



L-Tryptophan Depletion Bioreactor a New Approach to Diseases with Foreign Tissue Building Therapy

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Abstract

Most cancer therapeutic strategies known to date are not adequate for all cancer patients and are most followed by a high rate of severe side effects and complications. L-tryptophan, an essential amino acid, plays a key role in the growth of cells and organism development. Foreign tissue building can be limited by tryptophan depletion, a new therapy strategy for all diseases with foreign tissue building. A new bioreactor that contains immobilized tryptophan side-chain oxidase enzyme which degrades L-tryptophan, will be integrated into the Inuspheres system to treat all diseases with foreign tissue buildup, especially cancers, autoimmune and dementia diseases. The tryptophan side-chain oxidase has heme that can catalyze essentially similar reactions involving L-tryptophan as a substrate. Normal human cells or tumor cells cannot synthesize L-tryptophan and therefore tumor resistance is unlikely to develop. L-tryptophan is also constituent for different biomolecule such as Serotonin, Melatonin, and is needed for other synthesis process in the cell growth, especially for foreign tissue buildup.

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Introduction

In recent years, increasing attention has been directed toward diseases with foreign tissue buildup, such as benign and malignant tumors, autoimmune diseases, dementia, and others. Especially cancer remains one of the leading causes of morbidity and mortality worldwide despite substantial advances in surgery, radiotherapy, chemotherapy, targeted therapies, and immunotherapy. These treatment modalities have significantly improved outcomes for selected malignancies, therapeutic resistance, treatment-related toxicity, and tumor recurrence continue to limit long-term success.

Cancer cells exhibit profound alterations in nutrient utilization that support rapid proliferation, invasion, and immune evasion. Among these metabolic adaptations, L-tryptophan metabolism has emerged as a critical regulator for progression and antitumor immunity [1]. Tumor cells and other foreign tissues require not only increased amounts of L-tryptophan for protein synthesis and cell growth but also exploit tryptophan catabolism to establish an immunosuppressive microenvironment that facilitates malignant progression.

L-tryptophan is an essential aromatic amino acid that cannot be synthesized by human cells and must be obtained through dietary intake. Besides its role in protein synthesis, tryptophan serves as a precursor for numerous biologically active molecules, including serotonin, melatonin, nicotinamide adenine dinucleotide (NAD⁺), and several metabolites of the kynurenine pathway. Tryptophan metabolism influences a broad range of physiological processes, including immune regulation, neurological function, intestinal homeostasis, and cellular energy metabolism [1]. L-tryptophan, an essential amino acid, has been recognized as an important cancer nutrient, and its removal can lead to tumor destruction [2]. Normal human cells or tumor cells cannot synthesize L-tryptophan, and resistance in foreign tissue or tumor is unlikely to develop.

More than 90 % of systemic tryptophan metabolism occurs through the kynurenine pathway. The rate-limiting step of this pathway is catalyzed by indoleamine 2,3-dioxygenase 1 (IDO1), indoleamine 2,3-dioxygenase 2 (IDO2), and tryptophan 2,3-dioxygenase (TDO) [1]. These enzymes convert

tryptophan into kynurenine and related metabolites that exert profound immunomodulatory effects. Under normal conditions, this pathway contributes to immune homeostasis and tolerance. Many malignant tumors exploit this mechanism to suppress antitumor immune responses.

In numerous malignancies, such as breast cancer, hepatocellular carcinoma, melanoma, lung cancer, colorectal cancer, and glioblastoma, elevated expression of IDO1 and TDO leads to local depletion of tryptophan within the tumor microenvironment while simultaneously increasing concentrations of immunosuppressive kynurenine metabolites. This dual mechanism creates conditions that favor tumor immune escape.

