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AMINO ACID DEPRIVATION THERAPY: A PROMISING AVENUE IN CANCER TREATMENT

Bindu E[1], B S Harikumaran Thampi[2], Robert Antony[3]

[1,2]*Department of Life Science, University of Calicut, 673636, Kerala, India.*

[3]*Department of Microbiology, Govt. Arts and Science College, Kozhinjampara*

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Abstract

A promising method for treating cancer is amino acid deprivation therapy, which targets the metabolic reliance of cancer cells on particular amino acids. Because of their elevated rates of proliferation and dysregulated metabolic pathways, many cancer cells have a higher need for certain amino acids than normal cells. The therapeutic potential of amino acid deprivation is examined in this paper, with particular attention paid to the depletion of essential amino acids that are essential for the survival and proliferation of cancer cells, such as glutamine, methionine, and arginine. There is discussion of several tactics, such as the use of small-molecule inhibitors, dietary restrictions, and recombinant enzymes (such as arginine deiminase and asparaginase).The study also assesses preclinical and clinical research that shows these methods are safe and effective for various cancer types. Additionally examined are the mechanisms by which amino acid deficiency triggers cell cycle arrest, autophagy, and apoptosis. Potential combinatorial techniques to improve therapeutic efficacy are discussed, along with difficulties relating to toxicity and resistance mechanisms. Future directions in amino acid deprivation therapy are highlighted in the review's conclusion, with a focus on the necessity of individualized strategies catered to each tumors unique metabolic weakness.

***Keywords*:** Arginine deiminase, Cancer therapy, Amino acid deprivation, Enzyme inhibition, Amino acid and cancer.

***Corresponding Author**

Bindu E

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INTRODUCTION

Cancer continues to be one of the biggest threats to human health in the twenty-first century, affecting people individually, in families, and across global cultures. Prostate, colon, rectum, lung, and breast cancers are the most common killer cancers. Because of smoking behaviours, lung cancer has historically been one of the most common malignancies worldwide. According to estimates from the World Health Organization (WHO), there were 2.09 million new cases of lung cancer and 1.76 million deaths from the disease globally in 2018 (WHO, 2018) However, the incidence of lung cancer has been gradually reducing in some regions due to growing knowledge of the health dangers associated with smoking and efforts to quit[1]. The most common malignancy among women worldwide is breast cancer, with incidence rates that vary depending on the area and population. The past few decades, there has been a substantial rise in public knowledge of breast cancer, screening programs, and treatment options, which has improved survival rates and allowed for earlier disease detection.

The review paper offers a thorough examination of cancer treatments, with an emphasis on amino acid deprivation therapy in particular. It includes a thorough analysis of traditional cancer treatments, emphasizing their drawbacks and difficulties. The complex interaction between amino acid metabolism and cancer cells, which clarifies the vital role that amino acid dependencies play in the development of cancer, is at the center of the discussion. This also explores different approaches to amino acid deprivation, illuminating their modes of action and potential applications in medicine. The article provides an in-depth analysis of the benefits and drawbacks of amino acid restriction therapy, highlighting its ability to specifically target cancer cells while also addressing related drawbacks such tumor heterogeneity and acquired resistance. The study also provides insights on the potential applications of amino acid deprivation therapy in the future, including tailored treatment plans, novel combination medicines, and breakthroughs in targeted drug development. All things considered, the study is a useful tool for academics, physicians, and other stakeholders to use when navigating the rapidly

changing field of cancer therapy and realizing the full potential of amino acid deprivation tactics.

A Comprehensive Overview of Cancer Therapies.

The term "cancer therapy" describes the wide range of interventions used to treat cancer, a complicated and varied group of illnesses marked by the unchecked growth and spread of malignant cells [2]. Cancer therapy aims to improve patient outcomes and quality of life by eradicating cancer cells, stopping their progression, or effectively managing symptoms. Many therapeutic techniques targeting different aspects of cancer biology have been developed over the years as a result of major developments in cancer research. These treatments fall into a number of major categories, including as immunotherapy, targeted therapy, hormone therapy, surgery, chemotherapy, radiation therapy, and precision medicine. Surgery is frequently performed to remove localized malignancies that have not migrated to other parts of the body. It entails the physical excision of tumors and surrounding tissues. Chemotherapy employs medications that are given orally, intravenously, or by other methods in order to either kill cancer cells or stop them from growing. High-energy radiation beams are used in radiation therapy to target and kill cancer cells both within and outside. While immunotherapy employs the body's immune system to recognize and fight cancer cells, targeted therapy concentrates on substances or pathways that are essential for cancer cell growth and survival.

By preventing the synthesis or activity of hormones that stimulate tumor growth, hormone therapy is used to treat malignancies that are sensitive to hormones. Customizing a patient's course of treatment according to the genetic and molecular features of their particular cancer is known as precision medicine.

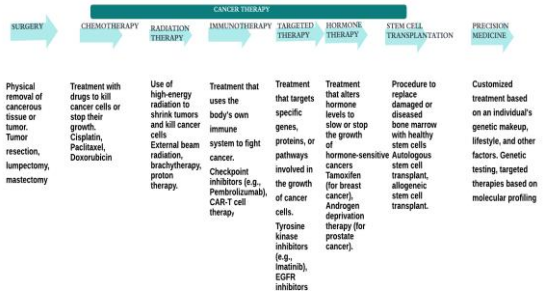

Fig 01. Overview of Cancer Therapy Modalities and Their Mechanisms

(Fig 01 shows the mechanisms and therapeutic targets of several cancer treatment modalities)

Even though oncology has made a lot of progress, all major cancer treatments have problems that make them less effective, more hazardous, and worse for patients. Surgery can cure localized tumors, but it doesn't work for metastatic cancer and can cause problems such infections after surgery, slow wound healing, and not removing all of the tumor [3]. Chemotherapy is still one of the most used treatments, but it has several problems. For example, it can kill normal cells that divide quickly, which can cause myelosuppression, gastrointestinal toxicity, hair loss, and long-term damage to organs. Also, the rise of multidrug resistance makes treatment less effective [4].

