

Editorial

L- Methionine, L-Methionine γ -Lyase, Cancer

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Resistance to conventional anticancer therapies in patients with advanced solid tumors has prompted the need of alternative cancer therapies. Moreover, the success of novel cancer therapies depends on their selectivity for cancer cells with limited toxicity to normal tissues. Restriction of methionine may be a useful strategy in limiting cancer growth. Methionine restriction may also prolong a healthy life-span.

Methionine is an essential amino acid necessary for normal growth and development in mammals. In every cell, methionine is partitioned between protein synthesis and the *de novo* pathway. Many human cancer cell lines and primary tumors have an absolute requirement for L-methionine, an essential amino acid. Why L-methionine essential? L-Methionine participates in protein synthesis. L-Methionine is a precursor of glutathione. L-Methionine is required for the formation of the polyamines spermine and spermidine. L-Methionine is the major source of methyl groups for methylation of DNA and other molecules. Therefore, restriction of L-methionine may be a useful strategy in limiting cancer growth [1-3].

Upon L-methionine depletion, L-methionine- dependent cancer cells are not able to divide and became arrested in the late-S/G₂ phase of the cell cycle. On the other hand, normal human cells are relatively resistant to exogenous L-methionine restriction. Thus, depletion of L-methionine is effective for cancer therapy [4-6].

L-Methionine γ -lyase (EC 4.4.1.11) is a pyridoxal 5'-phosphate (PLP)-dependent multifunctional enzyme which catalyzes α , γ -elimination and γ -replacement of L-methionine (Figure 1) and its derivatives and also α , β -elimination and β -replacement of S-substituted L-cysteines. The enzyme was composed of 398 amino acid residues corresponding to the subunit of the homotetramer. The enzyme composed of 398 amino acid residues [1,6-10].

Essential amino acids such as L-methionine and L-phenylalanine, as well as branched chain amino acids, have long been known to be important precursors of aroma volatiles in many fruits, including melon, tomato, banana, strawberry and apple. Recently, an Arabidopsis gene encoding a methionine- γ lyase enzyme that cleaves L-methionine into methanethiol, α -ketobutyrate and ammonia has been characterized [11].

The enzyme has been isolated from bacteria (*Pseudomonas putida*, *Aeromonas* sp., *Clostridium sporogenes*, *Phophyromonas gingivalis*, *Brevibacterium linens* BL2) also from primitive

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protozoa (*Trichomonas vaginalis* and *Entamoeba histolytica*) and H₂S in anaerobic bacteria, parasitic protozoa and is absent in fungi, plants and mammals. For this reason, L-methionine- γ -lyase can serve as a target for novel antibacterial drugs created on the basis of its inhibitors and/or suicidal substrates [6-10].

Many other studies confirmed that the activity of this enzyme could be low in methionine-dependent malignant cells.

Numerous studies focused on the potential antitumor activity of methionine restriction that exploits metabolic differences between neoplastic and normal cells. Numerous human cancer cell lines and primary tumors have an absolute requirement for L-methionine, an essential amino acid. Thus, depletion of L-methionine is effective for cancer therapy [7].

MGL assay rely on chromogenic detection of the α -keto acids, generated by this enzyme, using 3-methyl-2-benzothiazoline hydrazone to give the azine derivative.

The enzyme was efficiently expressed in *Pseudomonas putida* and *E. coli* and its potentiality as an antitumor agent, alone or in combination with other chemotherapeutic agents, was demonstrated in a number of solid tumors both *in vitro* and *in vivo* models. Therefore, enzymes that are able to reduce plasma levels of these tumor target amino acids (i.e. L-asparaginase, L-methionine- γ -lyase and arginine deiminase) are studied as therapeutic agents in cancer therapy [5].

Tumor cells are diverse and their sensitivity to methionine restriction is more or less pronounced [3].

A gene therapy approach using the L-methionine- γ -lyase gene derived from *Pseudomonas putida* has been recently developed. This gene was introduced into human lung cancer cells using a retroviral vector [3].

As cited above numerous cancers cell lines have high methionine requirements. Limitation of exogenous methionine

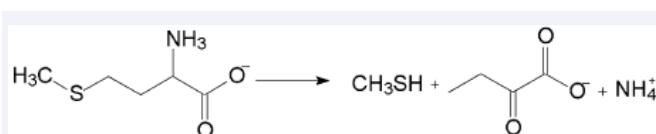


Figure 1 Conversion of methionine to α -ketobutyrate, methanethiol and ammonia.

through diets with low protein content does not allow the maintenance of good nutritional status. In such experiments, rats lost body weight rapidly and died from the profound alteration of their health status.

It is possible that such an effect can be achieved with further reduction of L-methionine- γ -lyase in certain tumors using existing technology.

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