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Review article

Metabolic pathways of L-arginine and therapeutic consequences in tumors

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ABSTRACT

Difference in the metabolism of normal and cancer cells inspires to search for new, more specific and less toxic therapies than those currently used.

The development of tumors is conditioned by genetic changes in cancer-transformed cells, immunological tolerance and immunosuppression. At the initial stages of carcinogenesis, the immune system shows anti-tumor activity, however later, cancer disrupts the function of Th1/Th17/Th2 lymphocytes by regulatory T (Treg) cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) and finally causes immunosuppression.

Recently, much attention has been devoted to the influence of L-arginine metabolism disorders on both carcinogenesis and the immune system. L-Arginine is essential for the maturation of the T cell receptor zeta (TCRζ), and its absence deprives T-cells of the ability to interact with tumor antigens. MDSCs deplete L-arginine due to a high expression of arginase 1 (ARG1) and their number increases 4–10 times depending on the type of the cancer.

L-Arginine has been shown to be essential for the survival and progression of arginine auxotrophic tumors. However, the progression of arginine non-auxotrophic tumors is independent of exogenous L-arginine, because these tumors have arginine-succinate synthetase (ASS1) activity and are available to produce L-arginine from citrulline.

Clinical studies have confirmed the high efficacy of arginine auxotrophic tumors therapy based on the elimination of L-arginine. However, L-arginine supplementation may improve the results of treatment of patients with arginine non-auxotrophic cancer.

This review is an attempt to explain the seemingly contradictory results of oncological therapies based on the deprivation or supplementation of L-arginine.

1. Introduction

L-Arginine is a conditionally essential amino acid. This means that in the adult organism L-arginine is produced *de novo* in sufficient quantities, but in developmental age and in some pathological conditions this quantity is not sufficient and therefore a dietary intake is required [1,2]. The total plasma concentration of L-arginine varies from 95 to 250 μmol/l and depends on the developmental stage and nutritional status of the body, while intracellular concentrations are within the range of 1–2 mmol/l. Adults take almost 5.4 g of L-arginine per day.

L-Arginine homeostasis depends on dietary supply, endogenous synthesis, catabolism, and transport efficiency of L-arginine through cell membranes. About 80% of L-arginine comes from recycled amino acids released by protein degradation. The decisive influence on the performance of endogenous L-arginine synthesis is the availability of cytokines produced by the enterocytes. The gut is the main source of citrulline for the synthesis of L-arginine occurring in proximal renal tubules, which is known as the intestinal-renal axis (Fig. 1) [3]. Following intravenous infusion, maximum plasma concentrations of L-arginine occur after 20–30 minutes, and after oral administration after 60 min [4]. Orally administered L-arginine is rapidly and almost completely absorbed by the intestinal cationic amino acid transporter (CAT) system.

L-Arginine is the precursor of many substances important for the organism. These are primarily proteins, nitric oxide, proline, creatine, agmatine and polyamine (Fig. 2). L-Arginine can stimulate secretion of hormones such as insulin, glucagon, growth hormone and prolactin. Moreover, it is involved in immunoregulation.

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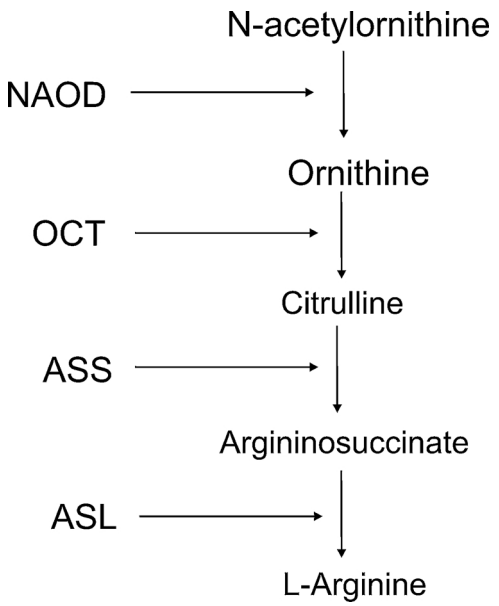

Fig. 1. Intracellular synthesis of L-arginine.
Abbreviations: NAOD - Acetyl-ornithase; OCT - Ornithine Transcarbamoyltransferase; ASS - Argininosuccinate Synthase; ASL - Argininosuccinate Lyase.

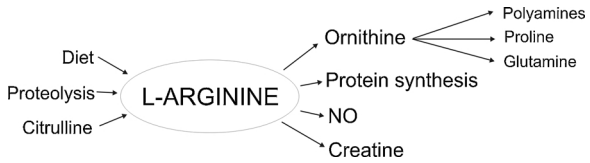

Fig. 2. Sources and metabolites of L-arginine.

The synthesis of about 60% of L-arginine occurs in the kidneys, where the citrulline- non- protein aminoacid, a product of endogenous protein catabolism, is extracted from the blood plasma. With the involvement of L-arginine succinate synthetase (ASS, EC 6.3.4.5) and arginine succinate lyase (ASL, EC 4.3.2.1), citrulline is converted into L-arginine. These reactions are the components of the ornithine cycle. The low efficiency of the ornithine cycle is due to the low rate of response maximal Velocity (*V*max) catalyzed by ASS1 and ASL and the limited availability of citrulline.

Apart from dietary sources and endogenous synthesis, the availability of L-arginine for metabolic functions is determined by the action of its transporters located in the plasma and mitochondrial membranes. The double lipid membrane of the cell is not permeable to the L-arginine molecule, and thus its cellular transport requires the involvement of a transporter system located in the cell membranes. CAT-1 occurs constitutively in all cells except hepatocytes, CAT-2 A occurs in hepatocytes, CAT-2B is a cytokine-induced transporter, and CAT-3 is involved in embryonic development [5]. CAT deficiency limits the transport of L-arginine from plasma to cells [6]. Cytokines, interferon and tumor necrosis factor (TNFα) stimulate the activity of L-arginine transporters and increase nitric oxide synthase activity (NOS, EC 1.14.13.39) [7,8].

L-arginine degradation is catalyzed by the four enzymes present in many isoforms: arginase (ARG, EC 3.5.3.1), NOS, arginine decarboxylase (ADC, EC 4.1.1.19) and arginine: glycine amidinotransferase (AGAT, EC 6.3.4.5) (Fig. 3). In mammals, there are two isomorphic ARG that differ in tissue distribution and subcellular localization. ARG I is a cytoplasmic protein expressed primarily in the liver, which catalyzes the last stage of the urinary cycle. ARG II is a mitochondrial protein found in many tissues.