Radiation therapy has the same problems, as ionizing radiation always affects healthy tissues around it, even with better targeted methods. Fibrosis, organ malfunction, and secondary cancers are some of the long-term problems that can happen [5]. Immunotherapies, such as checkpoint inhibitors and CAR-T cell therapies, demonstrate significant advantages; nonetheless, they are linked to immune-related side effects, including pneumonitis, colitis, endocrinopathies, cytokine release syndrome, and neurotoxicity. Additionally, only a limited number of patients respond because of variances in tumor immunogenicity [6].

Targeted treatments, while tailored to specific molecular pathways, often diminish in efficacy due to acquired resistance mechanisms and are constrained by high costs and limited application to malignancies harbouring actionable mutations [7]. Hormone therapy are helpful solely for hormone-dependent malignancies and may result in metabolic problems, osteoporosis, cardiovascular consequences, and hormone-resistant tumor development [8].

There are a lot of hazards with stem cell transplantation, such as death from the treatment, severe immunosuppression, and graft-versus-host disease (GVHD) in allogeneic transplantation [9]. Precision medicine has problems such high sequencing costs, not enough actionable targets, tumor heterogeneity, and difficulties in understanding genomics [10].

Apart from the conventional cancer treatments mentioned above, recent studies have illuminated innovative therapeutic approaches that focus on particular metabolic pathways in cancerous cells. Amino acid deprivation therapy is one such strategy that entails limiting specific amino acids that are necessary for the growth of cancer cells. Through the deprivation of these essential building components, this novel therapy seeks to suppress tumor growth and interfere with the evolution of cancer. The idea of amino acid deprivation therapy is examined in more detail in the section that follows, with an emphasis on how promising it is as an addition to current cancer treatments.

Amino Acid Dependencies for Cancer

Amino acids are necessary for cancer cells to proliferate because they help make proteins, produce energy, make nucleotides, protect cells from free radicals, send signals between cells, and grow new blood vessels. Cancer cells that divide quickly need more amino acids to make proteins, enzymes, and structural parts that are needed for them to grow. Dysregulated amino acid metabolism, frequently observed in cancer, facilitates these processes and promotes malignant growth. Amino acids are the

building blocks that cancer cells need to grow out of control, and pathways like mTOR are very affected by how many amino acids are available. This metabolic need renders amino-acid-regulated protein synthesis a compelling therapeutic target.

Amino acids also help cancer cells achieve their high metabolic needs by providing energy through the TCA cycle and oxidative phosphorylation. Research has shown the pivotal function of amino acid–mediated metabolism in facilitating cancer cell bioenergetics[11,12].A number of amino acids, such as glutamine, serine, and glycine, are essential for nucleotide biosynthesis, facilitating DNA/RNA synthesis required for fast cellular division. Their roles in one-carbon metabolism and purine/pyrimidine pathways underscore significant metabolic weaknesses in cancer [11,13].

Amino acids also control important signaling pathways. For example, leucine turns on the mTOR pathway, which makes cancer cells grow and do anabolic activities. Amino acids are also the building blocks of signaling molecules like NO, polyamines, and glutathione, which affect redox equilibrium and how the body responds to stress [14,15]. Amino acids, particularly those that make up glutathione, protect cancer cells from oxidative damage by acting as antioxidants. Glutathione helps keep redox equilibrium and helps cancer cells live longer, which makes them more resistant to oxidative damage [16]. Arginine facilitates tumor angiogenesis by generating nitric oxide (NO). Nitric oxide (NO) generated from arginine helps endothelial cells move, grow, and build new blood vessels, which helps tumors get nutrients and helps cancer grow [17].

Mechanisms of Amino Acid Acquisition in Cancer Cells

Cancer cells have modified amino acid metabolism and markedly enhance amino acid absorption to facilitate fast growth and proliferation. This increased uptake is mostly caused by the overexpression of certain amino acid transporters, notably ASCT2 and LAT1, which bring in important amino acids like leucine, glutamine, and serine[18]. Some cancer cells also take in amino acids by receptor-mediated endocytosis, especially methionine and arginine [19].

Cancer cells remodel metabolic pathways [20] to fulfill their elevated metabolic needs. Oncogenic pathways, like mTOR, make it easier for cancer cells to take in and use amino acids, which helps them live and grow [21]. Stress reactions that boost amino acid absorption and metabolism are triggered by conditions in the tumor microenvironment, like low oxygen levels, high acidity, and lack of nutrients [22]. Overall, higher amino acid absorption is an important change that helps tumors grow [23]. So, targeting amino acid transporters and metabolic pathways may stop cancer cells from growing while leaving normal cells alone.

Amino acids have also become possible treatments. Most anticancer therapies rely on limiting amino acids, although other studies demonstrate that taking more amino acids can help [24]. For instance, branched-chain amino acids (BCAAs) are advised for patients with cirrhosis and have demonstrated beneficial benefits in hepatocellular carcinoma [25,26,27,28]. Adding glutamine to the diet of mice slowed the growth of melanoma via changing oncogenic epigenetic markers[29]. Adding histidine to the diet made leukemia more sensitive to MTX treatment by speeding up its breakdown and lowering the levels of tetrahydrofolate [30].

A recent study shown that a diet high in essential amino acids (EAAs) inhibited tumor growth in mice[31]. Mechanistically, EAA enrichment initiated BCAA catabolism, suppressed mTOR signaling, diminished glycolysis, and induced cancer cell apoptosis via ATF4-mediated ER stress associated with intracellular glutamate depletion. These results indicate that amino acid supplementation could inhibit cancer proliferation via various pathways [31].

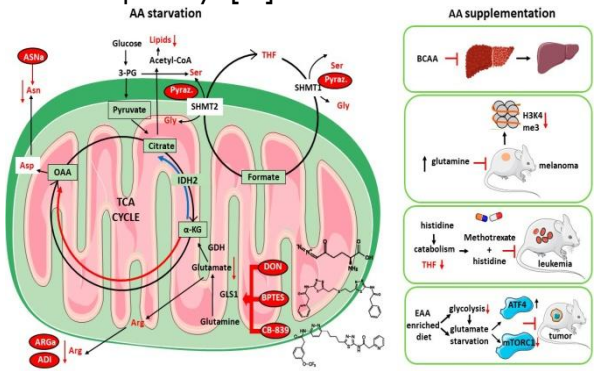

Fig 02.Metabolic Effects of Amino Acid Deprivation and Supplementation in Cancer

(Fig 2 [30]: Supplementation (right) and amino acid deprivation (left) are both effective anti-cancer tactics.

