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PERSPECTIVE

The arginine metabolism battlefield: how metabolite exchange in the tumor microenvironment shapes an immunosuppressive ecosystem

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Metabolic reprogramming is a prominent cancer hallmark that enables uncontrolled growth, survival, and dissemination of tumor cells. Among the diverse metabolic alterations, dysregulation of arginine metabolism has garnered significant attention due to its profound impact on cancer cells and the tumor microenvironment (TME). Arginine, a semi-essential amino acid, has a central role in various cellular processes, including protein synthesis, nitric oxide (NO) production, and polyamine biosynthesis. In the context of cancer aberrant arginine metabolism fuels tumor cell growth and orchestrates a complex interplay between tumor and immune cells, ultimately facilitating immune evasion and tumor progression.

Our latest research findings indicate that within the breast cancer TME there exists an interplay mechanism between tumor cells and other immune cells regarding arginine metabolism[1]. Tumor cell-derived arginine promotes polyamine biosynthesis in tumor-associated macrophages (TAMs), thereby shaping an immunosuppressive TME that suppresses CD8+ T cell function and ultimately contributes to the malignant progression of breast cancer. Based on this finding, this perspective article aimed to provide an in-depth overview of the current understanding of arginine metabolism in cancer with a particular focus on the implications for tumor immunology and potential therapeutic strategies.

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Arginine metabolism in the TME

Arginine can be synthesized from citrulline and aspartate *via* argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL). Arginase (ARG1/2) catalyzes the hydrolysis of arginine to ornithine and urea with ornithine serving as a precursor for polyamine biosynthesis. Arginine metabolism is tightly regulated in healthy cells. However, cancer cells often undergo metabolic reprogramming to meet the increased demands for growth and survival[2-4].

Arginine metabolism is essential for immune system function. Arginine is a key substance for the activation and function of immune cells, such as T cells, NK cells, and macrophages[5-7]. The TME is a complex ecosystem composed of tumor, immune, and stromal cells, in which cancer and immune cells compete for nutrients while exchanging immunosuppressive signals[8-10] (**Figure 1**).

The interaction of arginine metabolism in tumor and T cells

Arginine metabolism in the TME is highly dynamic and heterogeneous with different cell types competing for limited

