MINI REVIEW

Epigenetics and the toxicity of one-carbon metabolism

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Scarlett T. Albert J. Epigenetics and the toxicity of one-carbon metabolism. J Genet Disord Genet Med. 2022; 6(2)5-7.

ABSTRACT

One-carbon metabolism is a major metabolic hub that produces one-carbon units for important biosynthetic events as well as for the creation of epigenetic marks. The one-carbon carrier tetrahydrofolate (THF) plays the primary role in this hub, accepting formaldehyde generally from serine and creating one-carbon THF intermediates in a series of events known as the folate or one-carbon cycle. THF derivatives can provide one-carbon units for purine and thymidine synthesis, as well as the methionine cycle, which yields the universal methyl donor S-adenosylmethionine. AdoMet provides methyl groups for epigenetic methylation and is converted to Homocysteine (Hcy), which can enter the transsulfuration route to produce cysteine and, finally, glutathione (GSH), the primary cellular antioxidant. THF's critical function comes at a cost. THF and other folate derivatives are prone to oxidative breakdown, which results in the release of formaldehyde, which can damage DNA - a consequence avoided by the Fanconi Anaemia DNA repair process. Epigenetic demethylations catalyzed by lysine-specific demethylases (LSD) and Jumonji histone demethylases can potentially result in the release of formaldehyde, posing a risk to genome integrity. The toxicity of formaldehyde in animals is restricted by a metabolic pathway centered on the enzyme alcohol dehydrogenase 5 (ADH5/GSNOR), which oxidizes formaldehyde conjugated to GSH, eventually producing format. Surprisingly, this format can be a substantial source of one-carbon units, establishing a formaldehyde cycle that may limit the toxicity of one-carbon metabolism and epigenetic demethylations. This paper highlights current breakthroughs in one-carbon metabolism and epigenetics, with an emphasis on the stages that include formaldehyde flow and may result in cytotoxicity affecting human health.

Key Words: *Mitochondrial formate; Epigenetics; Genetics; Degradation*

INTRODUCTION

Folates (Vitamin B9) are often present in foods in a variety of forms, the majority of which are conjugated to a polyglutam-ate chain, which impacts their bio availability. Some cases of megaloblastic anemia are caused by folate-deficient diets, which also increase the risk of Neural Tube Abnormalities (NTDs) in neonates. In certain countries, foods are supplemented with synthetic folic acid to avoid folate deficiency. This oxidized folate form is more stable and inactive than natural folates. In cells, Dihydrofolate Reductase (DHFR) converts folic acid to Dihydrofolate (DHF), which is then polyglutamated by the enzyme Folyl-Polyglutamate Synthetize (FPGS). This phase is critical for retaining intracellular THF and increasing THF activity when it enters the one-carbon cycle. Some enzymes, such as serine hydroxyl methyltransferases and the Glycine Cleavage System (GCS), transfer formaldehyde from serine to THF, resulting in the formation of the critical intermediate 5, 10-methylene-tetrahydrofolate (5,10-CH2-THF). This intermediate, like DHF and THF, is intrinsically unstable and can undergo oxidative breakdown between the C-9 and N-10 bonds, yielding three products: Pteridine, p-Amino Benzoyl Glutamate (pABG), and formaldehyde. As a result, the movement of one-carbon units throughout the cell suggests the mobility of reactive formaldehyde, which poses a severe hazard to cell function). The release of reactive formaldehyde can result in genotoxicity, the generation of Reactive Oxygen Species (ROS), and proteotoxic stress, among other things. Furthermore, it has been claimed that the breakdown of THF derivatives into formaldehyde alters the availability of one-carbon units for critical biosynthetic reactions,

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Received: 1-Feb-2022, Manuscript No. puljgdgm-4628; Editor assigned: 3-Feb -2022,PreQC No. puljgdgm-4628(PQ); Reviewed: 17-Feb-2022, QC No. puljgdgm--4628(Q); Revised: 19-Feb-2022, Manuscript No. puljgdgm-4628(R); Published: 26-Feb-2022, DOI:10.37532/Puljgdgm22.6(2).5-7.

resulting in a nucleotide imbalance that causes replication stress and DNA damage [1-4].