Ornithine, a direct product of L-arginine metabolism, is a substrate for the synthesis of polyamines in a reaction catalyzed by ornithine

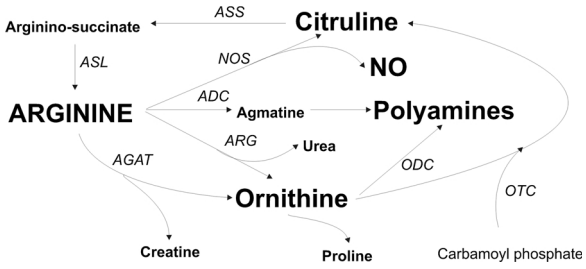

Fig. 3. L-arginine metabolism.
Abbreviations: ADC - arginine decarboxylase; AGAT - arginine glycine amidinotransferase; ARG - arginase; ASL - argininosuccinate lyase; ASS - argininosuccinate synthetase; ODC - ornithine decarboxylase; OTC - ornithine transcarbamylase; NOS - nitric oxide synthase.

decarboxylase (ODC, ornithine transcarbamylase) [9]. Polyamines are biogenic compounds formed in all cells by the decarboxylation of some amino acids, including L-arginine. Polyamines (including putrescine, spermidine, spermine) occurred in the cytoplasm of healthy cells are responsible for their proper development and functioning. Polyamines interact with DNA, RNA, proteins, phospholipids and other polyanions, stimulating biosynthesis of nucleic acids and proteins in cells, affecting growth, cell proliferation and differentiation. Polyamines protect the nucleic acids from the harmful effects of environmental factors. The activity of polyamines in the processes of replication, transcription and translation largely depends on the concentration.

Attention was paid to L-arginine after the ubiquitous NO signal transduction molecule was discovered. The decomposition reaction of L-arginine into citrulline and NO catalyses nitric oxide synthase (NOS). NOS occurs in three isoforms: eNOS (endothelial), nNOS (neuronal) and iNOS (inducible), derived from macrophages. It is estimated that about 1.5% of L-arginine enters the NO synthesis route.

K_m values for L-arginine of ARG I and II (~10 mmol/l) are much higher than that of iNOS (~5 μmol/L), whereas V_{max} of ARG I and II were 10^3–10^4 times higher than that of iNOS [10]. Thus, V_{max}/K_m values of ARG are close to iNOS value, and these enzymes were expected to compete for L-arginine in the cells. Therefore, the consumption of L-arginine by both *in vitro* enzymes is comparable and the *in vivo* consumption is variable and depends on the immunological polarization, which means the Th1/Th2 ratio. Th1 cytokines increase NOS activity and Th2 cytokines raise ARG activity.

Physiological plasma concentrations of L-arginine are about 50–100 μM and are many times lower than intracellular concentration, which is about 1 mM [11]. With the difference in L-arginine concentrations between the plasma and the cell, the so-called 'arginine paradox' is associated with the rate at which NO synthesis rates determine the concentration of extracellular L-arginine rather than intracellular. According to one hypothesis, dimethylarginine (ADMA) is the cause of this phenomenon, which by blocking eNOS reduces the synthesis of NO [12–14]. High plasma L-arginine displaces ADMA from eNOS, resulting in increased NO production [11,15].

The impact of L-arginine metabolism disorders on both carcinogenesis and on antitumor immune system activity, recently received a lot of attention. The results of these studies indicate that L-arginine and its metabolic products are crucial for the development and progression of cancer. The results of cell line studies indicate that L-arginine supplementation improves non-auxotrophic cancer therapy by improving the antineoplastic properties of the immune system, while the benefits of L-arginine deprivation result from the direct influence on auxotrophic tumor cells that cause their autophagy and apoptosis (Fig. 4). The role of L-arginine deprivation in the treatment of auxotrophic tumors increases with the increasing number of clinical trials, while there are still too few studies assessing the effectiveness of non-auxotrophic cancers therapy using L-arginine supplementation [16].

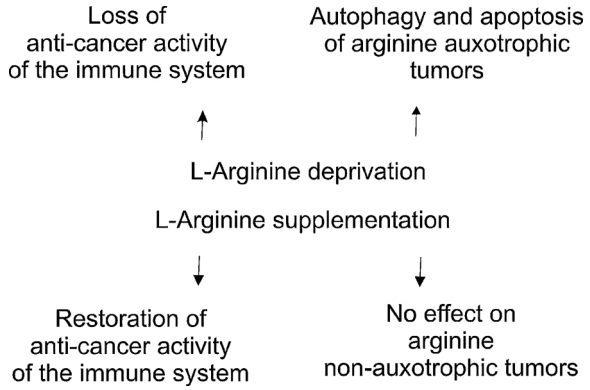

Fig. 4. The effect of L-arginine supplementation or deprivation on the immune system.

2. Review

2.1. Disorders of L-arginine metabolism in tumors

The development of normal cells in L-arginine-depleted conditions is stopped in the G0/G1 cycle of the cell cycle. However, placing them in the L-arginine culture medium restores the ability to divide [17]. Melanoma cells, kidney cancer, hepatocellular carcinoma, malignant pleural mesothelioma and other cancers are devoid of ASS1 expression, which is completely dependent on extracellular arginine [18,19]. This property is called an arginine auxotrophy [20,21]. In leukemia cell lines, the addition of citrulline or arginine succinate to the culture medium has not reduced the need for L-arginine due to low Vmax. ASS1 and ASL converts citrulline to arginine succinate and then L-arginine (Fig. 5) [22,23].

Depletion of L-arginine results in systemic and local effects associated with tumor microenvironment. On the basis of auxotrophy, a new strategy for treatment of tumors totally or particulary devoid of ASS1 expression was developed [24]. It is based on the elimination of L-arginine from the circulatory system by enzymes, which, like ARG, catalyze the degradation of L-arginine. The pegylated arginine deiminase (EC 3.5.3.6) (ADI-PEG20, BCT-100, PEG-BCT-100, rhArg1peg5000) is used instead of ARG because of adverse side effects and short half-life ($t_{1/2}$) [25,26]. ADI-PEG20 induced the death of the prostate cancer cell line (auxotrophic) by mitochondrial damage, nuclear leakage and chromatin autophagy ("self-eating") [27].

The removal of L-arginine from blood plasma results in the regression of auxotrophic tumors by autophagy and tumor cell apoptosis, but it also interferes with the relationship between tumor cells and its microenvironment [28–30]. The reduction of L-arginine does not induce autophagy or apoptosis of non-auxotrophic tumor cells that synthesize L-arginine de novo from citrulline.

The autophagy for cell survival is controlled by serine-threonine protein kinase assay (mTOR). L-arginine-induced activation induces the production of autophagosomes in the cells and their association with lysosomes, leading to their degradation [31,32]. Expression of ASS1 in the cell lines of different tumors of the same organ is often different (Table 1).

Some histological subtypes of ovarian, gastric and colorectal cancer overexpress ASS1, while others are devoid of expression [48,63]. The results indicate that low levels of ASS1 are a good predictor of the efficacy of L-arginine deprivation therapy [64]. The efficacy of ADI-PEG20 therapy has been confirmed in clinical trials in patients with hepatocellular carcinoma, melanoma, prostate cancer, and recently

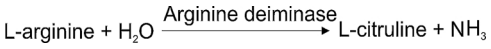

Fig. 5. Hydrolysis of L-arginine to L-citrulline.

