Targeted Amino Acid Deprivation Therapy (TAADT) for the Treatment of Malignancies

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Introduction

In the pursuit of discovering and developing natural and nontoxic means to treat cancer arises Targeted Amino Acid Deprivation Therapy (TAADT). TAADT is a powerful tool when appropriately combined with oxidative therapies. Incorporation of TAADT opens the door towards cancer treatment without surgery, chemotherapy and radiation. Targeting universal vulnerabilities in cancer cells is truly revolutionary and groundbreaking. TAADT is inexpensive, drug-free and is implemented in a home-based setting.

Decades of cancer research has been directed toward identifying and targeting specific amino acids for therapeutic potential in cancer treatment. Cancer cells are known to have unique requirements for amino acids that are beyond the level for normal cells. These differences may be exploited to slow tumor growth, inhibit metastasis, weaken cancer cells and trigger cell death while not affecting the viability of normal cells. Amino acids are largely supplied to the body through diet so an opportunity is available to modulate the availability of select amino acids that are critical to cancer cell growth and survival without causing any negative health consequences.

Targeted Amino Acid Deprivation Therapy (TAADT) represents a revolutionary breakthrough in nontoxic cancer treatment. TAADT is a combination of dietary amino acid restriction and enzymatic or non-enzymatic amino acid degradation. There are fundamental and foundational aspects of TAADT that will profoundly alter the landscape in both conventional and alternative cancer treatment. TAADT is the key to the development of highly effective nontoxic cancer therapies. The Nutritional Oncology Research Institute has already incorporated TAADT with alternative and integrative cancer treatment plans. Incorporation of TAADT is applicable to all forms and stages of cancer as all cancers exhibit the same metabolic adaptations.

It is estimated that about one third of cancer patients seek out and incorporate complementary, integrative, holistic or alternative elements into their treatment plan. A common approach is dietary intervention ranging from going organic, cutting out sugar, lowering carbohydrate intake, fasting, raw food diet, juicing, following a ketogenic diet, adopting a plant-based diet and taking lots of nutritional supplements. A set of unifying principles which can guide cancer patients towards the most effective dietary interventions would most certainly be quite helpful.

Dietary interventions are a key component of various alternative cancer treatment approaches. Regrettably, standard of care completely dismisses or ignores any dietary intervention that may have significant therapeutic benefit. Mainstream nutritional advise for cancer patients is to eat a balanced diet, get plenty of protein and sufficient calories. However, one who is pursuing an alternative or integrative treatment approach is likely to be quite confused from the widely divergent dietary recommendations. One such area of confusion centers around carbohydrates and fruits. The good news is that there is growing consensus that a plant-based diet is optimal for cancer prevention and treatment. The Mayo Clinic has recently recommended a plant-based diet for all cancer patients.

There has been a strong focus on targeting glucose metabolism as a basis for numerous alternative and integrative cancer treatment approaches. Is glucose metabolism an ideal therapeutic target? The ketogenic diet has been popularized as a method to “starve cancer”. This approach has not proven to be effective because cancer cells rewire metabolism in a manner where glutamine is the primary energy substrate. Cancer cells can also metabolize fatty acids for energy. Rather than targeting energy metabolism (ATP generation), targeting protein synthesis could be a much more viable target.

Cancer cells require specific amino acids at levels beyond the needs of normal cells. Amino acids support rapid growth and survival of cancer cells. Extensive scientific evidence points to key amino acids that are essential for cancer cells but not to normal cells.

Targeting Dietary Amino Acids

As building blocks of protein, amino acids are classified as essential, conditionally essential and non-essential. There are 20 different dietary amino acids found in food. Some amino acids can be synthesized from other amino acids.

Cancer is a growth process requiring amino acids for sustaining tumor progression. Amino acids are utilized for protein synthesis but are also utilized by cancer cells to regulate redox balance. Cancer cells are challenged by a higher than normal level of oxidative stress (ROS) and certain amino acids are necessary for maintaining antioxidant defense.