One-carbon cycle

The term "one-carbon metabolism" encompasses not only the one-carbon cycle, but also the methionine cycle, the transsulfuration route, and the recently identified formaldehyde cycle. THF acts as the minute hand of a clock in the one-carbon cycle, supplying methyl groups to various cellular compartments and metabolic activities. This cycle is divided into mitochondria, cytosol, and, during S-phase, the nucleus. The hydroxyl methylation of THF from serine, catalyzed by the enzyme Serine-Hydroxyl Methyl Transferase 2 (SHMT2), initiates the mitochondrial one-carbon cycle branch. Glycine can also provide a one-carbon unit to THF in this organelle via the GCS system. In addition, choline metabolism creates Dimethylglycine (DMG) and sarcosine, which can transfer formaldehyde units to THF, giving 5,10-CH2-THF in processes catalyzed by the DMG and sarcosine dehydrogenases, respectively .5,10-CH2-THF can be utilized to methylate tRNA, which is essential for mitochondrial mRNA translation. This THF product may also feed mitochondrial Thymidylate Synthase (TYMS) to produce thymidylate de novo[5].

In addition, mitochondrial 5, 10-CH2-THF is oxidized by the bifunctional NAD(P)-dependent enzyme methylene-THF dehydrogenase 2 (MTHFD2) or 2 like (MTHFD2L), resulting in 10-formyl-THF (10-CHO-THF). This molecule is a one-carbon unit donor in the synthesis of N-formyl methionine (fMet) for mitochondrial protein synthesis initiation, as well as a substrate for methylene-THF dehydrogenase 1 like (MTHFD1L), which produces formate and THF. In addition, choline metabolism produces dimethylglycine (DMG) and sarcosine, which can transfer formaldehyde units to THF, giving 5,10-CH2-THF in processes catalyzed by the DMG and sarcosine.

Although the identity of the transporter engaged in this process is unknown, mitochondrial formate can translocate to the cytosol.

The format can re-enter the one-carbon cycle in the cytosol via the reversible trifunctional NADP-dependent Methylene-Tetrahydrofolate Dehydrogenase 1 (MTHFD1), resulting in 10-CHO-THF. The high NAPDH/NADP ratio may favor this reductive path from formate and THF, yielding the first 10-CHO-THF and subsequently 5,10-CH2-THF [6].

Overflow of mitochondrial formate also favors the reductive direction of the cytosolic one-carbon cycle branch in cancer cells. This intermediate serves as a one-carbon donor for the production of the important amino acid residue methionine from Homo Cysteine (Hcy), the first step in the methionine cycle catalyzed by the enzyme methionine synthase (MS). The nucleus is also a recognized spot where the one-carbon cycle occurs during S-phase. There, 5, 10-CH2-THF plays a key role in promoting the synthesis of dTMP and the generation of DHF via the enzyme TYMS. Nuclear DHFR can use NADPH as a cofactor to convert DHF to THF. The enzyme MTHFD1 catalysis the production of 10-CHO-THF from THF and formate, followed by the reduction of this intermediate to 5,10-CH2-THF in the nucleus[7,8].

OXIDATIVE THF BREAKDOWN

In addition to the conventional formaldehyde transit from the one-carbon cycle to epigenetic methylations, THF and other THF derivatives can undergo spontaneous oxidative breakdown, releasing formaldehyde. The THF backbone is composed of a pteridine unit and a pABG moiety connected by a methylene group, which is the source of free formaldehyde during THF breakdown (solid red line in THF structure, It is currently unknown how much cellular THF undergoes oxidative breakdown. However, it is expected that a large portion of cellular THF will disintegrate. Recent findings show that pABG from THF and DHF accumulates in the absence of the mitochondrial one-carbon branch or when DHFR is inhibited by exposing cancer cells to the antifolate chemotherapeutic agent methotrexate. THF degradation can be avoided, at least in part, by the enzyme Quinoid Dihydropteridine Reductase (QDPR), which is involved in tetrahydrobiopterin metabolism and has been identified as a metabolite mending enzyme. In the presence of oxidants such as H2O2 or by raising the temperature, the breakdown of THF, DHF, and 5,10-CH2-THF is accelerated in vitro. Cellular H2O2 is mostly produced in peroxisomes. It can also be produced by oxidative protein refolding in the endoplasmic reticulum - a reaction catalyzed by Protein Di sulphide Isomerases (PDI) that are re-oxidized by ERO1-alpha, generating H2O2, FAD-dependent demethylations, and ROS generated in the mitochondrial Electron Chain (ETC). As a result, cells must maintain cellular redox homeostasis not just to prevent general oxidative damage, but also to limit the oxidative breakdown of THF derivatives, which would otherwise disrupt critical biosynthetic processes and lead to hazardous formaldehyde buildup.