Table 1
Expression of ASS1 in cells of different types of cancer.

Cancer types with low expression of ASS	References	Cancer types with high expression of ASS	References
Melanoma	[33–35]	Pulmonary neuroendocrine carcinoma	[36]
Breast cancer cells	[37,38]	Colon carcinoma	[38–40]
Prostate cancer cells	[26,41]	Gastric cancer	[42–44]
Hepatocellular carcinoma (HCC)	[26,45,46]	Serous subtype ovarian carcinoma	[47,48]
Pancreatic cancer cells	[49]		
Myeloid Leukemia	[50,51]		
Glioma	[52]		
Mesothelioma cell lines	[53,54]		
Renal cell carcinoma	[55]		
Lung cancer	[56,57]		
Non-serous ovarian carcinoma	[47,48]		
Endometrial carcinoma	[58]		
Sarcoma	[59,60]		
Bladder cancer	[61,62]		

with small cell lung cancer and acute leukemia [51,56,65,66].

2.2. Immune system and L-arginine

In the early stages of carcinogenesis, the immune system is anticancerous due to cytotoxic reactions, apoptosis and secreted cytokines, but later the cancer reprograms myeloid cells, allowing them to escape from immunological surveillance [67].

For example, colon cancer by T-cell regulators (Treg), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) disrupt Th1/Th17/Th2 lymphocyte function, causing immunosuppression [68,69]. The MDSCs expansion has been confirmed in all cancer models and in most types of cancer patients. MDSCs are a heterogeneous population of myeloid progenitor cells that are capable of potent T-cell suppression. In healthy individuals, MDSCs differentiate into mature granulocytes, macrophages and dendritic cells, and in cancer patients they do not mature but migrate to peripheral lymphatic organs and accumulate in the microenvironment. tumor. MDSCs in healthy peripheral blood account for less than 1% of myeloid cells, and in tumor microenvironment - approximately 5% of all cells [70]. The number of MDSCs increases 4–10 times according to the type and severity of cancer [71,72].

MDSCs development is regulated by a network of signals that foster their accumulation and activation. MDSCs accumulation is controlled by chemokines (CCLs) whose production increases in cancer. CCL2 mediates the recruitment of macrophages and stimulates tumor growth, progression and metastasis [73–75].

There are two major types of MDSC: granulocytic (G-MDSCs) morphologically and phenotypically like neutrophils and monocytic (M-MDSCs) showing similarity to monocytes. G-MDSCs differ from M-MDSCs by morphology and phenotype, and by immunosuppression. M-MDSCs represent 20–30% of the MDSCs population and retain the ability to differentiate into mature dendritic and macrophage cells and to produce reactive nitrogen forms. MDSCs are immunosuppressive by communicating with T-cells and with other immune cells [76].

The activation of TAMs is characterized by one of two states of polarization: M1 or M2. It has been shown that M1-MDSCs are converted to M2-MDSCs according to tumor stage. M1-MDSCs differ from M2 by L-arginine metabolism. Macrophages M2 have high ARG 1 activity, whereas macrophages M1 have high iNOS activity. Both populations, by affecting these enzymes, can regulate the immune response [77–79]. M2-MDSCs have pronounced cytoplasmic activity - they accelerate tumor growth mainly by increasing expression of ARG1 and activating regulatory lymphocytes (Treg). M1-MDSCs have antitumor activity [80,81]. Although MDSCs are responsible for

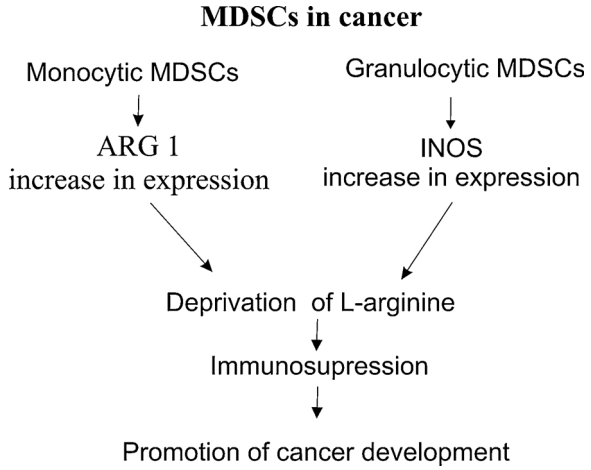

Fig. 6. The effect of MDSCs on cancer progression - one of several mechanisms. Abbreviations: MDSCs - Myeloid-Derived Suppressor Cells; INOS - Inducible Nitric Oxide Synthase; ARG 1 - Arginase 1.

immunosupression, T-cell activity is a standard in evaluating their function. Despite the significant development of flow cytometry, tumor cell phenotype analysis continues to pose a problem. Its main reason is the diversity of cells in the tumor microenvironment and the technical difficulties associated with the preparation of tumor samples for flow cytometry [82].

G-MDSCs in immune suppression use mainly reactive oxygen species (ROS) and M-MDSCs increase iNOS or ARG activity. Overexpression of iNOS is induced by cytokines produced by Th1 cells ie TNF-α, IL-1, IFN-γ and hypoxia and lipopolysaccharide (LPS) [79], and overexpression of ARG1 is mediated by cytokines produced by Th2 lymphocytes i.e. IL-4, IL-10 and IL-13 [83]. It has been shown that MDSCs play an important role in suppressing the immune response by ARG1 (Fig. 6) [84].

The increase in ARG1 activity results in the depletion of L-arginine from the tumor microenvironment and lowers its concentration in the circulatory system. L-arginine is essential for the maturation of the T-cell receptor ζ-chain (TCRζ), and lack of L-arginine lowers expression of this receptor and deprives T-cells to interact with antigens [85,86].

Recently, Feldmeyer et al. [87] described another previously unknown mechanism of T-cell suppression by low L-arginine levels. The authors demonstrated that L-arginine deficiency lowers the dephosphorylation of cofilin, which participates in the restoration of the actin necessary to create immune synapses and T-cell proliferation.

Available data indicate that the suppression of G-MDSCs and M-MDSCs in the tumor is stronger than in peripheral lymphoid organs. MDSC elimination restores the ability of the immune system to anti-tumor cytotoxicity [88,89]. MDSC elimination in oncological patients restores the ability of Th-cells to produce IFN-γ and proliferation [90].

The incubation of gastric cancer cells in L-arginine medium for 24–72 h causes their apoptosis [91]. Buis et al. [92] demonstrated a significant improvement in the treatment outcome of patients with head and neck squamous cell carcinoma who received perioperative L-arginine supplementation.

Research shows that supplementation of L-arginine renders T lymphocytes capable of reacting to tumor antigens and improves the outcome of non-auxotrophic cancer treatment to L-arginine. $CD4^+$ Th1 lymphocytes increase the production of tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1β) with potent anti-tumor (cytotoxic) activity and $CD4^+$ Th2 lymphocytes reduce the secretion of IL4 and IL10.