DIFFERENT STRATEGIES AND INTERVENTIONS ASSOCIATED WITH AMINO ACID METABOLISM IN CANCER THERAPY

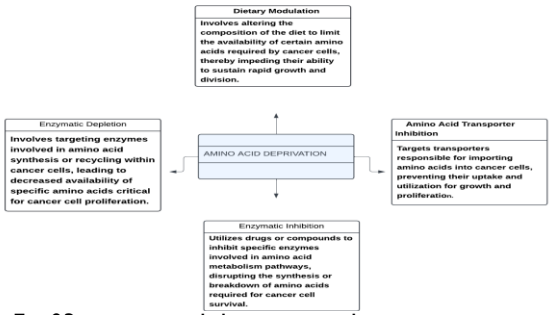

Fig 03. amino acid deprivation therapy.

Fig 03 outlines different strategies and interventions associated with amino acid metabolism in cancer therapy like enzymatic depletion, enzymatic inhibition, amino acid transporter inhibition and dietary modulation etc)

1. Enzymatic deprivation of amino acids

Amino acid deprivation therapy is an emerging strategy in cancer treatment that exploits the metabolic dependencies of tumor cells. Cancer cells, due to their high proliferation rates and altered metabolic pathways, often rely on certain amino acids that they cannot synthesize efficiently. By using enzymes to degrade these amino acids, this therapy disrupts cancer cell metabolism, leading to inhibited growth and apoptosis, while sparing normal cells that can adapt to amino acid depletion.

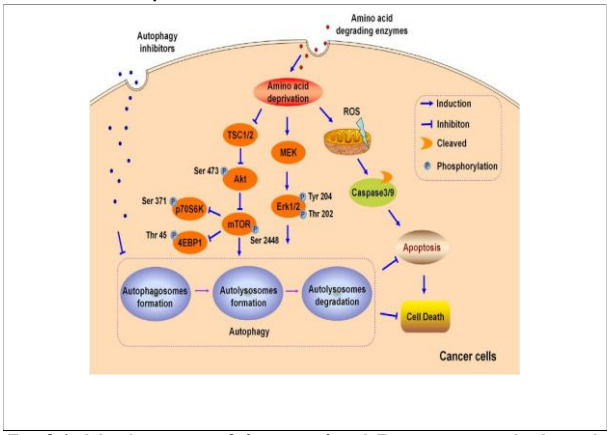

Fig 04. Mechanism of Amino Acid Deprivation-Induced Autophagy and Apoptosis in Cancer Cells.

(Fig 04: Diagrammatic representation of autophagy's cytoprotective function in cancer cells' cytotoxicity caused by amino acid-degrading enzymes (L-asparaginase, ADI, and rhArg) [32].

The approach utilizes specific enzymes to target key amino acids required for cancer cell survival. For instance, asparaginase depletes extracellular asparagine, a critical amino acid for leukemia cells, and is already widely used in treating acute lymphoblastic leukemia (ALL). Similarly, arginine deiminase and arginase target arginine metabolism, effective in cancers like hepatocellular carcinoma and melanoma. Methionase and glutaminase focus on methionine and glutamine metabolism, respectively, to address other amino acid-dependent tumors. The following sections will delve into the role of each enzyme from table 2 in detail, elaborating discussing their mechanisms, targeted amino acids, and therapeutic applications etc. This comprehensive exploration will highlight the potential and limitations of each enzyme in

Table 02: Enzymatic deprivation of amino acids

Enzyme	Function	Targeted Amino Acid	Therapeutic Approach
Asparaginase	Catalyses the hydrolysis of asparagine to aspartic acid	Asparagine	Depletion of extracellular asparagine
Methionase	Catalyses the hydrolysis of methionine	Methionine	Depletion of extracellular methionine
Arginase	Convert arginine to ornithine, urea, and proline	Arginine	Inhibitors of arginase activity to deprive cancer cells of arginine
Glutaminase	Catalyses the conversion of glutamine to glutamate	Glutamine	Inhibitors of glutaminase activity to limit glutaminase availability
Arginine deiminase	Convert arginine to citrulline	arginine	Depletion of extracellular arginine

(Table 02 focuses on particular amino acids that are essential for cancer cell viability in order to identify enzymes utilized in cancer therapy for metabolic targeting. In order to interfere with the metabolic requirements of cancer cells, each enzyme catalyses a distinct process involving its target amino acid.)

The treatment strategy of amino acid deprivation for cancer aims to restrict the access to certain amino acids in order to impede the development and viability of cancerous cells. This therapeutic approach capitalizes on the reliance of cancer cells on amino acids for crucial functions like protein synthesis and cellular proliferation. Nevertheless, it is crucial to acknowledge that the selection of specific amino acids to be targeted can differ depending on the unique attributes of the cancer being treated.

1.1. L-asparaginase

The first enzyme to be employed as an anticancer agent in clinical practice was L-asparaginase, which changes L-asparagine into L-aspartic acid.Its approval in 1978 as part of a treatment plan for children with acute lymphoblastic leukemia marked a significant turning point. Since then, there has been extensive research on the structural and biochemical properties of L-asparaginases, leading to a comprehensive understanding of the enzyme's structure and activity mechanism. Over the past three decades, the Protein Data Bank has included more than 100 structural models of L-asparaginases, contributing to our understanding of the unique hydrolase's enzymatic action [33].

Asparaginase (ASNase) therapy functions by eliminating the amino acid L-asparagine from leukemia cells, which they are unable to synthesis due to insufficient or faulty asparagine synthetase [34,35]. Reducing blood L-asparagine levels induces metabolic stress and interferes with signaling pathways in leukemia cells, resulting in apoptosis. The first time ASNase was used in a clinical setting for lymphoblastic leukemia, it was a partially purified guinea pig enzyme.