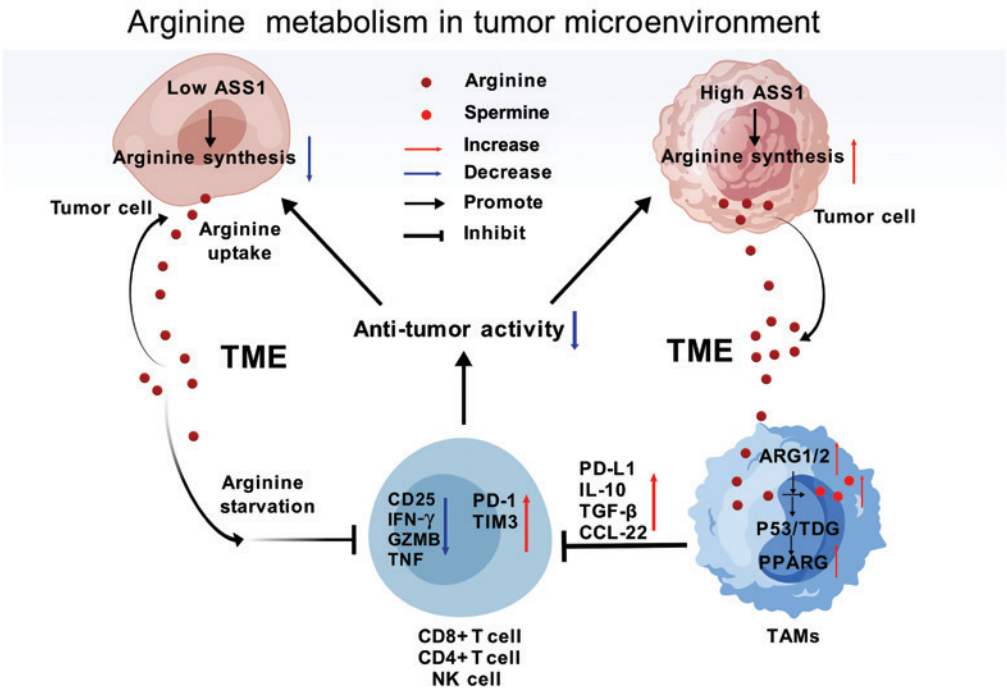


Figure 1 Impact of arginine metabolic reprogramming on the tumor microenvironment. Tumors with low ASS1 expression actively uptake arginine from the tumor microenvironment to fulfill tumor requirements for proliferation and division, thereby resulting in arginine deficiency within the tumor microenvironment. Arginine deficiency impedes the activation of immune cells, including CD4+ T, CD8+ T, and NK cells, and suppresses the synthesis of anti-tumor factors, such as GZMB, TNF-α, and IFN-γ, which diminishes the anti-tumor capacity of immune cells. Conversely, the arginine synthesized by tumor cells promotes the synthesis of spermine in TAMs of tumors with high ASS1 expression. Upregulation of spermine activates the P53/TDG/PPARG axis, which compels TAMs to secrete immunosuppressive factors, such as IL-10, PD-L1, and TGF-β. These immunosuppressive factors dampen the anti-tumor activities of CD4+ T, CD8+ T, and NK cells in the tumor microenvironment, ultimately contributing to tumor progression. ASS1, argininosuccinate synthase 1; GZMB, granzyme B; IFN-γ, interferon-gamma; IL-10, interleukin-10; PD-L1, programmed death-ligand 1; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor-beta; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha.

arginine resources. Tumor cells can be classified into two subtypes based on ASS1 expression [endogenous arginine synthesis-deficient tumors (low ASS1 expression) and arginine synthesis-proficient tumors (high ASS1 expression)]. Tumor cells in the low ASS1 expression subtype utilize extracellular arginine extensively to fuel biosynthetic demands for uncontrolled proliferation. Furthermore, some tumor cells frequently upregulate arginase and promote polyamine synthesis. Polyamines are essential for cell growth, proliferation, and stabilization of nucleic acids and membranes. The increased production of polyamines in cancer cells contributes to uncontrolled growth and enhanced survival[11-13]. Either low ASS1 expression or enhanced arginase activity can give rise to an arginine-deprived TME.

An arginine-deprived TME can impair T cell receptor (TCR) signaling, cytokine production, and cell proliferation, leading to T cell dysfunction and immunosuppression. Additionally, arginine deprivation can also promote T cell differentiation into regulatory T cells (Tregs), which are known to suppress anti-tumor immune responses. Similarly, NK cells require arginine for production of cytotoxic molecules, such as perforin and granzyme, the function of which can be compromised in an arginine-deprived TME. This metabolic perturbation not only impairs anti-tumor immune cells but also creates a pro-tumorigenic niche, ultimately driving malignant tumor progression.

The interaction of arginine metabolism in tumor cells and macrophages

Macrophages, an important component of the immune system, have a crucial role in arginine metabolism within the

TME. Arginine metabolism in macrophages is closely linked to the polarization state with M1 macrophages predominantly expressing NO synthase (NOS) and producing NO, while M2 macrophages mainly express arginase and promote polyamine biosynthesis[13].

Tumor cells regulate the function of TAMs in the TME by secreting various factors and metabolites[14]. Specifically, cytokines (CSF-1, VEGF, IL-10, and TGF-β) and metabolic products (lactic acid and succinic acid) secreted by tumor cells can drive TAMs to polarize towards the immunosuppressive M2 phenotype, which induces TAMs to highly express ARG1/2 and promote the malignant progression of tumors. Our latest research demonstrated that tumor cell-derived arginine is taken up by TAMs to enhance polyamine synthesis in tumors with high ASS1 expression, which triggers M2 polarization and induces the immunosuppressive characteristics of TAMs.

The interaction of arginine metabolism in macrophages and T cells

Although interferon-gamma (IFN-γ) secreted by CD8+ T cells has the potential to induce macrophages to polarize towards the anti-tumor M1 phenotype and augment anti-tumor activities, T cells frequently fail to effectively drive macrophage M1 polarization in the context of malignant tumors. Whether ASS1-low or -high tumors, CD8+ T cells are likely unable to acquire sufficient arginine to maintain anti-tumor activity. Cancer cells deplete arginine in the TME of ASS1-low tumors by directly consuming arginine or secreting factors and metabolites to induce TAMs to upregulate arginase ARG1/2 for arginine metabolism. TAMs take up most of the cancer cell-derived arginine in ASS1-high tumors given the substantial numerical dominance of TAMs over T cells within the TME.