As ARG inhibitors restore activity to the immune system, their development in view of overexpressing this enzyme in MDSCs is essential for clinical practice. Contrary to the appearances, the effects of ARG inhibitors are greater than the effects of L-arginine supplementation, as they further increase the production of NO by iNOS. This difference is important because low NO concentrations promote tumor growth and high concentrations inhibit the cell cycle and cause apoptosis of cancer cells. Several inhibitors specific to ARG have been tested *in vitro*. NG-hydroxy-L-arginine (NOHA) has been shown to inhibit tumor cell proliferation, by inhibiting ARG and ornithine decarboxylase (ODC), which are involved in the conversion of L-arginine to polyamines essential for cell proliferation [93]. For example, NOHA has been shown to restore tumor-invasive lymphocyte (TIL) activity in human prostate cancer cells [94].

2.3. Nitric oxide in malignant tumors

Nowadays, it is clear that NO plays a crucial role in the various stages of neoplasia, such as DNA damage, inhibition of DNA repair enzymes, oncogene activation and suppressor genes, as well as induction of apoptosis and metastasis of cancer [95–98]. In many tumors, the expression of iNOS is high, but its role is very complex because it can both promote and inhibit tumor growth.

Despite a very short half-life ($t_{1/2}$) and small local action, NO has a significant effect on many processes in the body. The effects of its action depend on the concentration. At low concentrations, NO acts as a signaling molecule, regulating smooth muscle diastole, increasing blood flow and inhibiting platelet aggregation and leukocyte aggregation. In turn, NO in high concentrations increases the antitumor activity of the immune system [99,100]. In general, low levels of NO (< 100 nM) by inhibiting apoptosis and stimulating endothelial cell proliferation are conducive to tumor progression, and high concentrations of NO (400-1000 nM) stop cell cycle, stimulate apoptosis and cell aging [101–106]. The main property of high NO concentrations is the cytotoxicity resulting from the condensation of thiol and/or amino groups and from DNA damage via the p53 protein pathway [107]. Free radical reactions with NO produce peroxynitrite (ONOO-), which directly causes cell necrosis. High concentrations of NO are produced by macrophages, neutrophils, endothelial cells, hepatocytes, cardiomyocytes and chondrocytes [108–110].

Approximately 1.5% of the L-arginine stream enters the NOS pathway, which converts it to NO and citrulline [111]. There are three NOS isoforms: neuronal NO synthase (nNOS, also known as NOS1), inducible NO synthase (iNOS or NOS2), and constitutive, endothelial NO synthase (eNOS or NOS3). Once induced, the enzyme continues to produce much higher NO concentrations for many hours or even days [112].

Two main routes participate in NO signaling, one of them is cGMP dependent and the other is independent - called the NO oxidation pathway. The inducible form (iNOS2) is independent of Ca^{2+} ions and its expression is expressed in macrophages and other immune cells in response to proinflammatory mediators (mainly TNF-α and IL-1, IL-6 and IL-8) or microbial products such as lipopolysaccharide (LPS) [113,114]. The cGMP-independent pathway is most often associated with protein modification by S-nitrosylation of cysteine residues. Such post-translational modifications affect transcriptional activity by modifying DNA binding proteins, particularly the NF-κB transcription factor, which loses its ability to bind DNA. NF-KBB-*N*-nitrosylation and matrix metalloproteinase 9 (MMP9) promotes cell death, while S-nitrosylation of caspase-3, caspase-9, c-Jun N-terminal kinase inhibits its action and inhibits apoptosis.

Expression of NOS has been detected in various cancers such as cervical, ovarian, breast, central nervous system, laryngeal, and head and neck cancers [115–118]. Higher NOS activity has been found in invasive breast tumors when compared with benign or normal breast tissue [119]. Glynn et al. [120] and Switzer et al. [121] demonstrated that iNOS is associated with poor survival in ER-negative breast cancer patients and was associated with epidermal growth factor receptor (EGFR) activation via s-nitrosylation. Increased activity of inducible

NOS (iNOS) in breast and colorectal cancer cells upregulates tumor growth, promoting Wnt/β-catenin signaling [122]. Sikora et al. [123] reported that the inhibition of inducible nitric oxide synthase (iNOS) repressed the growth of human melanoma in vivo and synergized with cisplatin. Eyler et al. [124] reported that glioblastoma stem cells expressed higher levels iNOS than normal stem cells and the iNOS inhibition reduced cell proliferation in vitro.

3. Conclusions and prospects for the future

Elimination of L-arginine from the circulatory system is a new strategy for the treatment of auxotropic tumors with L-arginine, using the difference in expression of key enzymes in the ornithine cycle. This leads to an increased protein turnover via reduced synthesis and an increased breakdown and triggers caspase-dependent and caspase-independent apoptotic cell death [26,61,125].

Currently, the attention of scientists is focused on the down-regulation of ASS1 expression in melanoma, liver cancer, prostate cancer, sarcoma, lymphoma and others. Although L-arginine deficiency causes immunosuppression, removal from the circulation improves the outcome of therapy, including partial or even complete remission of some arginine auxotrophic tumors.

A different behavior seems to be effective in non-auxotrophic cancers. Buijs *et al.* [92] have improved the outcomes of patients with non-auxotrophic to L-arginine for head and neck squamous cell carcinoma after short-term supplementation of L-arginine in the perioperative period. The group receiving arginine-enriched nutrition had a significantly better overall survival and a better disease-specific survival.

The removal of L-arginine from circulation does not inhibit the progression of non-auxotrophic tumors because they can synthesize L-arginine from citrulline by expressing ASS1. The high activity of ARG1 in MDSCs, which form one of the cell populations of microenvironment of non-auxotrophic tumors, is responsible for the decrease in L-arginine concentration, thereby weakening the ability of T-cells to react with neoplastic antigens.

Heterogeneity within the same type of cancer requires individual treatment of patients based on specific markers that distinguish them to implement an optimal schedule of oncological treatment.

Histological diagnosis of cancer is not sufficient to determine whether L-arginine deprivation or L-arginine supplementation is appropriate. For example, Qiu et al. [37] have shown that ASS1 was either low in abundance or absent in more than 60% of 149 random breast cancer biosamples.

However, besides the activity of ASS1 in cancer cells, several other parameters are needed, such as the concentration of L-arginine in the cardiovascular system and the status of the immune system, mainly T-lymphocytes.

Conflict of interests

The authors declare no conflict of interests.

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The author contribution

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Data Collection: Jarosław Szefel, Aleksandra Danielak, Wiesław Janusz Kruszewski.

Statistical Analysis: No statistical analysis was carried out for this review.

Data Interpretation: There was no need to analyze the data in this review.

Manuscript Preparation: Jarosław Szefel, Aleksandra Danielak, Wiesław Janusz Kruszewski.

Literature Search: Jarosław Szefel, Aleksandra Danielak, Wiesław Janusz Kruszewski.