After that, E. coli–derived ASNase (EcAII) became the predominant method of treatment. The FDA approved native EcAII in 1978 as Elspar for pediatric ALL. It was used until 2012, when PEGylated versions took its place [36,37]. Erwinia chrysanthemi (formerly E. carotovora) makes another clinically relevant ASNase called Erwinaze, which the FDA approved in 2011[38]. ASNase is found in many commercial medications, such as Kidrolase, Oncaspar, Elspar, Erwinase, Clofarabine (Clolar), Arranon, and Leukine. These products are commonly used to treat acute lymphoblastic leukemia and other associated illnesses
There are a number of medications and other substances that are based on asparaginase that are used to treat leukemia. Asparaginase is sold under the brand names Erwinaze, Kidrolase, and Elspar, and it is often used to treat acute lymphoblastic leukemia (ALL). Pegaspargase (Oncaspar), its pegylated version, is also commonly used for ALL since it has a longer half-life and needs to be taken less often. Clofarabine (Clolar) is used to treat ALL, while Nelarabine (Arranon) is used to treat T-cell acute lymphoblastic leukemia (T-ALL). Sargramostim (Leukine) helps people with myeloid leukemia and treats neutropenia by helping white blood cells recover.
L-asparaginase is an enzyme that does two things: it breaks down asparagine and glutamine into aspartate and glutamate and it targets cancer cells that don't have ASNS expression [39]. Its glutaminase activity may also help fight tumors in malignancies that have ASNS [39]. Preclinical studies demonstrate its extensive anti-cancer capabilities, including the induction of autophagy in ovarian cancer, the prevention of angiogenesis, and the stimulation of apoptosis in sarcoma [40,41]. Additionally, it exhibits synergy with medications like doxorubicin, which promotes cancer cell mortality [42]. In animal models, combining this drug with temozolomide has also been demonstrated to slow the formation of gliomas [41]. Despite these findings, its known clinical value remains mostly in acute lymphoblastic leukemia (ALL) and certain lymphomas, owing to side effects including hypersensitivity, thrombosis, and pancreatitis [43]. Resistance mechanisms encompass expedited drug breakdown, immune-mediated neutralizing antibodies [47,48], and elevated ASNS expression, which may be mitigated by ASNS inhibitors in vitro [49]. L-asparaginase therapy also depletes glutamine, which can lead to toxicities such pancreatitis, immunosuppression, and thrombosis [48,50]. This has led to attempts to create enzyme variations that don't contain glutaminase [51,52]. Different clinical formulations have different immunogenicity and half-lives. For example, native E. coli, pegylated E. coli, and Erwinia chrysanthemi L-asparaginase [54]. PEGylation increases half-life [55]. Antibodies against native E. coli may cross-react with PEG-ASNase [56], prompting doctors to utilize Erwinia ASNase as an alternate in instances of hypersensitivity or resistance.

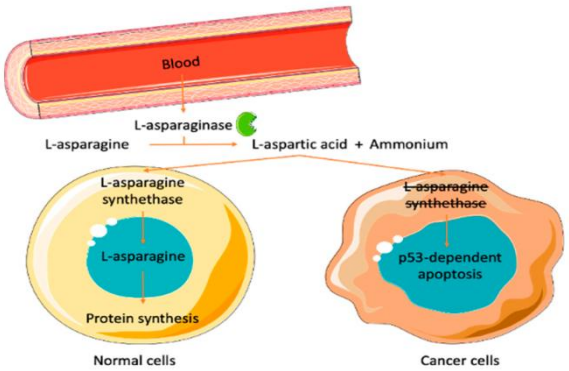

Fig 05: Role of L-Asparaginase in Targeting Cancer Cells via Amino Acid Deprivation.

(Fig 05 shows how L-asparaginase, an enzyme used to treat acute lymphoblastic leukemia (ALL), works and how it affects cancer and healthy cells differently.)

Pre-clinical studies show that L-asparaginase can inhibit the growth of several cancers. However, when evaluating both therapeutic benefits and adverse effects, L-asparaginase appears most effective in specific hematologic malignancies [57]. Improving formulations to achieve longer half-life, reduced immunogenicity, and lower glutaminase activity may enhance clinical outcomes. Monitoring anti-asparaginase antibody levels and performing allergy tests can help manage hypersensitivity. Developing human-derived L-asparaginase in the future may further reduce immunogenicity and expand its clinical use.

1.2. Methionase

L-Methionine-γ-lyase (MGL) is an enzyme that breaks down methionine and is made when L-methionine is present in the culture medium [58,59]. It usually appears as a tetramer with a mass of about 149–173 kDa, but there have been reports of variants, such as the heterodimeric form in Pseudomonas putida [60]. PLP is very important for decreasing the activation energy forMGL-catalyzedaminoacidtransformations [61].

Normal cells produce methionine via methionine synthase, however many tumor cells have minimal or no enzyme activity, which means they need methionine to survive [62,63]. This metabolic deficiency is associated with heightened methionine requirements for protein synthesis and DNA methylation, hence influencing malignancy risk and development [64-66]. Since cancer cells depend on methionine, restricting methionine and using MGL-based treatmentsare good ways to stop tumors from growing.
Recombinant P. putida MGL (PpMGL) exhibits antiproliferative activity against several malignancies, both independently and in conjunction with chemotherapeutic drugs such as cisplatin and 5-FU [67-69]. When MGL is supplied using viral vectors or combined with the prodrug selenomethionine (SeMET), it makes methylselenol, a toxic metabolite that causes oxidative stress, damage to mitochondria, and death of cancer cells [70-77]. Methylselenol

selectively inhibits the proliferation of cancer cells while preserving normal cells and impedes tumor cell migration via MMP/TIMP modulation [73-75].