Arginine deficiency resulting from the upregulated arginase activity in TAMs is widely recognized as a key contributor to the establishment of an immunosuppressive TME. Previous investigations have demonstrated that the ASS1 is highly expressed in some tumor cells, whereas arginase ARG1/2 expression, which is responsible for converting arginine to ornithine, remains low. Clearly, the theory that arginine deficiency gives rise to an immunosuppressive TME is not applicable to these special types of tumors. Our recent study revealed that the arginine level in the peripheral blood of breast cancer patients is positively correlated with tumor stage, which indicates that arginine deficiency might not be the sole reason underlying inhibition of T cell function. Therefore, we propose that there are additional non-arginine-deficiency mechanisms contributing to the formation of an immunosuppressive TME.

Our work further demonstrated that ASS1-high tumor cells supply arginine to fuel polyamine synthesis in TAMs. The upregulated polyamines, especially spermine, activates the TP53 signaling pathway and enhances the expression of thymine DNA glycosylase (TDG), thereby reducing the level of PPARG gene promoter methylation, which helps maintain the immunosuppressive phenotype of TAMs. In addition to increasing IL-10 and TGF-β transcription *via* PPARG, the elevated spermine can directly induce upregulation of PD-L1 in TAMs, thereby inhibiting the anti-tumor activity of CD8+ T cells.

These findings highlight spermine, an arginine metabolite, as a pivotal regulator of immune evasion by driving the transition from a static "nutritional competition" to a dynamic and multi-dimensional metabolic interplay model and providing a novel targetable molecule for improving the immunotherapy efficacy of malignant tumors (**Figure 2**).

Targeting arginine metabolism for cancer therapy

Targeting the arginine metabolic pathway has emerged as a promising therapeutic strategy given the critical role in cancer progression and immune evasion. Several approaches have been explored to disrupt arginine metabolism in tumor cells and the TME, including the utilization of arginine-degrading enzymes, inhibitors of arginine-metabolizing enzymes, and dietary interventions (**Figure 3**).

Arginine-depleting therapeutics

Arginine-degrading enzymes, such as arginine deiminase (ADI) and pegylated arginine deiminase (ADI-PEG20)[15, 16], have been developed to deplete arginine in the TME. These enzymes can starve ASS1-low tumor cells and impair growth and survival by removing arginine. In addition, arginine depletion can reverse immune suppression in the TME, thereby enhancing anti-tumor immune responses. ADI-PEG20 has shown promising results in preclinical and clinical studies, particularly in tumors that are auxotrophic for arginine, such as hepatocellular carcinoma and melanoma.