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References

[1] Luiking YC, Ten Have GA, Wolfe RR, Deutz NE. Arginine de novo and nitric oxide production in disease states. Am J Physiol Endocrinol Metab 2012;303:E1177–89.
[2] Wu G, Morris Jr. SM. Arginine metabolism: nitric oxide and beyond. Biochem J 1998;336(Pt 1):1–17.
[3] Brosnan ME, Brosnan JT. Renal arginine metabolism. J Nutr 2004;134:2791S–5S. discussion 6S-7S.
[4] Bode-Boger SM, Boger RH, Galland A, Tsikas D, Frolich JC. L-arginine-induced vasodilation in healthy humans: pharmacokinetic-pharmacodynamic relationship. Br J Clin Pharmacol 1998;46:489–97.
[5] Rath M, Muller I, Kropf P, Closs EI, Munder M. Metabolism via arginase or nitric oxide synthase: two competing arginine pathways in macrophages. Front Immunol 2014;5:532.
[6] Morris Jr. SM. Arginine metabolism: boundaries of our knowledge. J Nutr 2007;137:1602S–9S.
[7] Cendan JC, Topping DL, Pruitt J, Snowdy S, Copeland 3rd EM, Lind DS. Inflammatory mediators stimulate arginine transport and arginine-derived nitric oxide production in a murine breast cancer cell line. J Surg Res 1996;60:284–8.
[8] Cendan JC, Souba WW, Copeland 3rd EM, Lind DS. Characterization and growth factor stimulation of L-arginine transport in a human colon cancer cell line. Ann Surg Oncol 1995;2:257–65.
[9] Munder M. Arginase: an emerging key player in the mammalian immune system. Br J Pharmacol 2009;158:638–51.
[10] Mori M. Regulation of nitric oxide synthesis and apoptosis by arginase and arginine recycling. J Nutr 2007;137:1616S–20S.
[11] Bode-Boger SM, Scalera F, Ignarro LJ. The L-arginine paradox: importance of the L-arginine/asymmetrical dimethylarginine ratio. Pharmacol Ther 2007;114:295–306.
[12] Vallance P, Leone A, Calver A, Collier J, Moncada S. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992;339:572–5.
[13] Cardounel AJ, Cui HM, Samouilov A, Johnson W, Kearns P, Tsai AL, et al. Evidence for the pathophysiological role of endogenous methylarginines in regulation of endothelial NO production and vascular function. J Biol Chem 2007;282:879–87.
[14] Shin S, Thapa SK, Fung HL. Cellular interactions between L-arginine and asymmetric dimethylarginine: transport and metabolism. PLoS One 2017;12:e0178710.
[15] Boger RH. Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the "L-arginine paradox" and acts as a novel cardiovascular risk factor. J Nutr 2004;134:2842S–7S. discussion 53S.
[16] 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.
[17] Rodriguez PC, Quiceno DG, Ochoa AC. L-arginine availability regulates T-lymphocyte cell-cycle progression. Blood 2007;109:1568–73.
[18] Feun L, You M, Wu CJ, Kuo MT, Wangpaichitr M, Spector S, et al. Arginine deprivation as a targeted therapy for cancer. Curr Pharm Des 2008;14:1049–57.
[19] Szlosarek PW, Steele JP, Nolan L, Gilligan D, Taylor P, Spicer J, et al. Arginine deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma: a randomized clinical trial. JAMA Oncol 2017;3:58–66.
[20] Haines RJ, Pendleton LC, Eichler DC. Argininosuccinate synthase: at the center of arginine metabolism. Int J Biochem Mol Biol 2011;2:8–23.
[21] Grabon W. Arginine as a crucial amino acid in carcinogenesis and tumor growth. Postepy Hig Med Dosw (Online) 2006;60:483–9.
[22] Wheatley DN. Arginine deprivation and metabolomics: important aspects of intermediary metabolism in relation to the differential sensitivity of normal and tumour cells. Semin Cancer Biol 2005;15:247–53.
[23] Philip R, Campbell E, Wheatley DN. Arginine deprivation, growth inhibition and tumour cell death: 2. Enzymatic degradation of arginine in normal and malignant cell cultures. Br J Cancer 2003;88:613–23.
[24] Ascierto PA, Scala S, Castello G, Daponte A, Simeone E, Ottaiano A, et al. Pegylated arginine deiminase treatment of patients with metastatic melanoma: results from phase I and II studies. J Clin Oncol 2005;23:7660–8.
[25] Feun L, You M, Wu CJ, Kuo MT, Wangpaichitr M, Spector S, et al. Arginine deprivation as a targeted therapy for cancer. Curr Pharm Design 2008;14:1049–57.
[26] Kim RH, Coates JM, Bowles TL, McNerney GP, Sutcliffe J, Jung JU, et al. Arginine Deiminase as a novel therapy for prostate Cancer induces autophagy and caspase-independent apoptosis. Cancer Res 2009;69:700–8.
[27] Changou CA, Chen YR, Xing L, Yen Y, Chuang FY, Cheng RH, et al. Arginine starvation-associated atypical cellular death involves mitochondrial dysfunction, nuclear DNA leakage, and chromatin autophagy. Proc Natl Acad Sci U S A 2014;111:14147–52.
[28] Savaraj N, You M, Wu C, Wangpaichitr M, Kuo MT, Feun LG. Arginine deprivation, autophagy, apoptosis (AAA) for the treatment of melanoma. Curr Mol Med 2010;10:405–12.
[29] Kim RH, Bold RJ, Kung HJ. ADI, autophagy and apoptosis Metabolic stress as a