MGL therapy lowers plasma methionine levels to less than 2 μM, although it can also induce moderate side effects like less appetite or temporary alterations in blood cells [79]. PEGylated MGL variants (PEG-MGL, PEG-rMGL) enhance half-life and diminish immunogenicity, albeit occasionally at the expense of decreased methionine-depletion efficiency [80]. Cofactor supplementation, DTT addition, and deimmunization methods are some of the strategies that can make therapies even better [67,68]. Tumor cells rely heavily on methionine, so using MGL to lower methionine levels could be a good way to fight cancer [81]. Recent advancements, such as fusion proteins that merge MGL with human annexin-V, facilitate targeted elimination of tumor cells while reducing impact on normal tissues [64].

1.3. Arginase

L-arginase (EC 3.5.3.1, ARGase) catalyses the hydrolysis of L-arginine in the presence of divalent cations, producing urea and the non-protein amino acid L-ornithine. The normal cells remain unaffected when Arginase converts L-Arginine to ornithine and urea due to their capability to synthesize arginine from citrulline using the enzymes arginosuccinate synthase (AS) and arginosuccinate lyase. However, cancerous cells do not express these enzymes, which is why they are unable to perform this synthesis.

The utilization of this enzyme in amino acid depletion therapies for tumors offers numerous advantages due to the high demand for ARG. Firstly, it is non-immunogenic to humans, making it a suitable candidate for therapeutic applications. Secondly, it exhibits good stability in serum. However, the overexpression of ARGase leads to a significant increase in the concentration of L-ornithine within cells,this sets off the feedback system. In this mechanism, L-ornithine is changed back into L-citrulline by OCT and then recycled back to ARG by ASS/ASL. This amino acid homeostatic mechanism plays a crucial role in maintaining constant levels of various amino acids. Consequently, it is the primary reason why normal cells and certain tumors exhibit resistance to therapies involving ARGase [82].

Fig 06: Arginase-Catalyzed Hydrolysis of L-Arginine in the Urea Cycle.

(Fig 06 from www.wellnessadvocate .com illustrates how the addition of water (H2O) causes L-arginine to be broken down by arginase into L-ornithine and urea.)

1.4. Glutaminase

Tumor cells experience malnutrition as a result of glutaminase's conversion of L-glutamine to glutamic acid and ammonia, which eventually triggers apoptosis. This is due to the absence of the glutamine biosynthesis enzyme L-glutamine synthetase, which is typically found in normal cells. The uptake of essential L-glutamine from the bloodstream is crucial for the growth and survival of both normal and cancerous cells. Nevertheless, because of their unchecked development, cancer cells require more L-glutamine than normal cells. The expression of the Myc gene, which produces a transcription factor that promotes the development of the glutamine transporter and metabolic enzymes involved in biosynthesis, causes some cancer cells to show a glutamine dependency [83].

In normal cells, the conversion of L-glutamine to glutamic acid by L-Glutaminase does not affect their functioning because these cells possess the gene for Glutaminase synthetase, which converts glutamic acid back to glutamine, ensuring normal cell metabolism [84]. However, in cancer cells, the absence of Glutaminase synthetase disrupts the metabolic processes that require glutamine. This scarcity of glutamine ultimately leads to apoptosis in cancerous cells. The mechanism of the L-Glutaminase enzyme plays a crucial role in this process.

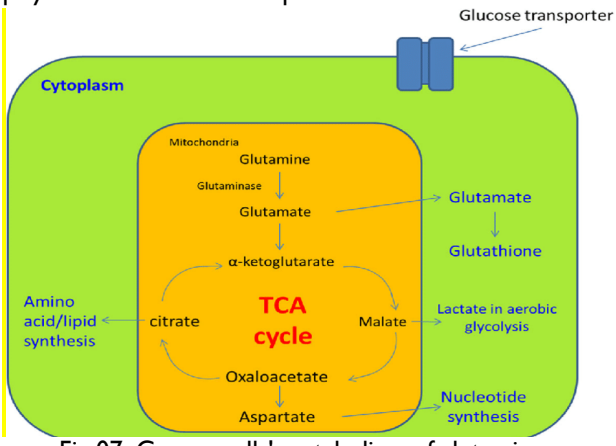

Fig 07: Cancer cells' metabolism of glutamine

(Fig 07 from www.researchgate.netShows the metabolic cycles of glutamine.)

1.5. Arginine deiminase

ARG serves as a crucial component in the process of protein synthesis across all organisms. However, in mammals, it plays a vital role as a precursor and mediator in various significant biological pathways.These pathways include the release of anabolic hormones, nitrogen metabolism, nitric oxide generation, agmatine, creatine, and polyamine synthesis [85]. ARG also has immunostimulatory and thymotrophic properties. It is classified as an amino acid that is semi- or conditionally essential. The word "conditionally" is used since ARG is a non-essential

amino acid in healthy individuals because the body produces enough of it internally [84]. Nevertheless, during periods of catabolic stress such as inflammation or infection, the endogenous synthesis of ARG may not meet the metabolic demands. In such cases, ARG becomes essential and requires an external supply

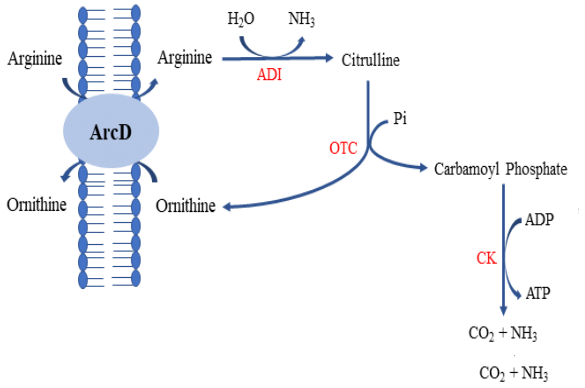

Fig 08: Arginine Metabolism and Transport via the ArcD System
(Fig 08 from www.researchgate.netillustrates Arginine metabolism.)

In mammals, arginine is made by turning citrulline into arginine with the help of arginosuccinate synthase (ASS) and argininosuccinate lyase (ASL). ASS catalyzes the condensation of citrulline and aspartate to create argininosuccinate, which ASL then cleaves to make fumarate and arginine [86]. Initially recognized in the liver as a urea cycle enzyme, ASS is now understood to be extensively present in mammalian tissues [87].

