Mini Review

L-methioninase: a mini review

Abstract

L-Methioninase (MGL) is a pyridoxal phosphate-dependent enzyme that catalyzes the conversion of L-methionine to α-ketobutyrate, methanethiol, and ammonia. Due to its ability to deplete methionine, MGL has gained attention for its therapeutic potential, particularly in cancer treatment, as cancer cells exhibit high methionine dependence. While MGL is widely produced by bacteria, fungal sources offer advantages such as extracellular secretion, reduced immunogenicity, and higher substrate specificity. Beyond oncology, MGL has applications in food industries, biosensors, and gas odorants due to its role in methanethiol production. Recent research explores novel formulations, including PEGylation and recombinant oral administration, to enhance its therapeutic efficacy. This review highlights the sources, mechanisms, and diverse applications of MGL while emphasizing its potential as a promising biotherapeutic agent.

Keywords: L-Methioninase, methionine depletion, cancer therapy, enzyme biotechnology, fungal MGL, methanethiol production, recombinant methioninase

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Anjana K Vala
Department of Life Sciences, Maharaja Krishnakumarsinhji Bhavnagar University, India

Correspondence: Anjana K Vala, Department of Life Sciences, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar-364001, India

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Introduction

L-Methioninase (L-Methionine-γ-lyase; EC 4.4.1.11; MGL), also known as methionase, L-methionine-γ-demethiolase, and L-methionine methanethiol-lyase (deaminating) is a pyridoxal phosphate dependent enzyme that catalyzes conversion of L-methionine to α-ketobutyrate, methanethiol, and ammonia by α, γ-elimination reaction.[1,2] MGL has gained much attention as a therapeutic enzyme for treatment of malignancies as most cancer cells have increased methionine dependence.

Sources of MGL

Occurrence of MGL has been reported in prokaryotes as well as eukaryotes. Mohkam et al.[3] reported production of MGL from soil bacteria *Alkaligens* sp. Genera *Streptomyces*, *Aeromonas*, *Achromobacter*, *Arthrobacter*, *Bacillus*, *Citrobacter*, *Brevibacterium*, *Pseudomonas*, etc. have exhibited production of MGL[4-9] Anaerobic bacteria *Porphyromonas gingivalis*[10] and *Treponema denticola*[11] have also been identified as source of MGL. Yeasts and filamentous fungi both have been reported to produce MGL.[2,12] MGL is produced intra cellularly by bacteria and extracellularly by fungi. Fungal MGLs have been suggested to impart fewer immunogenic and allergic reactions, have high substrate specificity and display less problems during tumor therapy.[13,14] Due to extracellular nature of fungal MGL, their downstream processing could be more cost-effective. Despite wide applications of MGL, advantages of using fungal MGL, and limitations associated with its bacterial sources, MGLs from fungi have been comparatively less studied.[15] Fungi from marine habitats have been reported as a source of anti-cancer enzyme L-asparaginase,[16] however, Occurrence of MGL from such fungi demands attention. Goyer et al. carried out functional characterization of MGL in plant *Arabidopsis*. Huang et al.[17] reported presence of MGL in potatoes. MGL is not found in mammals.[2]

Applications of MGL

MGL has diverse applications. Several workers have reported MGL as promising anticancer agent.[2,18,19] Addiction of cancer cells to methionine is a fundamental and general hallmark of cancer. This hallmark, known as "the Hoffman effect" is apparent because of overuse of methionine for elevated levels of aberrant trans methylation. Because of methionine restriction, the cell cycle of cancer cells is arrested in the S/G2 phase leading to suppression of tumor growth.[20] Methionine restriction also enhances effectiveness of cytotoxic chemotherapeutic drug. As methionine is present in all foods it's not easy to limit it by diet alone. This is the base of rationale behind use of L-methinioninase (MGL), which catalyses conversion of L-methionine to α-ketobutyrate, methanethiol, and ammonia by α, γ-elimination reaction, depriving cancer cells of circulating methionine leading to cell death. Kubota et al.[21] have proposed combining current therapy to methionine restriction for all cancer types as the next disruptive generation of cancer chemotherapy. Abo Qoura et al.[22] recently reviewed potential of MGL for cancer treatment and suggested PEGylation, encapsulation in RBCs and site-directed mutagenesis in overcoming the issues related to poor *in vivo* stability of MGL, high immunogenicity as well as enzyme-induced inactivating antibodies. Effective oral administration of MGL has been a big breakthrough. Miyake et al.[23] observed the combination of 5-flurouracil and oral recombinant methioninase (o-rMETase) promising for transformative therapy for poorly differentiated gastric cancer in the clinic. Miyake et al.[24] reported recombinant meithioninase to have future as potent therapeutic for colorectal cancer liver metastasis. Sato et al.[25] reported that a low-dose Trastuzumab deruxtecan (T-DXd) combined with oral recombinant MGL and a low methionine diet exhibited a rapid decrease in breast cancer biomarkers to normal levels in a patient with HER 2-positive recurrent stage IV metastatic breast cancer. Regression of metastatic lesions was also observed. They suggested recombinant MGL to be effective in cancer treatment due to its ability to target methionine addiction.

MGL is useful for other therapeutic purpose also. Hoffman and Han[26] suggested usefulness of oral recombinant MGL in coronavirus treatment. The authors proposed to restrict availability of methionine by treatment of patient with oral recombinant MGL. Restricting methionine availability helps in tackling coronavirus by multiple ways.

MGL is important in food industries as well. Products formed by methionine degradation are important in cheese flavor. Various cheese types contain volatile sulfur compounds. MGL imparts a distinctive aroma to some fermented foods by degrading L-methionine and releasing volatile sulphur compounds.[27]

Over the years, methanethiol has received much attention due to its commercial applications ranging from in gas odorants, jet fuel additives, in preparation of modified gold biosensors, manufacturing of plastics and pesticides and as a precursor for the production of dimethyl trisulfide, S-methylthio-esters and 2,4-dithiapentane.[4,28] Microbial production of methanethiol could be more promising than its chemical synthesis.[29]

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None.

Conflicts of interest

The author declares that there is no conflicts of interest.

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