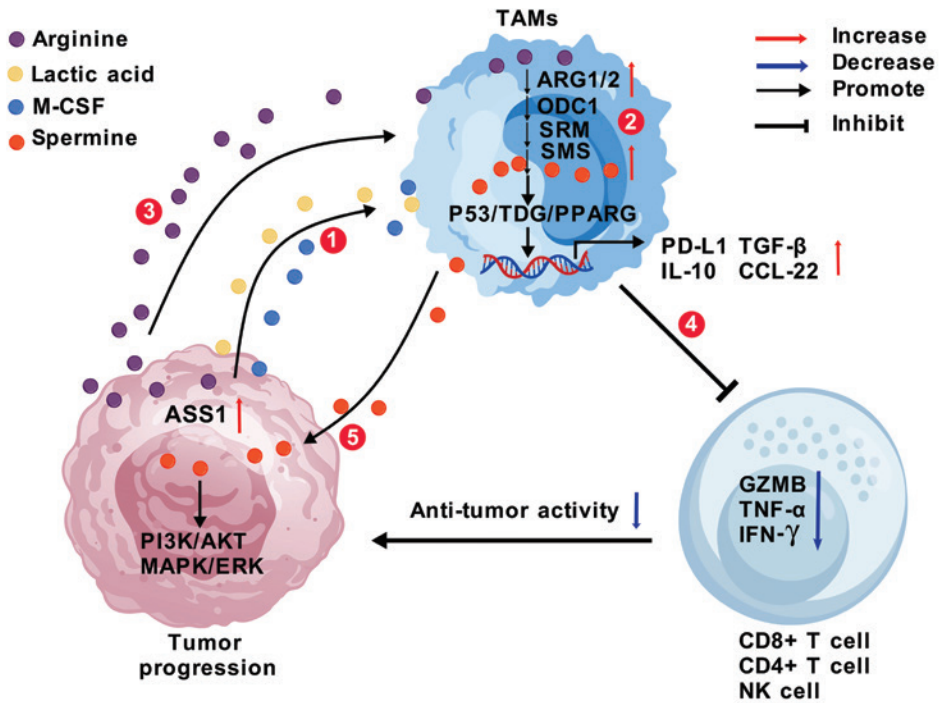


Figure 2 Reprogramming arginine metabolism drives tumor malignancy. ① Tumor cells secrete M-CSF and small molecules like lactic acid, thereby inducing polarization of TAMs and upregulating expression of ARG1 or ARG2. ② Through the coordinated action of a series of enzymes, including ARG1/ARG2, ODC1, SRM, and SMS, TAMs convert arginine into spermine. ③ Tumor cells with high arginine-synthesizing capacity can supply arginine to TAMs, thus facilitating the generation of spermine in TAMs. Upon an increase in spermine levels, ④ spermine suppresses the anti-tumor activities of CD4+ T, CD8+ T, and NK cells by upregulating the expression of immune-inhibitory factors, such as PD-L1, TGF-β, and IL-10 in TAMs. ⑤ Alternatively, spermine directly activates proliferation-associated signaling pathways within tumor cells, such as the PI3K/AKT and MAPK/ERK pathways, further fueling the malignant progression of tumors. ASS1, argininosuccinate synthase 1; ARG1, arginase 1; ARG2, arginase 2; IL-10, interleukin-10; M-CSF, macrophage colony-stimulating factor; ODC1, ornithine decarboxylase 1; PD-L1, programmed death-ligand 1; SRM, spermidine synthase; SMS, spermine synthase; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor-beta.

Our recent findings and multiple published studies have demonstrated that arginine can prominently enhance the growth of xenograft tumors in immunocompetent mice. Consequently, a low-arginine diet is also considered to be a potential adjuvant therapeutic approach for controlling tumors, particularly ASS1-low tumors. Dietary interventions targeting arginine metabolism have also been explored. For example, a low-arginine diet has been shown to reduce tumor growth and metastasis in preclinical models. By restricting arginine intake, this dietary approach can starve tumor cells and disrupt metabolic reprogramming.

Although arginine deprivation therapy exhibits promising clinical potential in ASS1-low tumors, challenges like arginine metabolic compensation and intratumoral heterogeneity must be considered. In addition, it should be noted that arginine depletion therapy may unintentionally inhibit T and NK cell anti-tumor activity.

Targeting polyamine biosynthesis

High ASS1 expression in cancer cells promotes tumor growth and reshaping the immunosuppressive TME *via* the arginine-polyamine metabolic axis. Consequently, blocking polyamine synthesis with use of polyamine synthesis inhibitors might offer an effective therapeutic approach for ASS1-high tumors or tumors with strong polyamine synthesis capacity. ARG1/2 and ornithine decarboxylase 1 (ODC1) serve as key rate-limiting enzymes in the polyamine biosynthesis pathway. Currently, clinical drug development of arginase inhibitors is in the nascent stage and no drugs have entered clinical studies to date.