In the last twenty years, a lot of tumors have been shown to not express ASS, which means they need arginine to grow. ASS deficiency has been shown in metastatic melanoma, prostate and cervical cancers, breast and ovarian carcinomas, colon and lung cancers, leukemias, lymphomas, osteosarcoma, gliomas, pancreatic cancer, and malignant mesothelioma. Some tumors also show reduced levels of ornithine transcarbamyl transferase (OCT), blocking the salvage pathway that regenerates arginine from ornithine. Research has validated the lack of OCT expression in various human cancer cell lines.Arginine deprivation therapy relies on enzymes that breakdown arginine, such as arginase (ARGase), arginine decarboxylase (ADC), and arginine deiminase (ADI). Human ARGase-I and bacterial ADI exhibit the highest therapeutic potential, while ADC is deemed inappropriate due to its cytotoxicity to normal cells [76].

Cancer cells with low ASS1 levels are very sensitive to a lack of arginine. When cells don't get enough arginine, they die in many ways, the most common of which is caspase-dependent apoptosis. This happens in mesothelioma, lymphoma, pancreatic cancer, ovarian tumors, sarcomas, leukemia, liver cancer, and melanoma [89]. Caspase-independent apoptosis or autophagic cell death occurs in certain tumors, such as glioma and small-cell lung cancer. Arginine deficiency also inhibits mTOR, inducing robust autophagy [89]. Autophagy initially aids cellular survival under nutrient scarcity; however, extended deficiency results in excessive autophagy, reactive oxygen species (ROS)-induced DNA damage, and a phenomenon known as chromatophagy, wherein damaged chromatin is eliminated through autolysosomes, culminating in caspase-independent cell death [90]. Researchers have seen this in cancer cells from the prostate, breast, liver, and pancreas.

Preclinical investigations in various cancer models demonstrate that targeting arginine metabolism, particularly by ADI-PEG20–mediated arginine depletion, reliably inhibits tumor cell proliferation and viability. In malignancies including bladder, breast, colon, cholangiocarcinoma, head and neck, pancreatic, prostate, renal, melanoma, ovarian, sarcoma, and small-cell lung cancer, ADI-PEG20 elicits apoptosis, autophagy-related cell death, mitochondrial dysfunction, and reduced proliferation-especially in ASS1-deficient cells. Certain studies indicate that cancers may develop resistance via the overexpression of ASS1 and associated signaling pathways. Numerous studies indicate that the combination of ADI-PEG20 with chemotherapeutic drugs such as cisplatin, 5-FU, gemcitabine, docetaxel, oxaliplatin, paclitaxel, or temozolomide promotes cytotoxicity, mitigates drug resistance, and elevates anti-tumor efficacy. Combining with chloroquine or metabolic inhibitors makes cancer cells even more sensitive by disrupting processes that let them survive. In general, these results show that arginine-deprivation–based therapies have a lot of potential as treatments for many different forms of cancer [91-114].

2.2 Aminoacid deprivation by enzyme inhibition

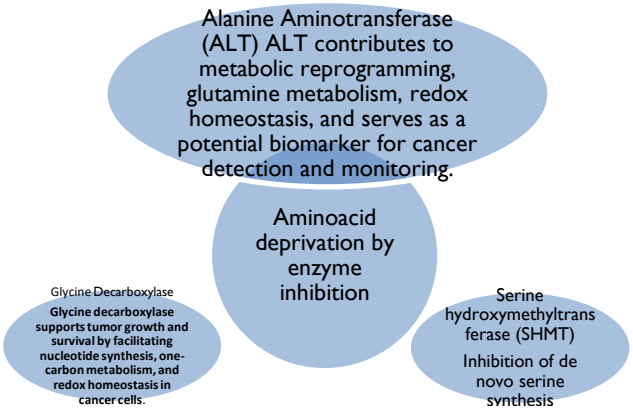

Fig 09. Amino Acid Deprivation Therapy: Targeting Enzymes for Cancer Treatment
(The function of enzyme inhibition in amino acid deprivation therapy for the treatment of cancer is illustrated in this graphic.)

2.1. Alanine amino transferase

Cancer cells can live in places where there aren't many nutrients by changing how they use energy and finding other sources of nutrients. Hodakoski et al. [115] discovered that a specific group of non-small cell lung cancer (NSCLC) cells endures glucose deprivation by

employing Rac-driven macropinocytosis to internalize and degrade extracellular proteins. This mechanism makes amino acids, especially alanine, which serve as intermediates for glycolysis and the TCA cycle when there is no glucose. Blocking Rac-dependent macropinocytosis stops cells from growing when there isn't enough glucose, which shows that this pathway could be a good target for treatment [115].

Alanine transaminase (ALT) changes alanine into pyruvate and glutamate. ALT1 is in the cytosol, and ALT2 is in the mitochondria [117]. Expression data from CCLE demonstrate that ALT2 is higher than ALT1 in several lung cancer cell lines. This means that ALT2 is very important for adaptive cancer metabolism. Hodakoski et al. [115] identified ALT2 protein in H1299 and H1975 cells, whereas ALT1 was not present in H1975. The CRISPR-Cas9 deletion of ALT2 significantly diminished transaminase activity and rendered cells more susceptible to glucose deprivation; cell viability was restored by exogenous pyruvate, thereby affirming ALT2's function in the conversion of alanine to pyruvate under conditions of glucose scarcity. The ALT inhibitor L-cycloserine also lowered transaminase activity and cell life when there wasn't enough glucose, and adding alanine only partially restored cell viability. This shows that more than one amino acid is needed for cells to stay alive [115]. In general, ALT2-mediated alanine transamination is necessary for the body to adjust to not having glucose.

