմունային հսկողությունից խուսափելու և մետաբոլիկ սթրեսի պայմաններին հարմարվելու նպատակով: Այս մետաբոլիկ ճկունությունն ապահովվում է առանցքային ֆերմենտային հանգույցների համակարգված կարգավորմամբ, այդ թվում՝ արգինինոսուկցինատսինթազ 1-ի, արգինինոսուկցինատիլազի, արգինազի իզոմերների (ARG1 և ARG2) և ազոտի օքսիդի սինթազների, որոնք միասին վերահսկում են ներբջջային արգինինի հասանելիությունը և դրա հաջորդ օղակի հետագա ազդանշանային ազդեցությունը: Ուռուցքային միկրոմիջավայրում արգինինի մետաբոլիզմը դառնում է մրցակցության հարթակ չարորակ բջիջների և իմունային բջիջների պոպուլյացիաների միջև: Ուռուցքներն օգտագործում են արգինինը՝ միելոիդ ծագման սուպրեսոր բջիջներում և ուռուցքի հետ ասոցացված մակրոֆագերում արգինազի ակտիվության բարձրացման միջոցով, ինչը հանգեցնում է T-բջիջների ակտիվացման խանգարման և հակաուռուցքային իմունիտետի ճնշման: Չուզանալով, արգինինի մետաբոլիզմի ընթացքում առաջացող ազոտի օքսիդը դրսևորում է կոնցենտրացիայից կախված ազդեցություն. այն կարող է ինչպես խթանել ուռուցքի առաջընթացը անգիոգենեզի և բջջային գոյատևման ազդանշանային ուղիների միջոցով, այնպես էլ ավելի բարձր կոնցենտրացիաներում առաջացնել ցիտոտոքսիկ սթրես և ապոպտոզ: Բացի այդ, արգինինի կատաբոլիզմից ածանցվող պոլիամինների կենսասինթեզը լրացուցիչ նպաստում է ուռուցքի աճին, քրոմատինի վերաձևավորմանը և բջջային մահվան նկատմամբ կայունությանը: Սույն ակնարկում ներկայացված է քաղցկեղի ժամանակ L-արգինինի մետաբոլիկ ուղիների համապարփակ վերլուծություն՝ հատուկ շեշտադրմամբ դրանց դերի վրա ուռուցքի հետ ասոցացված բորբոքման, ապոպտոզի կարգավորման և անգիոգենեզի գործընթացներում: Քննարկվում են նաև արգինինից կախվածությանն ուղղված թերապևտիկ ռազմավարությունները, այդ թվում՝ արգինինային դեպրիվացիայի թերապիան, արգինազի արգելակման մոտեցումները և նոր համակցված իմունոմետաբոլիկ ռազմավարությունները, ինչպես նաև ռեգիստենտության առանցքային մեխանիզմները,

ինչպիսիք են արգինինսուկցինատսինթազ 1-ի վերաէքսպրեսիան և մետարոլիկ վերակառուցումը: Ամփոփելով՝ L-արգինինի մետարոլիզմը բազմֆունկցիոնալ մետարոլիկ հանգույց է, որը կապում է ուռուցքի առաջընթացը իմունային կարգավորման հետ և առաջարկում է բազմաթիվ հեռանկարային թերապևտիկ թիրախներ ուռուցքաբանության մեջ:

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МЕТАБОЛИЗМ L-АРГИНИНА ПРИ РАКЕ: СВЯЗЬ ОПУХОЛЕВОГО ВОСПАЛЕНИЯ, АПОПТОЗА И АНГИОГЕНЕЗА

Метаболизм L-аргинина стал рассматриваться как центральная регуляторная ось в биологии рака, объединяющая метаболическое перепрограммирование, иммунную модуляцию и ремоделирование опухолевого микроокружения. Опухолевые клетки часто перестраивают пути поглощения, синтеза и деградации аргинина, чтобы поддерживать пролиферацию, уклоняться от иммунного надзора и адаптироваться к условиям метаболического стресса. Эта метаболическая пластичность обеспечивается согласованной регуляцией ключевых ферментативных узлов, включая аргининосукцинатсинтазу 1, аргининосукцинатлиазу, изоформы аргиназы (ARG1 и ARG2) и синтазы оксида азота, которые в совокупности контролируют внутриклеточную доступность аргинина и его нижестоящие сигнальные эффекты. В опухолевом микроокружении метаболизм аргинина становится ареной конкуренции между злокачественными клетками и популяциями иммунных клеток. Опухоли используют истощение аргинина за счет повышенной активности аргиназы в миелоидных супрессорных клетках и опухолеассоциированных макрофагах, что приводит к нарушению активации Т-клеток и подавлению противоопухолевого иммунитета. Параллельно оксид азота, образующийся в ходе метаболизма аргинина, оказывает концентрационно-зависимые эффекты: он может как способствовать прогрессии опухоли посредством ангиогенеза и сигнальных путей выживания, так и индуцировать цитотоксический стресс и апоптоз при более высоких концентрациях. Кроме того, биосинтез полиаминов, связанный с катаболизмом аргинина, дополнительно поддерживает рост опухоли, ремоделирование хроматина и устойчивость к клеточной гибели. В настоящем обзоре представлен всесторонний анализ путей метаболизма L-аргинина при раке с особым акцентом на их роль в опухолеассоциированном воспалении, регуляции апоптоза и ангиогенезе. Также обсуждаются терапевтические стратегии, направленные на зависимость опухолей от аргинина, включая терапию на основе аргининовой депривации, подходы с ингибированием аргиназы и новые комбинированные иммунометаболические стратегии, а также ключевые механизмы резистентности, такие как повторная экспрессия аргининосукцинатсинтазы 1 и метаболическая перестройка. В целом метаболизм L-аргинина представляет собой многофункциональный метаболический узел, связывающий прогрессию опухоли с иммунной регуляцией и открывающий множество перспективных терапевтических мишеней в онкологии.