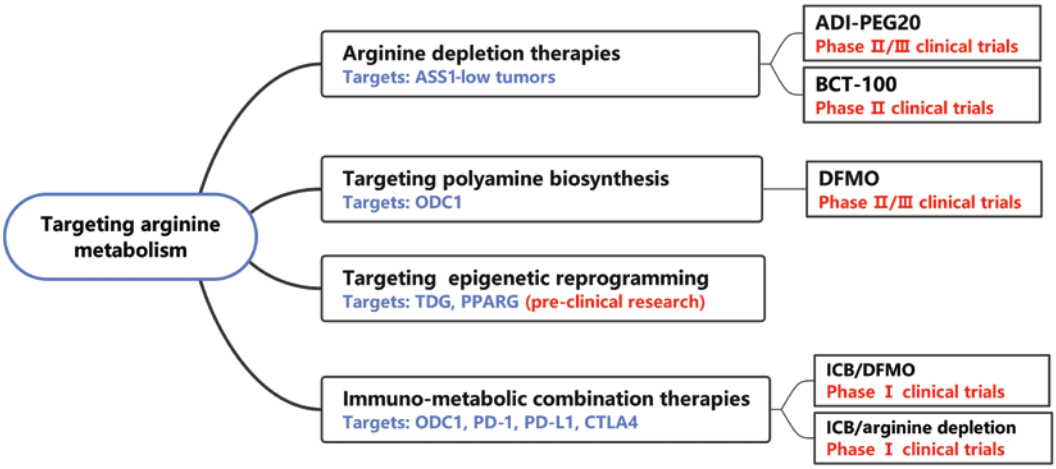


Figure 3 Cancer therapeutic strategies targeting the arginine metabolic pathway. (1) Tumor growth can be inhibited through arginine deprivation therapy in tumors with arginine synthesis defects. Drugs that have entered clinical trials include ADI-PEG20 and BCT-100. (2) Polyamine synthesis can be inhibited by suppressing the activity of the rate-limiting enzyme (ODC1) in polyamine synthesis for tumors with increased polyamine synthesis. Currently, the ODC1 inhibitor (DFMO) has entered clinical trials. (3) The pro-tumor effects of polyamines can be inhibited by suppressing the activation of downstream pathways (TDG, PPARG) induced by polyamines for tumors with increased polyamine synthesis. The related inhibitors are in the preclinical research stage. (4) The anti-tumor function of immune cells can be activated from multiple angles by combining immune checkpoint blockade therapy (anti-PD-L1 and anti-PD-1 therapy) with targeted arginine metabolism therapy (ODC1 inhibitors and arginine deprivation). Currently, related therapies have entered phase I clinical trials. ADI-PEG20, pegylated arginine deiminase; ASS1, argininosuccinate synthase 1; DFMO, difluoromethylornithine; ICB, immune checkpoint blockade; ODC1, ornithine decarboxylase 1;TDG, thymine DNA glycosylase.

However, ODC1 inhibitors and combination therapies have been tested in clinical investigations in a variety of malignant tumors, including gliomas, small cell lung cancer, Hodgkin's lymphoma, and digestive tract tumors, and have demonstrated positive anti-cancer efficacy[17-19]. Our recent work revealed that difluoromethylornithine (DFMO), an ODC1 inhibitor approved by the FDA for the treatment of African trypanosomiasis, disrupts the arginine-polyamine axis between tumor cells and TAMs, reversing immunosuppressive TME and inhibiting tumor progression. This finding suggested that DFMO holds significant translational potential in the treatment of malignant tumors.

Targeting spermine-mediated epigenetic reprogramming

Our recent study demonstrated that as a core molecule in the interplay between metabolism and epigenetics, spermine decreases the level of PPARG methylation by enhancing the activity of TDG and facilitates the formation of an immunosuppressive TME. Consequently, we proposed that interfering with the TDG demethylation activity or PPARG transcription activity induced by spermine might potentially constitute a novel strategy for reversing the immunosuppressive TME. At present, the relevant targeted drugs are in the experimental research stage.

Immuno-metabolic combination therapies

Immune checkpoint blockade (ICB), such as anti-PD-1 and anti-PD-L1 antibody therapy, release the brakes on the immune system and enhance anti-tumor immune responses. However, PD-L1 upregulation and the immunosuppressive TME resulting from arginine metabolic reprogramming can contribute to ICB resistance[20]. Therefore, combining therapies that target arginine metabolism with other immunotherapeutic approaches may hold great promise. For example, combining ADI-PEG20 or DFMO with ICB therapy may overcome ICB resistance in the arginine-dysregulated TME. Notably, ADI-PEG20 directly impedes the proliferation of tumor cells and downregulates the expression of PD-L1 on the surface of TAMs, which weakens suppression of other immune cells. DFMO serves a dual function through polyamine synthesis blockade. First, DFMO directly impairs polyamine-promoted tumor cell proliferation. Second, DFMO modulates the TME by inhibiting the polarization

of TAMs towards the M2 phenotype, reducing the secretion of immunosuppressive factors, such as IL-10 and TGF-β by TAMs, which indirectly lowers PD-L1/PD-1 expression on tumor and immune cells and enhances the anti-tumor activity of immune cells. Consequently, the combination of targeting arginine metabolism and immunotherapy holds great promise in more potently activating the immune system and exerting a more robust anti-tumor effect.