2.2. Serine hydroxy methyltransferase

An important enzyme in one-carbon metabolism, which is a metabolic route required for the synthesis of nucleotides, amino acids, and other cellular constituents, is serine hydroxy methyltransferase (SHMT). Because of its essential function in serine production and the interconversion of serine and glycine, SHMT has become a promising target in cancer treatment research [117]. In order to sustain their rapid growth and multiplication, cancer cells frequently show an elevated requirement for serine. The goal of blocking SHMT is to prevent serine from being synthesized from scratch, which will cause cancer cells to become less capable of growing and surviving. Targeting SHMT can also interfere with one-carbon metabolism, upsetting the equilibrium of one-carbon metabolites necessary for DNA methylation and other cellular functions that are vital for the growth of cancer cells. Furthermore, by making cancer cells more sensitive to current treatments or circumventing drug resistance mechanisms, combining SHMT inhibitors with conventional cancer medicines like chemotherapy or targeted therapy has promise for improving treatment outcomes. Even though preclinical research has produced encouraging results in a variety of cancer models, more investigation is required to fully understand the therapeutic potential of SHMT inhibition and assess its efficacy and safety in real-world clinical settings.

2.3. Cystathionine beta-synthase

The involvement of cystathionine beta-synthase (CBS) in redox balance and sulphur metabolism makes it a multifunctional agent in cancer therapy [119]. The primary function of CBS is to catalyse the condensation of homocysteine and serine, which results in cystathionine, a precursor in the transculturation pathway. However, abnormalities in its expression and activity have been linked to a number of malignancies. The overexpression of CBS in cancer cells results in changesto the redox balance and the metabolism of sulphur amino acids, both of which support the growth and survival of tumors. By giving cancer cells, a source of cysteine, which is needed to synthesize glutathione, CBS-mediated cystathionine production boosts the antioxidant capacity of the cells and shields them from harm brought on by oxidative stress. Furthermore, the generation of hydrogen sulphide (H2S), An involved signaling molecule in a number of physiological processes, including vasodilation and cell proliferation, is encouraged by CBS activity. Targeting CBS has come to light as a viable tactic in the context of cancer therapy, one that could upset redox equilibrium, stop tumor development, and improve the effectiveness of traditional cancer treatments. It has been demonstrated that blocking CBS expression or activity reduces the ability of cancer cells to proliferate, triggers oxidative stress-induced apoptosis, and makes tumors more susceptible to radiation or chemotherapy. Consequently, CBS is a good therapeutic target for the treatment of cancer, and more study into its molecular mechanisms and the creation of CBS inhibitors could result in the development of innovative anticancer tactics.

2.4. Glycine decarboxylase

Glycine decarboxylase (GLDC) is an important enzyme in the glycine cleavage system. It affects cellular metabolism and redox equilibrium, which makes it relevant for cancer treatment [120]. GLDC helps keep folate pools full and promotes important biosynthetic activities including nucleotide synthesis and methylation by breaking down glycine into ammonia, carbon dioxide, and one-carbon units. A lot of cancers have too much GLDC, which makes tumors grow quickly, spread to other parts of the body, and defy treatment. Targeting GLDC has so become a promising therapeutic strategy. Blocking GLDC messes with glycine metabolism, lowers nucleotide production, causes metabolic stress, and makes cancer cells more sensitive to chemotherapy. Inhibiting GLDC also changes the redox balance by reducing the one-carbon units that are utilized to protect against oxidative stress. This makes cancer cells more sensitive to radiation and chemotherapy. Consequently, GLDC signifies a prospective metabolic target, and current research endeavors to elucidate its dysregulation and formulate effective GLDC inhibitors for forthcoming anticancer treatments [118].

AMINO ACID DEPRIVATION BY BLOCKING OF AMINO ACID TRANSPORTERS

The need of mammalian cell lines on exogenous glutamine was initially observed in the 1950s. Glutamine aids in the proliferation of cancer cells by providing energy, preserving redox equilibrium, and facilitating the production of nucleotides, fatty acids, and non-essential amino acids [121]. However, the glutamine needs of different malignancies vary according on where the tissue comes from, genetic changes, and the tumor microenvironment [121]. Even though glutamine synthetase can make glutamine, many tumors don't make enough of this enzyme, therefore they depend on outside glutamine [122]. These types of cancer grow weak when glutaminase, the enzyme that changes glutamine into glutamate, is stopped or missing.

Targeting glutamine metabolism has become a potential treatment strategy. This includes preventing the uptake of glutamine, reducing the amount of glutamine in the blood, and stopping enzymes that are involved in using glutamine [123]. One of the most advanced techniques is to stop glutaminase. Telaglenastat (CB-839), a glutaminase inhibitor, has demonstrated significant antitumor efficacy in preclinical models, encompassing B-cell lymphoma, non-small cell lung cancer (NSCLC), and triple-negative breast cancer [124]. In a patient-derived breast cancer xenograft, telaglenastat alone decreased tumor development by 61%, while in conjunction with paclitaxel, it achieved complete (100%) tumor growth inhibition.

Phase I clinical trials have shown that telaglenastat is safe and works well to lower glutaminase activity in malignancies. This has been shown to work in patients with lymphoma and multiple myeloma [127,129]. Other early-phase studies have demonstrated that renal cell carcinoma can be treated with everolimus alone or in conjunction with other drugs [128]. Phase 2 trials that are still going on keep showing good results. Initial data suggest that telaglenastat combined with everolimus resulted in a twofold increase in progression-free survival (3.8 months versus 1.9 months) compared to placebo plus everolimus [130]. These results bolster telaglenastat as a potent treatment candidate aimed at glutamine metabolism in cancer.

AMINO ACID DEPRIVATION BY DIETARY MODULATION

Branched-chain amino acids (BCAAs)-leucine, isoleucine, and valine-are crucial in metabolic pathways and control various vital signaling processes, which is why they are interesting targets in cancer research. Research indicates that modifying BCAA availability can markedly affect tumor proliferation. For instance, a lack of leucine causes apoptosis, lowers cell viability, and stops breast cancer cells from growing in vitro while reducing the growth of tumors in vivo [131]. Related studies examining serine and glycine limitation further elucidate the impact of amino acid metabolism on tumor progression, demonstrating decreased tumor growth, heightened necrosis, and a potential augmentation of anti-tumor effects when used in conjunction with mitochondrial complex I inhibitors. Responses differ: metformin exhibits no significant survival advantage, while phenformin reveals toxicity in amino acid–restricted environments [131].

