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Radiolabelled Methionine Analogues for Applications in Oncology

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ABSTRACT

The first step towards an effective and timely treatment for cancer is an early diagnosis. Of the many available detection methods, examination of radiolabelled biomolecules specific to tumour cells has lately appeared as an attractive area invoking further investigation. Till date, several metabolic analogues such as glucose, choline, etc. have been identified for oncologic imaging. However, radiolabelled methionine analogues have established themselves as the more specific and sensitive biomolecule for accurately detecting tumours as well as estimating therapy efficacy. Being the fundamental methyl group donor in cells and an indispensable molecule of various central processes such as polyamine synthesis, trans-sulphuration, trans-methylation, etc., methionine governs a significant part of the overall cell physiology. Further, these metabolic demands get altered and accentuated in cancer cells, mandating higher uptake of methionine. Thus, it allows for specific and early molecular imaging of developing tumours using PET or SPECT, even before a tumour is visible in CT or MRI scans. With more research and an optimized pharmacokinetic profile, this tool can be successfully applied for an improved diagnosis and prognosis of various cancers.

KEYWORDS: Methionine, Amino Acid, LAT Transporters, Radiolabelled.

INTRODUCTION

Amino acids make up an important group of nutrients required for a variety of metabolic

pathways providing building blocks for the synthesis of proteins and precursors in the formation of several other biomolecules like nucleotides, fats, ketone bodies, glucose, signalling molecules, and neurotransmitters. Amino acids (AA) are used as fuels in the generation of metabolic energy and also play important roles in the biochemical processes of trans-methylation, transamination, and trans-sulphuration.

It is important to maintain the plasma levels of amino acids relatively constant, to carry out the diverse functions according to the needs of various tissues and organs. Inter-organ fluxes of amino acids, transport across cellular membranes, and modulation of enzyme activities by competition kinetics are the key elements in this homeostasis; however, owing to the several interactions and networking between various pathways, the regulation of amino acid metabolism is very complex.

Amino acids from the blood enter the cells mainly through multiple carrier-mediated amino-acid-specific (neutral, acidic, and basic) transport systems, with passive diffusion processes contributing marginally. The amino acid transport systems are protein complexes that recognise, bind, and transport the amino acids across cellular membranes. Because the isolation and determination of the molecular structures of the AA transporters have been undertaken only in recent years, they have been identified and characterised depending on their functional properties (such as substrate specificities, kinetics, ion dependence, etc.), and generally categorised as Na^+ dependent and Na^+ independent. Many AA transporters have broad and overlapping substrate specificities, permitting an individual amino acid to be transported in parallel by more than one transport system.

The Na+-dependent systems utilise the potential energy present in the transmembrane Na^+ electrochemical gradient, maintained largely by the Na^+/K^+-ATPase, to drive the uptake of amino acids against their concentration gradient. The neutral amino acids are mainly transported through Na^+ independent system L (leucine preferring) and Na^+ dependent system A (alanine preferring), ASC (alanine, serine, cysteine), and N (preferring amino acids with N in the side chains). Each cell type usually expresses a unique complement of amino acid transport systems (1-6).

In humans, nine amino acids are essential as these amino acids are not synthesized in the body. Serine, glycine, and methionine are linked to 1C metabolism in the coupling of folate and methionine. Alterations in the metabolism of these vital amino acids are linked to cancer

and oncogenic transformation. Among which, the necessity of methionine is indispensable not only because it is required for one-carbon unit transportation in 1C metabolism but also acts as a precursor for various metabolic intermediates (including SAM, tetrafolate, cysteine, glutathione, and homocysteine) for several biochemical reactions. The metabolic state of methionine in most tumours is greatly altered which provides a potential opportunity for its biomedical applications. It can be said that methionine is a hallmark of cancer cell metabolism. Hence, methionine is a desirable target for molecular imaging applications.

METHIONINE

Methionine (Met), an essential amino acid containing sulphur, is transported mainly through systems L, A, and ASC. System L has broad substrate specificity and transports large neutral amino acids (LNAA) with linear or branched side chains with high affinity including several essential amino acids and amino acid-related compounds such as L-DOPA, tri-iodothyronine, thyroxine, and certain drugs like melphalan. Two membrane-spanning proteins, LAT1 (high substrate affinity) and LAT2 belonging to system L have been isolated; both requiring an additional membrane-spanning protein identified as the heavy chain of 4F2 surface antigen (4F2hc/ CD98) for their functional expression (7-9).

The 4F2 antigen (CD98) associated with an array of cellular activities, such as cell proliferation, cell transformation, and cell adhesion forms a heterodimeric complex with LAT1/LAT2 via a disulphide bond. LAT1, highly expressed in malignant glioma cells (10-12), is also present in the membranes of brain capillary endothelial cells and mediates the permeation of amino acids through the blood-brain barrier (BBB) (13-14). The second system L isoform, LAT2, is more ubiquitously expressed than LAT1 and transports not only LNAA but also small neutral amino acids (15).