therapeutic option for prostate cancer. Autophagy 2009;5:567–8.
[30] Fletcher M, Ramirez ME, Sierra RA, Raber P, Thevenot P, Al-Khami AA, et al. l-Arginine depletion blunts antitumor T-cell responses by inducing myeloid-derived suppressor cells. Cancer Res 2015;75:275–83.
[31] Huang J, Brumell JH. Bacteria-autophagy interplay: a battle for survival. Nat Rev Microbiol 2014;12:101–14.
[32] Jin S, White E. Role of autophagy in cancer: management of metabolic stress. Autophagy 2007;3:28–31.
[33] Feun LG, Marini A, Walker G, Elgart G, Moffat F, Rodgers SE, et al. Negative argininosuccinate synthetase expression in melanoma tumours may predict clinical benefit from arginine-depleting therapy with pegylated arginine deiminase. Br J Cancer 2012;106:1481–5.
[34] Manca A, Sini MC, Izzo F, Ascierto PA, Tatangelo F, Botti G, et al. Induction of arginosuccinate synthetase (ASS) expression affects the antiproliferative activity of arginine deiminase (ADI) in melanoma cells. Oncol Rep 2011;25:1495–502.
[35] Savaraj N, Wu CJ, Li YY, Wangpaichitr M, You M, Bomalaski J, et al. Targeting argininosuccinate synthetase negative melanomas using combination of arginine degrading enzyme and cisplatin. Oncotarget 2015;6:6295–309.
[36] Walts AE, Bomalaski JS, Ines D, Orsulic S. Argininosuccinate synthetase (ASS) deficiency in high-grade pulmonary neuroendocrine carcinoma: an opportunity for personalized targeted therapy. J Cancer Res Clin 2015;141:1363–9.
[37] Qiu F, Chen YR, Liu X, Chu CY, Shen LJ, Xu J, et al. Arginine starvation impairs mitochondrial respiratory function in ASS1-deficient breast cancer cells. Sci Signal 2014;7:ra31.
[38] Park KGM, Heys SD, Harris CI, Steele RJC, Mcnurlan MA, Eremin O, et al. Arginine metabolism in benign and malignant disease of breast and colon - evidence for possible inhibition of tumor-infiltrating macrophages. Nutrition 1991;7:185–8.
[39] Bateman LA, Ku WM, Heslin MJ, Contreras CM, Skibola CF, Nomura DK. Argininosuccinate synthase 1 is a metabolic regulator of colorectal cancer pathogenicity. ACS Chem Biol 2017;12:905–11.
[40] Rho JH, Qin SZ, Wang JY, Roehrl MHA. Proteomic expression analysis of surgical human colorectal cancer tissues: up-regulation of PSB7, PRDX1, and SRP9 and hypoxic adaptation in cancer. J Proteome Res 2008;7:2959–72.
[41] Liu JB, Ma JG, Wu Z, Li W, Zhang D, Han L, et al. Arginine deiminase augments the chemosensitivity of argininosuccinate synthetase-deficient pancreatic cancer cells to gemcitabine via inhibition of NF-kappa B signaling. BMC Cancer 2014:14.
[42] Shan YS, Hsu HP, Lai MD, Yen MC, Luo YP, Chen YL. Increased expression of argininosuccinate synthetase protein predicts poor prognosis in human gastric cancer. Oncol Rep 2015;33:49–57.
[43] Shan YS, Hsu HP, Lai MD, Yen MC, Chen WC, Fang JH, et al. Argininosuccinate synthetase 1 suppression and arginine restriction inhibit cell migration in gastric cancer cell lines. Sci Rep-Uk 2015:5.
[44] Tsai CY, Chi HC, Chi LM, Yang HY, Tsai MM, Lee KF, et al. Argininosuccinate synthetase 1 contributes to gastric cancer invasion and progression by modulating autophagy. FASEB J 2018;32:2601–14.
[45] McAlpine JA, Lu HT, Wu KC, Knowles SK, Thomson JA. Down-regulation of argininosuccinate synthetase is associated with cisplatin resistance in hepatocellular carcinoma cell lines: implications for PEGylated arginine deiminase combination therapy. BMC Cancer 2014:14.
[46] Thongkum A, Wu CJ, Li YY, Wangpaichitr M, Navasumrit P, Parnlob V, et al. The combination of arginine deprivation and 5-fluorouracil improves therapeutic efficacy in argininosuccinate synthetase negative hepatocellular carcinoma. Int J Mol Sci 2017:18.
[47] Szlosarek PW, Grimshaw MJ, Wilbanks GD, Hagemann T, Wilson JL, Burke F, et al. Aberrant regulation of argininosuccinate synthetase by TNF-alpha in human epithelial ovarian cancer. Int J Cancer 2007;121:6–11.
[48] Cheon DJ, Walts AE, Beach JA, Lester J, Bomalaski JS, Walsh CS, et al. Differential expression of argininosuccinate synthetase in serous and non-serous ovarian carcinomas. J Pathol Clin Res 2015;1:41–53.
[49] Bowles TL, Kim R, Galante J, Parsons CM, Virudachalam S, Kung HJ, et al. Pancreatic cancer cell lines deficient in argininosuccinate synthetase are sensitive to arginine deprivation by arginine deiminase. Int J Cancer 2008;123:1950–5.
[50] Tsai HJ, Jiang SS, Hung WC, Borthakur G, Lin SF, Pemmaraju N, et al. A phase II study of arginine deiminase (ADI-PEG20) in relapsed/refractory or poor-risk acute myeloid leukemia patients. Sci Rep-Uk 2017:7.
[51] Miraki-Moud F, Ghazaly E, Ariza-McNaughton L, Hodby KA, Clear A, Anjos-Afonso F, et al. Arginine deprivation using pegylated arginine deiminase has activity against primary acute myeloid leukemia cells in vivo. Blood 2015;125:4060–8.
[52] Syed N, Langer J, Janczar K, Singh P, Lo Nigro C, Lattanzio L, et al. Epigenetic status of argininosuccinate synthetase and argininosuccinate lyase modulates autophagy and cell death in glioblastoma. Cell Death Dis 2013;4:e458.
[53] Szlosarek PW, Steele JP, Nolan L, Gilligan D, Taylor P, Spicer J, et al. Arginine deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma a randomized clinical trial. JAMA Oncol 2017;3:58–66.
[54] Beddowes E, Spicer J, Chan PY, Khadeir R, Corbacho JG, Repana D, et al. Phase 1 dose-escalation study of pegylated arginine deiminase, cisplatin, and pemetrexed in patients with argininosuccinate synthetase 1-deficient thoracic cancers. J Clin Oncol 2017;35:1778-+.