Tryptophan depletion impairs the proliferation and activation of effector T lymphocytes, which are particularly sensitive to amino acid availability [1]. Reduced intracellular tryptophan concentrations activate the general control nonderepressible-2 kinase pathway and suppress the mammalian target of rapamycin signaling cascade, resulting in cell cycle arrest, energy depletion, and apoptosis of activated T cells. In parallel, kynurenine metabolism promotes the differentiation and expansion of regulatory T cells while inhibiting the function of natural killer cells and antigen-presenting cells. These effects collectively impair antitumor immunity and facilitate tumor progression.

The tryptophan-kynurenine axis has emerged as a central component of the tumor microenvironment and an attractive therapeutic target. Conventional therapeutic strategies have attempted to interrupt this pathway primarily through the development of small-molecule inhibitors targeting IDO1 and TDO. These approaches demonstrated promising activity; clinical trial results have been inconsistent, highlighting the complexity and redundancy of tryptophan metabolism within the tumors [1]. Indoleamine 2,3-dioxygenase 1 is the key enzyme in the catabolism of L-tryptophan through the kynurenine pathway (KP), and this enzyme is found in advanced-stage cancer and is associated with poor disease prognosis and immune suppression [3]. During malignant tumor diseases, IDO 1 activity seems to be a part of the tumoricidal immune defense strategy, when L-tryptophan deprivation and production of pro-apoptotic tryptophan catabolism counteract T

cell responsiveness [4].

L-Tryptophan Depletion Bioreactor

Experimental studies have demonstrated that tryptophan deprivation inhibits tumor cell proliferation, impairs protein synthesis, disrupts genome replication, and suppresses cellular growth [1]. Reduced tryptophan availability alters the tumor microenvironment by decreasing kynurenine production and restoring antitumor immune response. This suggests that systematic tryptophan depletion may simultaneously target both malignant cells and the immunosuppressive networks that support tumor progression, and other foreign tissue building will be stopped.

Therefore, an alternative therapy strategy is tryptophan depletion by the L-tryptophan-degrading enzyme tryptophan side-chain oxidase (TSO), which is immobilized on silica beads and packed in a column, and integrated in the Inuspheres system. The L-tryptophan-degrading enzyme has three isoenzymes, called TSO I, II, and III; they can be differentiated by tryptic digestion and have different molecular weights and efficiencies. The TSO enzymes have heme and catalyze essentially similar reactions involving L-tryptophan as the substrate. A column that contains TSO III, the most effective TSO enzyme, immobilized on silica beads is integrated in the Inuspheres system, between the two hollow fiber membranes.

The bioreactor, a column with immobilized TSO, in a plasmapheresis system was tested by Schmer et al in different animals and different tumor cell lines [5]. In sheep and rabbits, L-tryptophan depletion in plasma was 95% and 100%, respectively, after a single pass through the bioreactor; the results in immune-suppressed rats with tumors and in 20 different tumor cell lines were impressive, too. The greatest efficacy of L-tryptophan depletion was observed in breast cancer and medulloblastoma. TSO gene technology from *Pseudomonas* is associated with endotoxin formation; therefore, for TSO production, the gene technology must use a fungal source. Blood tryptophan depletion by TSO results in significant antineoplastic activity. A combination with all other available cancer therapies is possible [6].

Schmer and Sucher et al. found that the treatment of certain tumors by deprivation of the essential

amino acid L-tryptophan has the advantage over non-essential amino acid deprivation because tumor cells cannot synthesize L-tryptophan, but need it for their growth [5,7]. Hepatocellular carcinoma was suppressed by degradation of tryptophan by TSO purified from *Pseudomonas* [8]. The bioreactor developed by Schmer et al. is based on silica, and the amino groups containing silica beads were activated with 25% glutaraldehyde [5,6]. The activated amino-silane beads can be stored in a buffer of 0.2 M sodium acetate, pH 5.5, at 4° C and remain fully active for more than 6 weeks. The different washing procedures and the equilibration with 0.2 M sodium acetate is described elsewhere [5]. The silica-based enzyme reactor was filled in columns, washed, and sterilized.