Challenges and future perspectives

Although our latest research has shown that the interaction between tumor and immune cells is no longer a simple "nutrient competition," it involves multidimensional metabolic interactions. There are still important issues that warrant further investigation. First, the precise mechanisms governing how arginine metabolites modulate immune cell polarization and function across cancer types have not been established. Distinct types of tumors can drive tumor progression through diverse patterns of metabolic remodeling. This finding implies that investigations into arginine metabolism must be tailored to the specific tumor types, rather than adopting a simplistic "one fits all" approach. Second, the TME exhibits remarkable spatial and temporal heterogeneity in arginine metabolism, driven by diverse ASS1 expression levels, cell-cell interactions, and metabolic adaptability. Analyzing the spatiotemporal heterogeneity of arginine metabolism in the TME can help uncover the key mechanisms of treatment resistance but also provide theoretical basis for drug delivery regions and timing, thereby facilitating the implementation of precise treatment for patients. With advances in science and technology, integrating spatial metabolomics (e.g., mass spectrometry imaging), single-cell RNA sequencing, and immune profiling will enable high-resolution mapping of arginine metabolic interactions in the TME. For example, identifying "arginine desert" hotspots *via* microsatellite instability (MSI) and correlating the hotspots with immune cell dysfunction (e.g., CD8+ T cell exhaustion markers) could validate the spatial-temporal dynamics of metabolic immunosuppression. Single-cell analyses may also uncover rare cell populations (e.g., arginine-resistant tumor subsets or metabolically reprogrammed macrophages) driving therapy resistance.

To translate current research into clinical practice, tumors need to be classified as ASS1-low or -high subtypes. Developing ASS1-centric predictive biomarkers requires consensus on detection standards (e.g., IHC scoring algorithms and RNA-seq expression cutoffs). Multi-center investigations of training and validation sets across different detection platforms are required to determine the optimal cut-off value of ASS1 expression in tumor specimens. Moreover, incorporating circulating arginine metabolites (e.g., ornithine and spermine) and immune-related parameters (e.g., T cell receptor diversity) into liquid biopsies could enable real-time monitoring of treatment response. Machine learning models trained on multi-omics data may predict patient sensitivity to arginine depletion *vs*. polyamine inhibition, facilitating personalized combination therapies. The implementation and application of standardized assays, dynamic monitoring, and precision combination therapies hold the promise of inaugurating a new era for arginine metabolism targeted therapies.

Conclusions

Arginine metabolism has a pivotal role in cancer biology, bridging metabolic reprogramming and immune evasion. Our latest study advanced the metabolic-immunology cross-discipline by revealing novel mechanisms of arginine metabolites (e.g., spermine) in regulating immune cell polarization, which provides a paradigm for metabolic microenvironment research across cancer types. Clinically, tumors can be stratified by ASS1 expression for personalized therapy (i.e., arginine depletion for ASS1-low tumors and polyamine synthesis inhibition for ASS1-high tumors). Combining arginine metabolism inhibitors (e.g., ADI-PEG20 and DFMO) with PD-1 blockade can potentially reverse immunotherapy resistance. Moreover, circulating arginine metabolites (ornithine and spermine) may be utilized in liquid biopsy for dynamic monitoring of therapeutic efficacy. Together, targeting arginine metabolism may unlock new frontiers in cancer treatment, particularly in overcoming immune evasion and enhancing immunotherapy responses.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Man-Li Luo, Hai Hu, Hongbo Hu, Hongde Li.
Wrote the manuscript: Yinghua Zhu, Man-Li Luo.