[55] Yoon CY, Shim YJ, Kim EH, Lee JH, Won NH, Kim JH, et al. Renal cell carcinoma does not express argininosuccinate synthetase and is highly sensitive to arginine deprivation via arginine deiminase. Int J Cancer 2007;120:897–905.
[56] Kelly MP, Jungbluth AA, Wu BW, Bomalaski J, Old LJ, Ritter G. Arginine deiminase PEG20 inhibits growth of small cell lung cancers lacking expression of argininosuccinate synthetase. Br J Cancer 2012;106:324–32.
[57] Kobayashi E, Masuda M, Nakayama R, Ichikawa H, Satow R, Shitashige M, et al. Reduced argininosuccinate synthetase is a predictive biomarker for the development of pulmonary metastasis in patients with osteosarcoma. Mol Cancer Ther 2010;9:535–44.
[58] Ohshima K, Nojima S, Tahara S, Kurashige M, Hori Y, Hagiwara K, et al. Argininosuccinate synthase 1-deficiency enhances the cell sensitivity to arginine through decreased DEPTOR expression in endometrial cancer. Sci Rep-Uk 2017:7.
[59] Kim Y, Kobayashi E, Kubota D, Suehara Y, Mukaihara K, Akaike K, et al. Reduced argininosuccinate synthetase expression in refractory sarcomas: impacts on therapeutic potential and drug resistance. Oncotarget 2016;7:70832–44.
[60] Huang HY, Wu WR, Wang YH, Wang JW, Fang FM, Tsai JW, et al. ASS1 as a novel tumor suppressor gene in myxofibrosarcomas: aberrant loss via epigenetic DNA methylation confers aggressive phenotypes, negative prognostic impact, and therapeutic relevance. Clin Cancer Res 2013;19:2861–72.
[61] Allen MD, Luong P, Hudson C, Leyton J, Delage B, Ghazaly E, et al. Prognostic and therapeutic impact of argininosuccinate synthetase 1 control in bladder cancer as monitored longitudinally by PET imaging. Cancer Res 2014;74:896–907.
[62] Sahu D, Gupta S, Hau AM, Nakashima K, Leivo MZ, Searles SC, et al. Argininosuccinate synthetase 1 loss in invasive bladder cancer regulates survival through general control nonderepressible 2 kinase-mediated eukaryotic initiation factor 2 alpha activity and is targetable by pegylated arginine deiminase. Am J Pathol 2017;187:200–13.
[63] Delage B, Fennell DA, Nicholson L, McNeish I, Lemoine NR, Crook T, et al. Arginine deprivation and argininosuccinate synthetase expression in the treatment of cancer. Int J Cancer 2010;126:2762–72.
[64] Dillon BJ, Prieto VG, Curley SA, Ensor CM, Holtsberg FW, Bomalaski JS, et al. Incidence and distribution of argininosuccinate synthetase deficiency in human cancers: a method for identifying cancers sensitive to arginine deprivation. Cancer 2004;100:826–33.
[65] Cheng PN, Lam TL, Lam WM, Tsui SM, Cheng AW, Lo WH, et al. Pegylated recombinant human arginase (rhArg-peg5,000mw) inhibits the in vitro and in vivo proliferation of human hepatocellular carcinoma through arginine depletion. Cancer Res 2007;67:309–17.
[66] Izzo F, Marra P, Beneduce G, Castello G, Vallone P, De Rosa V, et al. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from phase I/II studies. J Clin Oncol 2004;22:1815–22.
[67] Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 2012;21:309–22.
[68] Galon J, Angell HK, Bedognetti D, Marincola FM. The continuum of cancer immunosurveillance: prognostic, predictive, and mechanistic signatures. Immunity 2013;39:11–26.
[69] Kang JC, Chen JS, Lee CH, Chang JJ, Shieh YS. Intratumoral macrophage counts correlate with tumor progression in colorectal cancer. J Surg Oncol 2010;102:242–8.
[70] Yang L, DeBusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Shyr Y, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 2004;6:409–21.
[71] Almand B, Clark JI, Nikitina E, van Beynen J, English NR, Knight SC, et al. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol 2001;166:678–89.
[72] Almand B, Resser JR, Lindman B, Nadaf S, Clark JI, Kwon ED, et al. Clinical significance of defective dendritic cell differentiation in cancer. Clin Cancer Res 2000;6:1755–66.
[73] Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature 2011;475:222–5.
[74] Fader AN, Rasool N, Vaziri SA, Kozuki T, Faber PW, Elson P, et al. CCL2 expression in primary ovarian carcinoma is correlated with chemotherapy response and survival outcomes. Anticancer Res 2010;30:4791–8.
[75] Shojaei F, Wu XM, Malik AK, Zhong CL, Baldwin ME, Schanz S, et al. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b(+)Gr1(+) myeloid cells. Nat Biotechnol 2007;25:911–20.
[76] Ostrand-Rosenberg S, Sinha P, Beury DW, Clements VK. Cross-talk between myeloid-derived suppressor cells (MDSC), macrophages, and dendritic cells enhances tumor-induced immune suppression. Semin Cancer Biol 2012;22:275–81.
[77] Allavena P, Mantovani A. Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment. Clin Exp Immunol 2012;167:195–205.
[78] Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis 2012;33:949–55.
[79] Modolell M, Corraliza IM, Link F, Soler G, Eichmann K. Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by TH1 and TH2 cytokines. Eur J Immunol 1995;25:1101–4.
[80] Ma G, Pan PY, Eisenstein S, Divino CM, Lowell CA, Takai T, et al. Paired immunoglobin-like receptor-B regulates the suppressive function and fate of myeloid-derived suppressor cells. Immunity 2011;34:385–95.
[81] Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell 2009;16:183–94.
[82] Kotsakis A, Harasymczuk M, Schilling B, Georgoulias V, Argiris A, Whiteside TL. Myeloid-derived suppressor cell measurements in fresh and cryopreserved blood samples. J Immunol Methods 2012;381:14–22.
[83] Popovic PJ, Zeh 3rd HJ, Ochoa JB. Arginine and immunity. J Nutr 2007;137:1681S–6S.
[84] Highfill SL, Rodriguez PC, Zhou Q, Goetz CA, Koehn BH, Veenstra R, et al. Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by