The columns with the sterilized bioreactor containing immobilized TSO III are integrated in the Inuspheres system between the two hollow fiber membranes. The first hollow fiber module completely separates blood cells from plasma; the second hollow fiber module separates inflammatory mediators, circulating immune complexes, and protein- or lipid-bound environmental toxins, and other toxic substances from the plasma [9].

After different tests and a clinical study after the revised Declaration of Helsinki in different cancer diseases, this system can be used in the treatment of all diseases with foreign tissue building such benign, malign tumors, autoimmune diseases, dementia, etc. For the different diseases, different treatment plans are necessary. One to a maximum of 25 treatments, daily for 4-5 hours, 5 days a week over a maximum of 4 - 5 weeks (1 cycle) are enough for one patient to reach a remission. If no remission is reached, another cycle can be repeated 2 to 3 months later [6].

L-tryptophan blood level must be kept at a very low level over some hours during the treatment. In this phase, L-tryptophan can leave the cells and enter the blood, and can be split by the TSO enzyme into metabolites, which results in a very low L-tryptophan blood level. In the next treatment, the blood level of L-tryptophan increased; L-tryptophan is probably removed from vulnerable cells to increase the blood level [10]. Tryptophan depletion can be used in all diseases with foreign tissue building, especially in breast cancer and medulloblastoma. Resistance development is not possible; the therapy can be used in the same

patient again and again [11].

All other diseases with foreign tissue building can be treated with the bioreactor, containing TSO, all autoimmune diseases with antibodies such as multiple sclerosis, dementia with Tau protein, rejection in organ transplantation, monoclonal gammopathy, endometriosis, and Long COVID disease, after different treatment strategies [9,12]. The production of antibodies against foreign tissue requires tryptophan for building. The therapy can only affect tryptophan degradation. Alterations in the activity of TSO cause imbalances in the levels of serotonin and other neuroactive metabolites, which can contribute to motor, psychiatric, gastrointestinal, and other dysfunction often seen in Parkinson's disease [13]. In Alzheimer's disease, in which the Tau protein is found, tryptophan depletion is also indicated with the bioreactor; that means in all diseases with foreign tissue building the therapy with tryptophan depletion is indicated.

The side effects of the treatment with the TSO bioreactor can be the same, such as serotonin deficiency, fatigue, cognitive impairment, negative thoughts, agitation, chronic pain, feeling worse, etc., if the bioreactor treatment will be longer than 20 to 25 treatments, because healthy organs could be contacted, such as liver, muscle, brain, etc. Degrading L-tryptophan in the blood to a very low level, which influences serotonin metabolism, can be prevented by treatments of 4 to a maximum of 5 weeks with daily sessions of 4 to 5 hours. This cycle of treatments can be repeated every 2 to 3 months.

However, the great advantage of the bioreactor integrated in the Inuspheres system is the improvement of the hemorheological properties and reduction of alpha-2 macroglobulin, pro-inflammatory oxidized lipoproteins, and other toxic substances, besides the tryptophan depletion [11]. Another advantage is that no resistance against the tryptophan depletion is possible because L-tryptophan is one of the most important nutrients for all metabolism and cell growth, and without L-tryptophan no foreign tissue growth is possible, because the tryptophan depletion is indicated in all diseases with foreign tissue building, such as all cancer forms, autoimmune diseases, dementia, and others. A tryptophan-free diet is not necessary.

However, it could be applied during the treatment time with the bioreactor.

Conclusion

A new bioreactor containing immobilized TSO enzyme integrated in the Inuspheres system for the possible treatment of all diseases with foreign tissue building. The bioreactor is placed between the two hollow fibers of the Inuspheres system. The bioreactor with the TSO enzyme degrades L-tryptophan in the blood, which is of advantage for diseases such as cancer, autoimmune diseases, dementia, and others. L-tryptophan is an essential amino acid and must be supplied to the organism and is one of the most important nutrients for protein development and cell growth. Therefore, the bioreactor with immobilized TSO enzyme can be used as therapy in all diseases with foreign tissue building, such as all cancers, autoimmune diseases, and dementia.

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