Manipulating dietary amino acid intake profoundly affects the viability of cancer cells while causing no harm to normal healthy cells. This fact is in stark contrast to statements by oncologists who suggest that diet has no effect on cancer progression or treatment response. Research on the addiction of cancer cells to the amino acid methionine spans nearly 60 years and has recently ben applied clinically at a small scale.

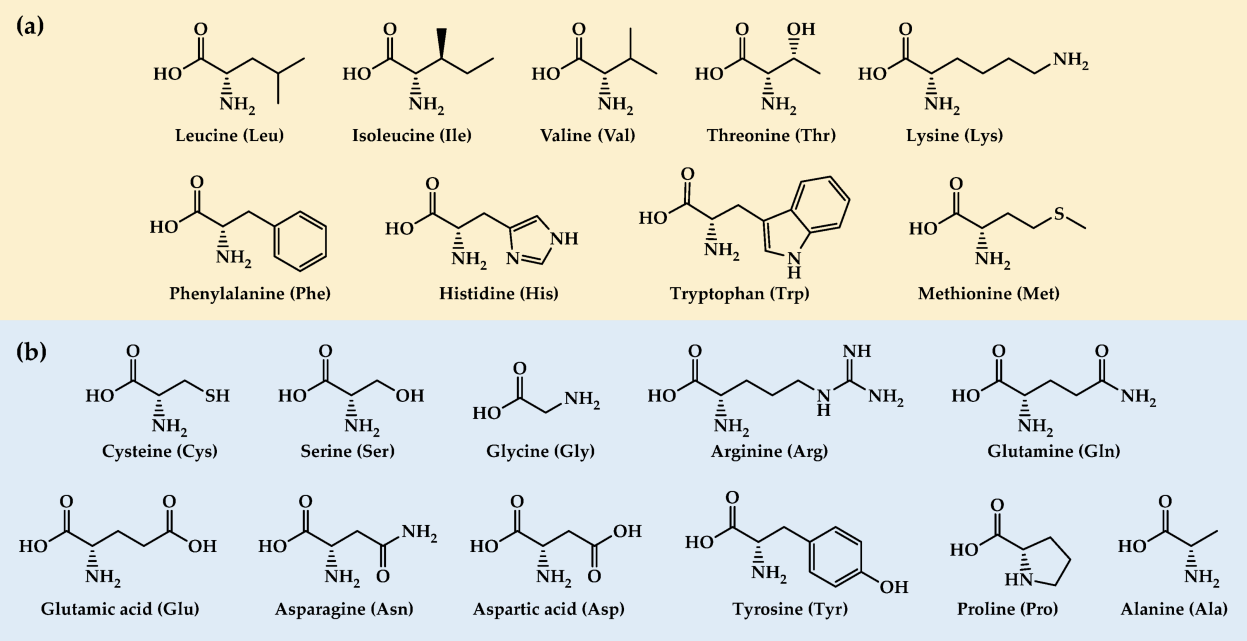


Figure 1. Chemical structure of proteinogenic AAs: EAAs (**a**) and NEAAs (**b**).

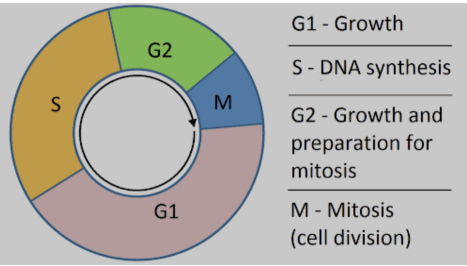
Methionine

Methionine is a sulfur containing amino acid which is found in nearly every biological protein. In other words, methionine is a very basic building block of all types of protein molecules.

Methionine has been recognized for over 50 years as an amino acid critical for cancer cell growth and survival. Dietary methionine restriction coupled with enzymatic methionine degradation has been demonstrated to be highly effective as an adjuvant therapy in small scale clinical studies.

Methionine is a sulfur containing amino acid found at very high levels in animal foods such as chicken and fish. All other animal foods including beef, pork, dairy products and eggs contain a substantial level of methionine. Plant foods contain much less with fruits containing the least amount. Certain processed foods like oils contain zero methionine. Therefore, a plant-based diet centered around fruits and vegetables will form a low methionine diet. To reduce methionine intake sufficiently to reach a therapeutic window, methionine intake should be less than 2 mg per kg of body weight per day. This is achievable with careful food selection.