interleukin-13. Blood 2010;116:5738–47.
[85] Yachimovich-Cohen N, Even-Ram S, Shufaro Y, Rachmilewitz J, Reubinoff B. Human embryonic stem cells suppress T cell responses via arginase I-dependent mechanism. J Immunol 2010;184:1300–8.
[86] Rodriguez PC, Zea AH, DeSalvo J, Culotta KS, Zabaleta J, Quiceno DG, et al. L-arginine consumption by macrophages modulates the expression of CD3 zeta chain in T lymphocytes. J Immunol 2003;171:1232–9.
[87] Feldmeyer N, Wabnitz G, Leicht S, Luckner-Minden C, Schiller M, Franz T, et al. Arginine deficiency leads to impaired cofilin dephosphorylation in activated human T lymphocytes. Int Immunol 2012;24:303–13.
[88] Talmadge JE. Pathways mediating the expansion and immunosuppressive activity of myeloid-derived suppressor cells and their relevance to cancer therapy. Clin Cancer Res 2007;13:5243–8.
[89] Ko JS, Bukowski RM, Fincke JH. Myeloid-derived suppressor cells: a novel therapeutic target. Curr Oncol Rep 2009;11:87–93.
[90] Ochoa AC, Zea AH, Hernandez C, Rodriguez PC. Arginase, prostaglandins, and myeloid-derived suppressor cells in renal cell carcinoma. Clin Cancer Res 2007;13:721s–6s.
[91] Nanthakumaran S, Brown I, Heys SD, Schofield AC. Inhibition of gastric cancer cell growth by arginine: molecular mechanisms of action. Clin Nutr 2009;28:65–70.
[92] Buijs N, Buijs N, van Bokhorst-de van der Schueren MA, Langius JA, Leemans CR, Kuik DJ, Vermeulen MA, et al. Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. Am J Clin Nutr 2010;92:1151–6.
[93] Buga GM, Wei LH, Bauer PM, Fukuto JM, Ignarro LJ. NG-hydroxy-L-arginine and nitric oxide inhibit Caco-2 tumor cell proliferation by distinct mechanisms. Am J Physiol 1998;275:R1256–64.
[94] Bronte V, Kasic T, Gri G, Gallana K, Borsellino G, Marigo I, et al. Boosting antitumor responses of T lymphocytes infiltrating human prostate cancers. J Exp Med 2005;201:1257–68.
[95] Lala PK, Orucevic A. Role of nitric oxide in tumor progression: lessons from experimental tumors. Cancer Metastasis Rev 1998;17:91–106.
[96] Wink DA, Ridnour LA, Hussain SP, Harris CC. The reemergence of nitric oxide and cancer. Nitric Oxide 2008;19:65–7.
[97] Burke AJ, Sullivan FJ, Giles FJ, Glynn SA. The yin and yang of nitric oxide in cancer progression. Carcinogenesis 2013;34:503–12.
[98] Rapozzi V, Della Pietra E, Bonavida B. Dual roles of nitric oxide in the regulation of tumor cell response and resistance to photodynamic therapy. Redox Biol 2015;6:311–7.
[99] Wink DA, Mitchell JB. Chemical biology of nitric oxide: insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide. Free Radic Biol Med 1998;25:434–56.
[100] Rao CV. Nitric oxide signaling in colon cancer chemoprevention. Mutat Res 2004;555:107–19.
[101] Lechner M, Lirk P, Rieder J. Inducible nitric oxide synthase (iNOS) in tumor biology: the two sides of the same coin. Semin Cancer Biol 2005;15:277–89.
[102] Oronsky B, Fanger GR, Oronsky N, Knox S, Scicinski J. The implications of hyponitroxia in cancer. Transl Oncol 2014;7:167–73.
[103] Choudhari SK, Chaudhary M, Bagde S, Gadbail AR, Joshi V. Nitric oxide and cancer: a review. World J Surg Oncol 2013;11:118.
[104] Vannini F, Kashfi K, Nath N. The dual role of iNOS in cancer. Redox Biol 2015;6:334–43.
[105] Ridnour LA, Isenberg JS, Espey MG, Thomas DD, Roberts DD, Wink DA. Nitric oxide regulates angiogenesis through a functional switch involving thrombospondin-1. Proc Natl Acad Sci U S A 2005;102:13147–52.
[106] Isenberg JS, Ridnour LA, Perruccio EM, Espey MG, Wink DA, Roberts DD. Thrombospondin-1 inhibits endothelial cell responses to nitric oxide in a cGMP-dependent manner. Proc Natl Acad Sci U S A 2005;102:13141–6.
[107] Messmer UK, Brune B. Nitric oxide-induced apoptosis: p53-dependent and p53-independent signalling pathways. Biochem J 1996;319(Pt 1):299–305.
[108] Li LM, Kilbourn RG, Adams J, Fidler IJ. Role of nitric oxide in lysis of tumor cells by cytokine-activated endothelial cells. Cancer Res 1991;51:2531–5.
[109] Jiang H, Stewart CA, Fast DJ, Leu RW. Tumor target-derived soluble factor synergizes with IFN-gamma and IL-2 to activate macrophages for tumor necrosis factor and nitric oxide production to mediate cytotoxicity of the same target. J Immunol 1992;149:2137–46.
[110] Xiao L, Eneroth PH, Qureshi GA. Nitric oxide synthase pathway may mediate human natural killer cell cytotoxicity. Scand J Immunol 1995;42:505–11.
[111] Castillo L, Beaumier L, Ajami AM, Young VR. Whole body nitric oxide synthesis in healthy men determined from [15N] arginine-to-[15N]citrulline labeling. Proc Natl Acad Sci U S A 1996;93:11460–5.
[112] Moncada S, Palmer RMJ, Higgs EA. Nitric-oxide - physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43:109–42.
[113] Groeneveld PH, Kwappenberg KM, Langermans JA, Nibbering PH, Curtis L. Relation between pro- and anti-inflammatory cytokines and the production of nitric oxide (NO) in severe sepsis. Cytokine 1997;9:138–42.
[114] Menshikova EB, Zenkov NK, Reutov VP. Nitric oxide and NO-synthases in mammals in different functional states. Biochemistry (Mosc) 2000;65:409–26.
[115] Nomelini RS, de Abreu Ribeiro LC, Tavares-Murta BM, Adad SJ, Murta EF. Production of nitric oxide and expression of inducible nitric oxide synthase in ovarian cystic tumors. Mediat Inflamm 2008;2008:186584. https://doi.org/10.1155/2008/186584.
[116] Dong J, Cheng M, Sun H. Function of inducible nitric oxide synthase in the regulation of cervical cancer cell proliferation and the expression of vascular endothelial growth factor. Mol Med Rep 2014;9:583–9.
[117] Yanar K, Cakatay U, Aydjn S, Verim A, Atukeren P, Ozkan NE, Karatoprak K, Cebe T, Turan S, Ozkök E, Korkmaz G, Cacına C, Küçükhüseyin O, Yaylım İ. Relation between endothelial nitric oxide synthase genotypes and oxidative stress markers in larynx cancer. Oxid Med Cell Longev 2016;2016:4985063. https://doi.org/10.1155/2016/4985063.
[118] Cobbs CS, Brenman JE, Aldape KD, Bredt DS, Israel MA. Expression of nitric-oxide synthase in human central-nervous-system tumors. Cancer Res 1995;55:727–30.
[119] Loibl S, von Minckwitz G, Weber S, Sinn HP, Schini-Kerth VB, Lobysheva I, et al. Expression of endothelial and inducible nitric oxide synthase in benign and malignant lesions of the breast and measurement of nitric oxide using electron paramagnetic resonance spectroscopy. Cancer 2002;95:1191–8.
[120] Glynn SA, Boersma BJ, Dorsey TH, Yi M, Yfantis HG, Ridnour LA, et al. Increased NOS2 predicts poor survival in estrogen receptor-negative breast cancer patients. J Clin Invest 2010;120:3843–54.
[121] Switzer CH, Glynn SA, Cheng RY, Ridnour LA, Green JE, Ambs S, et al. S-nitrosylation of EGFR and Src activates an oncogenic signaling network in human basal-like breast cancer. Mol Cancer Res 2012;10:1203–15.
[122] Du Q, Zhang XL, Liu Q, Zhang XH, Bartels CE, Geller DA. Nitric oxide production upregulates Wnt/beta-catenin signaling by inhibiting dickkopf-1. Cancer Res 2013;73:6526–37.
[123] Sikora AG, Gelbard A, Davies MA, Sano D, Ekmekcioglu S, Kwon J, et al. Targeted inhibition of inducible nitric oxide synthase inhibits growth of human melanoma in vivo and synergizes with chemotherapy. Clin Cancer Res 2010;16:1834–44.
[124] Eyler CE, Wu QL, Yan K, MacSwords JM, Chandler-Militello D, Misuraca KL, et al. Glioma stem cell proliferation and tumor growth are promoted by nitric oxide synthase-2. Cell 2011;146:53–66.
[125] Morrow K, Hernandez CP, Raber P, Del Valle L, Wilk AM, Majumdar S, et al. Anti-leukemic mechanisms of pegylated arginase I in acute lymphoblastic T-cell leukemia. Leukemia 2013;27:569–77.