Sodium-dependent transport system A is highly pH sensitive and preferably transports short non-branched side-chain NAA, including alanine, glycine, serine, glutamine, and methionine, into and out of cells. A chief feature of system LAT observed in copious cell types is its positive correlation with the rate of cell proliferation and its capability to undergo adaptive regulation in response to changes in cellular environment, presence of growth factors, hormones, and cellular amino acid availability (16-18)

Radiolabelled L-^{11}C-methionine (L^{11}C MET) was the first radiotracer used in amino acid-based molecular tracing of cancer. Radiolabelled methionine has been widely used in Positron Emission Tomography (PET) imaging of various types of malignancies, thereby providing notions for personalised management of cancer patients. ^{11}C methionine is highly assimilated in the cancer cells due to up-regulated methionine metabolism. It directly correlates amino acid transport, protein biosynthesis, and 1C carbon metabolism. ^{11}C methionine can be easily metabolized by the liver and pancreas without renal excretion and is also rapidly cleared from blood making it a suitable candidate for PET. It has also been observed that ^{11}C methionine is more effective, sensitive, and accurate than other radiolabelled analogues for malignant tumours and metastasis of cancer. Methionine can also be used for detecting brain tumours since it is not physiologically absorbed by the brain.

Another radiolabelled analogue of methionine, ^{99m}Tc methionine is also highly specific and sensitive. It can differentiate between benign and malignant tumours. It has been used to detect axillary lymph node metastasis and internal mammary lymph node metastasis in patients with invasive ductal carcinoma.

METHIONINE METABOLISM

Methionine, an essential sulphur amino acid, is necessary for growth and development. The major metabolic functions of methionine are:

(a) Protein synthesis

(b) Conversion to S-Adenosyl Methionine (SAM), which is required in multiple metabolic pathways: (1) as the predominant biological methyl group donor, (2) a precursor in polyamine synthesis, and (3) as an intermediate in the Trans-sulphuration (TS) pathway leading to cystathionine, cysteine, and further derivatives of cysteine such as glutathione. SAM is the methyl donor in numerous biologically significant Trans-methylation (TM) reactions. S-adenosyl homocysteine (SAH), a product of these reactions, is hydrolysed to yield Homocysteine (HCY), the immediate precursor of methionine. HCY, which does not occur in the normal diet, can be re-methylated (RM) to methionine by accepting a methyl group from 5-methyltetrahydrofolate or betaine. Thus, in normal cells, methionine can be reformed from HCY by two pathways in methionine recycling; one catalysed by Betaine-homocysteine

methyltransferase (BHMT) and the other by methyltetrahydrofolate-vitamin-B12-dependent Methionine Synthetase (MS). Thus, HCY could replace methionine in the presence of vitamin B12 and folic acid or if betaine or its precursor choline were present in the diet (Figure 1). SAM is also utilized as the propylamine donor in the synthesis of spermidine, spermine, and other higher polyamines. Polyamines have multiple functions: as growth factors (19-20), in the stabilization of membranes and sub-cellular particles (21), and stabilization of DNA (22-23). Polyamine synthesis closely parallels RNA and protein synthesis in cell multiplication.

Rapidly growing tissues, both normal and neoplastic, contain high concentrations of polyamines (24-30). Putericine levels and rates of its metabolism in human brain tumours are higher than in normal brains and could be correlated with the degree of malignancy (31-32). The activity of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis, in tumour samples from glioma patients show higher values than in peritumoral non-neoplastic tissue and are correlated with tumour grades (33-34). Methionine also acts as a precursor of cysteine and its derivatives such as glutathione, which plays an important role in maintaining the cellular redox potential. Through trans-sulphuration reactions, HCY is converted to cystathionine and subsequently, to cysteine and glutathione.