The formaldehyde cycle and human health: The excess formaldehyde produced by THF breakdown can represent a substantial hazard to cells. Formaldehyde is a well-known genotoxin that is designated as a human carcinogen by the World Health Organization (WHO) and is produced through methanol metabolism, methylamine, and various cellular demethylations, reaching blood concentrations close to 50 M This aldehyde has been linked to a variety of DNA lesions, including base damage, DNA-protein, DNA-interstrand, and DNA-intrastrand crosslinks Formaldehyde has also been shown to degrade proteins, inducing proteotoxic stress and activating Heat Shock Transcription Factor 1. (HSF1) Formaldehyde's high electrophilicity renders it exceedingly reactive against electron-rich moieties, particularly those containing thiol groups, such as GSH and free cysteine, and also probable against thiol-rich proteins such as thioredoxins. Indeed, formaldehyde interacts quickly with GSH to create S-hydroxymethyl-GSH (HSMGSH). This spontaneous reaction inhibits GSH's redox-active thiol group, limiting its antioxidant activity and inducing ROS buildup Cells developed the alcohol dehydrogenase 5 (ADH5/GSNOR) enzymes to metabolize HSMGSH, restoring redox-active GSH and finally producing formate. This formate, which is produced by ADH5, may be integrated into purines and thymine, providing still another relevant supply of one-carbon units and defining a formaldehyde cycle that turns a toxin into a one-carbon source for anabolic reactions. The formaldehyde cycle not only generates one-carbon units for anabolic processes but also keeps the endogenous formaldehyde level from increasing. Indeed, animals missing ADH5 were shown to accumulate N2-hydroxymethyl-deoxyguanine as a result of the interaction between formaldehyde and deoxy guanine on DNA. DNA crosslink repair becomes critical in these animals and the combined silencing of the Fanconi Anaemia DNA Repair pathway and ADH5 causes bone marrow failure (BMF), liver and renal dysfunction, and leukemia [9,10].

In addition, formaldehyde has been postulated to be the cause of mortality, progeria, and hepatocellular cancer in people with Ruijs-Aalfs syndrome, a hereditary disorder caused by mutations in the gene coding for the DNA dependent protease Spartan (DVC1).

CONCLUSIONS AND PERSPECTIVES

THF, a folate derivative, plays an important function in one-carbon metabolism by absorbing a formaldehyde molecule from multiple donors and distributing it to important biosynthetic activities such as purine and pyrimidine synthesis, as well as to AdoMet for methylations and epigenetic mark writing. THF metabolic

dysregulation can cause considerable cellular damage by modifying those synthetic processes, as has been shown for CpG methylations in settings of dietary folate shortage. Formaldehyde is produced during epigenetic demethylation events involving LSD, Jumonji, and Alk demethylases, posing serious harm to the DNA. To avoid formaldehyde-caused damage, a two-tier control mechanism is in place. Endogenous formaldehyde is converted into formate in one tier, lowering its free concentration. The Fanconi Anaemia DNA repair pathway, which repairs DNA damage caused by formaldehyde, makes up the second layer. THF, DHF, and 5,10-CH2-THF have also been found to be hazardous to cancer and hemopoietic cells missing the formaldehyde catabolic enzyme ADH5.

THF-induced cytotoxicity has been explained by two ideas. On the one hand, oxidative breakdown of THF might result in the formation of formaldehyde, which has been demonstrated to harm ADH5-deficient cells. The underlying cause of this toxicity might be a combination of high ROS caused by a GSH redox homeostasis imbalance and DNA damage, which would result in cell death. THF toxicity is explained by the second theory, which argues that THF condenses with endogenous formaldehyde, raising the amount of 5,10-CH2-THF, which may lead to TYMS hyper activation, nucleotide imbalance, and DNA replication stress Independent of the underlying mechanism, the enhanced toxicity of THF in ADH5-lacking cells might be employed as a therapeutic intervention in cancer by combining THF with the ADH5 inhibitor N6022, particularly in cancer cells that are sensitive to THF. Surprisingly, organisms lacking one-carbon cycle enzymes can nevertheless live by eating formate produced from endogenous formaldehyde through ADH5. This survival strategy may be significant in cancer cells that develop resistance to anti-folates such as methotrexate, a chemotherapy medication that inhibits the one-carbon cycle by inhibiting DHFR.

As a result, the combination of anti-folates and N6022 may aid in the treatment of chemotherapy resistance in cancer cells.

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