References

1. Zhu Y, Zhou Z, Du X, Lin X, Liang ZM, Chen S, et al. Cancer cell-derived arginine fuels polyamine biosynthesis in tumor-associated macrophages to promote immune evasion. Cancer Cell. 2025; 43(6): 1045-60.e7.
2. Feng X, Ji Z, Fan X, Kong Y, Yu Y, Shao Y, et al. ASS1 enhances anoikis resistance via AMPK/CPT1A-mediated fatty acid metabolism in ovarian cancer. Cancer Lett. 2024: 22: 217082.
3. Lim LQJ, Adler L, Hajaj E, Soria LR, Perry RB, Darzi N, et al. ASS1 metabolically contributes to the nuclear and cytosolic p53-mediated DNA damage response. Nat Metab. 2024; 6: 1294-309.
4. Mossmann D, Müller C, Park S, Ryback B, Colombi M, Ritter N, et al. Arginine reprograms metabolism in liver cancer via RBM39. Cell. 2023; 186: 5068-83.e23.
5. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, et al. L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell. 2016; 167: 829-42.e13.
6. Oberlies J, Watzl C, Giese T, Luckner C, Kropf P, Müller I, et al. Regulation of NK cell function by human granulocyte arginase. J Immunol. 2009; 182: 5259-67.
7. Furuke K, Burd PR, Horvath-Arcidiacono JA, Hori K, Mostowski H, Bloom ET. Human NK cells express endothelial nitric oxide synthase, and nitric oxide protects them from activation-induced cell death by regulating expression of TNF-alpha. J Immunol. 1999; 163: 1473-80.
8. de Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. Cancer Cell. 2023; 41: 374-403.
9. Zhou S, Gu J, Liu R, Wei S, Wang Q, Shen H, et al. Spermine alleviates acute liver injury by inhibiting liver-resident macrophage pro-inflammatory response through ATG5-dependent autophagy. Front Immunol. 2018; 9: 948.
10. Kaymak I, Williams KS, Cantor JR, Jones RG. Immunometabolic interplay in the tumor microenvironment. Cancer Cell. 2021; 39: 28-37.
11. Puleston DJ, Buck MD, Klein Geltink RI, Kyle RL, Caputa G, O'Sullivan D, et al. Polyamines and eIF5A hypusination modulate mitochondrial respiration and macrophage activation. Cell Metab. 2019; 30: 352-63.e8.
12. Sun Y, Zhou P, Qian J, Zeng Q, Wei G, Li Y, et al. Spermine synthase engages in macrophages M2 polarization to sabotage antitumor immunity in hepatocellular carcinoma. Cell Death Differ. 2025; 32: 573-86.
13. Xu H, Zhang X, Wang X, Li B, Yu H, Quan Y, et al. Cellular spermine targets JAK signaling to restrain cytokine-mediated autoimmunity. Immunity. 2024; 57: 1796-811.e8.
14. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature. 2014; 513: 559-63.
15. Chang KY, Chiang NJ, Wu SY, Yen CJ, Chen SH, Yeh YM, et al. Phase 1b study of pegylated arginine deiminase (ADI-PEG 20) plus Pembrolizumab in advanced solid cancers. Oncoimmunology. 2021; 10: 1943253.
16. Kwong TT, Deng HH, Wong CH, Chan AWH, Chan LL, Chok SK, et al. PEG-BCT-100 and canavanine synergistically induce apoptosis in arginine biosynthetic enzyme-deficient pancreatic cancer. Cancer Res Commun. 2024; 4: 3180-9.
17. Paudyal S, Vallejo FA, Cilingir EK, Zhou Y, Mintz KJ, Pressman Y, et al. DFMO carbon dots for treatment of neuroblastoma and bioimaging. ACS Appl Bio Mater. 2022; 5: 3300-9.
18. Travers M, Brown SM, Dunworth M, Holbert CE, Wiehagen KR, Bachman KE, et al. DFMO and 5-azacytidine increase M1 macrophages in the tumor microenvironment of murine ovarian cancer. Cancer Res. 2019; 79: 3445-54.
19. Alexiou GA, Vartholomatos E, I Tsamis K, Peponi E, Markopoulos G, A Papathanasopoulou V, et al. Combination treatment for glioblastoma with temozolomide, DFMO and radiation. J BUON. 2019; 24: 397-404.
20. Aaboe Jørgensen M, Ugel S, Linder Hübbe M, Carretta M, Perez-Penco M, Weis-Banke SE, et al. Arginase 1-based immune modulatory vaccines induce anticancer immunity and synergize with anti-PD-1 checkpoint blockade. Cancer Immunol Res. 2021; 9: 1316-26.

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