A methionine restricted diet should be cycled on and off for best results and to avoid excessive weight loss. Cycling is also important in advancing cancer cells through the cell cycle.



Methionine restriction induces cell cycle arrest meaning that the cell ceases to advance through the cell cycle and does not attempt to divide.

Dietary Amino Acid Deprivation

Is it practical and feasible to manipulate amino acid levels in the blood through dietary manipulations? The answer is YES for certain amino acids. Dietary methionine restriction has been proven to be safe and effective within small scale clinical studies.

Incorporating a plant-based diet significantly lowers the intake of methionine, cysteine and branched chain amino acids. With careful food selection, amino acid intake can be fine tuned where cancer cells are deprived of these essential nutrients. A methionine and cysteine restricted diet looks like is a diet composed of primarily fruits of all types and select vegetables. This represents an incredibly healthy diet that is recommended for the prevention and management for all degenerative diseases and for prolonging lifespan.

Non-Dietary Amino Acid Deprivation

Since all whole foods contain amino acids, methods must be incorporated to further decrease the availability to cancer cells. One method is enzymatic degradation. The orally administered enzyme, methioninase, has been demonstrating safety and efficacy in treating a wide array of malignancies.

The enzyme, asparaginase, has been utilized as a treatment for ALL (acute lymphoblastic leukemia) and LBL (lymphoblastic lymphoma). Asparaginase is administered intravenously and is limited by allergic reactions to the foriegn protein.

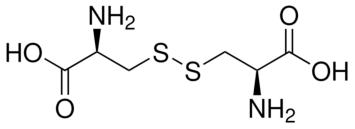
Vitamin B6 (P5P) has been identified by the Nutritional Oncology Research Institute as an agent that non-enzymatically degrades cysteine and may also degrade methionine. Vitamin B6 (P5P) dosage is 300-500 mg per day.

Cyst(e)ine

Another amino acid of intense research interest is cysteine. Just as cancer cells are addicted to methionine, cancer cells are highly addicted to cysteine. Why is cysteine so important for the cancer cell?

Cysteine is essential for the synthesis of glutathione. Glutathione is essential for the survival of cancer cells by controlling redox balance.

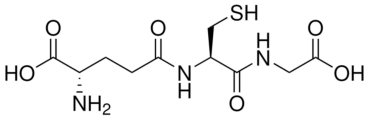
Cysteine comes from two sources. The primary source of cysteine is dietary. Cystine is the form of cysteine found in food. Cystine the oxidized form of cysteine which is comprised of two cysteine molecules. The Foods highest in cystine parallel methionine so animal proteins contain very high amounts. Fruits and vegetables contain the least. Some cysteine comes from the transsulfuration of methionine. This portion is believed to be very small.



Molecular Structure of Cystine
Note the disulfide bridge linking two cysteine molecules together.

Glutathione - The Achilles Heel of Cancer Cells

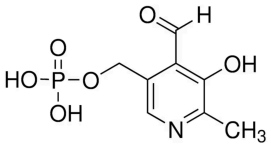
Glutathione is the master antioxidant within our cells that regulates redox homeostasis or stated differently, the level of oxidative stress. Glutathione is often confused with glutamine which is an amino acid. Glutathione is made up from the amino acids, cysteine, glycine and glutamate. Without cysteine, glutathione synthesis is not possible and oxidative stress can not be efficiently regulated. Elevated glutathione is responsible for chemoresistance and weakened response to anticancer agents.



Glutathione Molecular Structure

There are various approaches to depleting glutathione but the simplest method is to limit the availability of cysteine from the diet. A small percentage of cysteine is derived from methionine so limiting both amino acids is both practical and effective.

An additional method of lowering cysteine is supplementation with vitamin B6 (pyridoxal 5-phosphate). This bioactive form of vitamin B6 acts like an enzyme and degrades cysteine into ammonia and hydrogen sulfide. The aldehyde group pyridoxal 5-phosphate is active in binding to either sulfur or the amino group of the cysteine molecule as the first step in degradation.