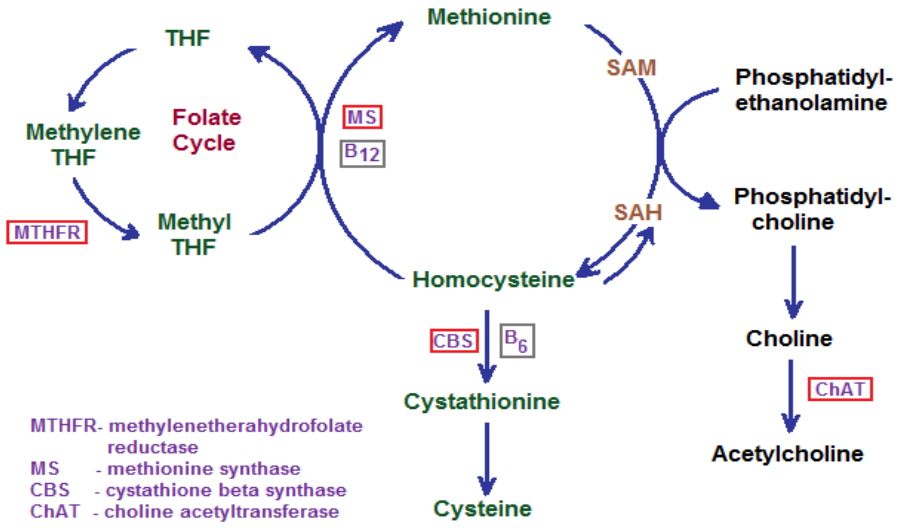

Figure 1: Metabolic pathway of Methionine

ALTERATIONS OF METHIONINE TRANSPORT AND METABOLISM IN CANCER

In cancer cells, there is an intensified demand for methionine (Met) caused by increased flux in the pathways of protein synthesis, trans-methylation, and trans-sulphuration which is reflected by the higher uptake. Metabolic defects in cancer cells are frequently manifested by the inability to grow in a media where Met has been replaced by its precursor HCY. The molecular mechanisms underlying this methionine dependence remain yet to be completely elucidated; however, methionine-dependent cell lines have much higher basal trans-methylation rates than methionine-independent cell lines (35-38). One of the earliest events associated with *in vitro* transformation is the increase in amino acid uptake (39). Facilitated transport of amino acids is known to be enhanced across glioma capillaries, and tumours can induce up-regulation of amino acid transporter expression in their supporting vasculature (40-41).

The role of enhanced expression of transporter systems of neutral amino acids in cancer cells is well known (5). Important differences in the L-system transporters in glioma cells and normal astrocytes have been recently reported (7,10). LAT1, which preferably transports LNAA is strongly expressed in malignant tumours (5,7,8, 10, 42) including glioma (10). In contrast, LAT2 with its associated subunit 4F2hc is expressed in normal astrocytes, shows broader substrate selectivity than LAT1, and transports both large and small neutral amino acids (9,43). Overall rates of trans-methylation are frequently increased in human tumour cells (37,44) leading to excess demand for methionine.

Around 45 years ago, cancer cells synthesized methionine endogenously yet they are insufficient to maintain growth. It was discovered that cancer cells overuse methionine due to an increase in methylation reactions in the cells making cancers selectively addicted to methionine. Cancer cells depend on an exogenous methionine source (Hoffman effect). This alteration in cells is being recognised as a fundamental hallmark of oncogenic transformation. Therefore, cancer cells are sensitive to methionine restriction. As in a study, cancer cells growing on a methionine restriction diet, resulted in selective arrest of cancer growth in late S/G2-phase of the cell cycle. It was due to a decrease in trans-methylation reaction because of lower levels of S-adenosylmethionine which is a derivative of methionine. In another study, infected mice treated with recombinant methionine showed a decrease in their tumour volume.

Methionine dependence of *in vitro* culture (Hoffman effect) has been shown in several human cell lines of different cellular origins (18, 37, 44-46) including gliomas. It may reflect a

general imbalance in trans-methylation resulting in the hypermethylation of some substances and hypomethylation of others within cancer cells. Transfer RNA (tRNA) is the nucleic acid that has the highest percentage of its bases and nucleosides methylated. Altered methylation of tRNA may affect its coding properties (47-49), the ability of tRNA to bind ribosomes (50), and may inhibit the aminoacylation of tRNA. Unfractionated tRNA from human gliomas showed a higher amount of methylated bases and nucleosides compared to normal brains (51). In a study of eight different human ovarian carcinomas, it was found that more rapid metastasizing, poorly differentiated carcinomas had higher tRNA methylase activity than slower metastasizing, well-differentiated, and intermediately differentiated carcinomas (52).

Upregulation of methionine transport in several types of cancer provides biological underpropping of molecular imaging with radiolabelled methionine-based tracers. Radiolabelled methionine can be used to detect recurrent locus-specific cancer, its metastasis, response to therapy, and image-guided treatment modulation.

Till date, the available retrospective analysed data are indicative of the promising useful application of amino acid imaging, particularly in the detection and differential diagnosis of low-grade gliomas, more accurate delineation of tumour extent and integration of the data in treatment planning, and post-treatment detection of tumour recurrence and differentiation from delayed radiation-induced lesions. Therefore, based on the available information more of research should be carried forward to develop improved reliable therapeutic outcomes.

CONCLUSION

A deeper understanding of radiolabelled amino acid analogues in the field of oncology has combined molecular imaging, precision medicine, and targeted therapy. The link between cancer cells and altered amino acid metabolism provided the basis for the discovery of amino acids as radiolabelled analogues. Amino acids accumulate in rapidly dividing cancer cells which results in increased amino acid transportation. The use of methionine radiolabelled amino acids in positron emission tomography has enabled clinicians to visualize tumours with great accuracy. Apart from diagnostics, methionine radiolabelled amino acids can also be used for targeted therapeutics. The same transport mechanisms used by the cancer cells can be used to deliver localized radiation therapy. This will greatly reduce the damage caused by the radiation therapy to other healthy tissues of the body. These radiolabelled analogues can serve as major tools in precision medicine. The ability to characterize the metabolic

profile of malignancy through imaging allows an in-depth understanding of cancer heterogeneity, thereby paving the way for effective and targeted therapies. As with any medical discovery, the journey is not without challenges. Standardization of imaging protocols, regulatory approvals, and addressing the economic viability of these techniques are some of the current challenges. Combined efforts of researchers, clinicians, and the government bodies are essential to navigate these challenges and incorporate radiolabelled amino acid analogues into routine clinical practice.

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