Animal studies show that diets low in leucine make animals eat less, but controlled pair-feeding tests show that tumor suppression comes from not getting enough leucine, not from eating less. Dietary leucine restriction alone did not significantly reduce melanoma tumors in vivo; nevertheless, it induced caspase-dependent cell death in melanoma cells in vitro [132]. These findings underscore the intricate involvement of BCAAs in tumor development and advocate for ongoing investigation of amino acid restriction as a therapeutic approach.

1. Keto diet

A glycolytic dependence caused by abnormal metabolism in cancer can be taken advantage of by reducing the amount of glucose available to the tumor. By reducing blood glucose and increasing blood ketones, the low-carb, high-fat ketogenic diet (KD) has been shown to prevent the development of cancer in both humans and animals. The formation of hypoxic pockets by abnormal tumor vasculature aids in the advancement of cancer and increases the tumours' reliance on glycolysis. By flooding tumors with oxygen, hyperbaric oxygen therapy (HBO2T) counteracts the effects of tumor hypoxia that promote malignancy. We evaluated the combined effects of these non-toxic medicines on cancer progression in a realistic model of metastatic disease because they take advantage of the overlapping metabolic deficits of cancer [133].

AMINO ACID DEPRIVATION BY METHIONINE RESTRICTION

Komninou et al. [134] examined the effects of lifelong methionine restriction (MR) on the development of preneoplastic aberrant crypt foci (ACF) in the colons of rats treated with azoxymethane (AOM). Rats on a low-methionine diet exhibited a notable decrease in ACF production relative to control subjects. This decrease happened both during and after AOM exposure, which shows that MR stops colon cancer from growing, especially in the early stages. MR also slowed down the growth of cells in the colon, which suggests that this is how it works to fight cancer.

Amino acid depletion techniques show a lot of promise for cancer treatment because they are not very toxic and don't create long-term DNA damage-related adverse effects. Before clinical translation, it is essential to comprehensively elucidate the metabolic dependencies of various tumor types and their microenvironments to ascertain the most efficient amino acid targets. Because metabolic adaption during amino acid restriction can lead to therapeutic

resistance, just cutting back on amino acids is probably not enough. Future therapeutic applications will necessitate combinatorial techniques, incorporating metabolic inhibitors or sensitizers, to avert resistance and guarantee the persistent eradication of cancer cells. Multidrug strategies that inhibit various metabolic pathways and take into account tumor-microenvironment interactions will improve therapy duration and efficacy [135].

ADVANTAGES AND LIMITATIONS OF AMINOACID DEPRIVATION THERAPY

Amino acid deprivation therapy offers significant benefits in cancer treatment by specifically targeting tumor cells while minimizing side effects on healthy organs. This approach enhances the effects of conventional treatments and addresses drug resistance, as cancer cells often remain sensitive to amino acid depletion. However, the therapy also has limitations, as not all tumors rely on the same amino acids, and cancer cells may develop resistance over time. Potential side effects include fatigue and weakened immunity due to the depletion of essential nutrients. Identifying suitable patients is complicated by the lack of reliable biomarkers, and more clinical evidence is needed to establish the therapy's safety and effectiveness in routine cancer care.

FUTURE PROSPECTUS OF AMINO ACID DEPRIVATION THERAPY

The future of amino acid deprivation therapy looks good. Advances in molecular profiling should help find patients whose cancers respond best to metabolic targeting, which will allow for more customized and successful treatments. Combining amino acid restriction with chemotherapy, radiation, or immunotherapy may improve results even more. Researchers are still looking for the best combinations and treatment sequences to stop resistance. As our knowledge of tumor metabolic requirements increases, more targeted medications that block certain enzymes, transporters, or signaling pathways could make treatment more precise and less harmful to healthy cells. Amino acid metabolism is also critical for controlling the immune system, which suggests that deprivation techniques may boost antitumor immunity and work well with immunotherapies. Aside from cancer, changing how amino acids are broken down may be helpful in treating metabolic, neurological, and viral illnesses. To put these techniques into reality in the clinic, researchers, doctors, and regulatory agencies will need to work together on large, long-term trials. To fully incorporate amino acid deprivation therapy into cancer treatment, patient-centered strategies must focus on nutrition, emotional support, and overall quality of life.

CONCLUSION

To sum up, amino acid deprivation therapy is a potential direction in cancer treatment that offers focused and specific methods to interfere with the metabolic processes that cancer cells rely on. To maximize its clinical utility and efficacy, however, like with any therapeutic modality, there are related constraints and problems that must be addressed. In order to address the imperfections of amino acid deprivation therapy, a number of important areas should be the focused of future study. First and foremost, in order to pinpoint predictive biomarkers and patient subgroups most likely to benefit from this treatment, a greater comprehension of tumor heterogeneity and metabolic plasticity is required. Furthermore, research should focus on understanding the mechanisms underlying acquired resistance and creating counter measures, such combination treatments and tailored medication development.

Optimizing the safety profile of amino acid deprivation therapy also requires the addressing of off-target effects and limiting systemic toxicity. This means developing new strategies to target cancer cells specifically while preserving healthy tissues, improving drug delivery methods, and optimizing treatment regimens. Furthermore, converting preclinical findings into clinical applications requires cooperation between basic science, clinical researchers, pharmaceutical industries and regulatory bodies. A variety of patient populations will require extensive clinical studies with strong research designs and long-term follow-up to confirm the effectiveness, safety, and long-term results of amino acid deprivation therapy.

In conclusion, even though a therapy has a lot of promise as a tailored and targeted cancer treatment approach, minimising its imperfections will require interdisciplinary knowledge sharing, careful research, and creative problem-solving. Through overcoming these imperfections, amino acid deprivation therapy can maintain its position as a powerful therapeutic tool in the fight against cancer in future.

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AUTHORS CONTRIBUTION STATEMENT

Bindu E conceptualized the review topic, performed the literature search, and drafted the manuscript. Dr. Harikumaran Thampi provided overall guidance and critical revision of the manuscript. Dr. Robert Antony contributed to content development, organization, and manuscript editing. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

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