Pyridoxal 5-Phosphate Molecular Structure

Cysteinase

An enzyme called cysteinase has been studied as another means to deplete glutathione. Cysteinase is being developed as a drug and is not available as a supplement that can be taken orally like methioninase.

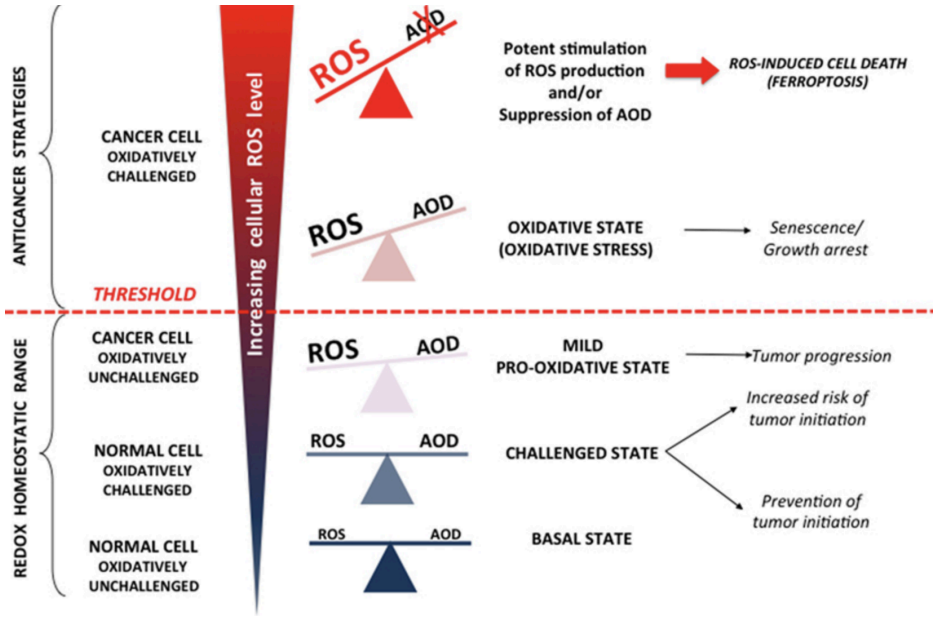


Illustration depicting pro-oxidant therapy by depleting antioxidant defense.

Thioredoxin

A secondary but very important antioxidant system is thioredoxin. Several different drugs and nutraceuticals can inhibit the thioredoxin antioxidant system. Simultaneous knockout of the glutathione and thioredoxin antioxidant systems is lethal to cancer cells while harmless to normal cells.

Simultaneous knockout of both antioxidant systems can be accomplished by combining TAADT with nutraceuticals such as sodium selenite or piperlongumine. Sodium selenite and piperlongumine are thioredoxin (TRXRD1) reductase inhibitors.

mTOR (mechanistic target of rapamycin) Signaling

mTOR is a signaling pathway involved in cancer progression. A drug has been developed called Everolimus which is a mTOR inhibitor. TAADT may be as or more effective than any pharmaceutical mTOR inhibitor.

Branched chain amino acid availability is sensed by mTOR and high levels of branched chain amino acids can stimulate tumor progression. Methionine is also sensed by mTOR and methionine depletion reduces mTOR signaling which slows tumor progression. mTOR inhibition may be a potential side benefit of incorporating TAADT.

Conclusion

TAADT is foundational for the treatment of cancer both conventionally and naturally. The primary target is the amino acid cysteine which is essential for the synthesis of glutathione. All pro-oxidant focused therapies are synergistic with TAADT. Pro-oxidant therapies include ozone therapy, high ozonide ozonated oils, hydrogen peroxide and other modalities that increase oxidative stress. Chemotherapy and radiation generate oxidative stress and are therefore enhanced by the incorporation of TAADT.

The Nutritional Oncology Research Institute is the innovator and leader in TAADT which is the culmination of 20 years of translational research.

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