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Formaldehyde metabolism and its impact on human health

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Abstract

Human health is threatened by exposure to reactive toxins that can damage fundamental biomolecules such as DNA and proteins. One of these molecules is formaldehyde, the simplest and one of the most reactive aldehydes. Formaldehyde is ubiquitous in the environment, and can be derived from some food components. However, a great burden of formaldehyde is also generated endogenously as a result of cellular metabolism. In fact, recent work has shown that endogenous formaldehyde is produced at sufficient levels to pose a significant threat to genome stability. To counteract this reactive molecule, organisms have evolved a detoxification system centered on the enzyme alcohol dehydrogenase 5 (ADH5). This system converts formaldehyde to formate, a less reactive molecule that can be used for nucleotide biosynthesis. The Fanconi Anemia (FA) DNA repair pathway guarantees additional protection against formaldehyde by alleviating DNA damage. Indeed, the simultaneous inactivation of both ADH5 and the FA DNA repair pathway in mice leads to dysfunction of vital organs and cancer. These findings suggest that formaldehyde might be a driver of the human disease FA. Additional work also links this genotoxin to the etiology of other human illnesses, such as the Ruijs-Aalfs syndrome and the cancer predisposition of BRCA2 mutation carriers. This review discusses the recent advances in formaldehyde biology and the impact of this toxic metabolite on human health.

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Formaldehyde, ADH5, FANCD2, Fanconi Anemia, SPRTN, BRCA1, BRCA2, Folate cycle, Ruijs-Aalfs syndrome.

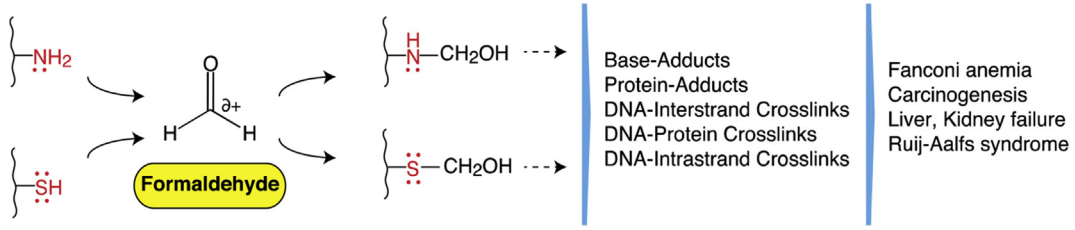
1. Introduction

Formaldehyde has been extensively used as a tissue fixative and exploited to study DNA-protein interactions. The strong reactivity of this molecule lies on the electrophilic carbon, which can rapidly attack electron-rich thiol and amino groups forming covalent adducts. The reaction of formaldehyde with these nucleophilic groups present in nucleic acids and proteins can cause several lesions such as base and protein adducts, DNA-interstrand crosslinks (ICLs) and DNA-protein crosslinks (DPCs) (Fig. 1) [1]. ICLs and DPCs can block both the transcription and replication machineries leading to mutagenesis and cell death [2,3].

Formaldehyde is an environmental toxin that has been classified as a known carcinogen (group 1) to human and animals by the International Agency for Research on Cancer (IARC). This classification is based on the observation that formaldehyde inhalation can cause nasopharyngeal cancer in humans and squamous cell carcinomas in the nasal passages of rats [4]. While environmental exposure to formaldehyde is a well-established risk to human health, recent reports indicate that endogenously produced formaldehyde also poses a significant threat [5–7]. Endogenous formaldehyde is generated by various sources. Some of these sources are essential metabolic processes, such as folate metabolism [8]. Histone, DNA and RNA demethylation reactions can also contribute to endogenous formaldehyde [9,10]. The level of endogenous formaldehyde in blood is remarkably high for such a reactive molecule (10–100 μM, Table 1) [11–16], and therefore organisms have evolved mechanisms to counteract this genotoxic metabolite.

Protection against formaldehyde mainly involves two systems: formaldehyde detoxification (ADH5) and DNA-crosslink repair [5]. When these two systems are simultaneously inactivated in mice, endogenous formaldehyde causes widespread DNA damage leading to bone marrow failure, liver and kidney dysfunction, and cancer – liver cancer and leukemia [5]. These findings indicate that endogenous formaldehyde is genotoxic, cytotoxic and carcinogenic in mammals. In addition to the deleterious effects caused by this simple aldehyde, endogenous formaldehyde can also support essential metabolism. Recent work has shown that formaldehyde can play a significant role in nucleotide biosynthesis [8]. These discoveries change our view of formaldehyde as a mere toxic compound, and highlight the importance of maintaining cellular formaldehyde homeostasis not only to prevent genotoxicity but also to promote cell growth.

Fig. 1



Formaldehyde reaction with thiol and amino groups. The carbon present in the carbonyl group has a positive charge density that avidly reacts with electron-rich groups (shown in red). The formaldehyde-adducts formed can suffer further reactions generating lesions to biomolecules such as the ones enumerated in the figure. Those formaldehyde-lesions may drive some of the diseases described in the right side.

2. Formaldehyde sources

2.1. Exogenous sources

2.1.1. Environment

The human body can be exposed to formaldehyde by direct inhalation or ingestion of formaldehyde-containing products or molecules that can be metabolized into formaldehyde. Industrial pollution, biomass combustion, car fumes, household products, cosmetics, preservatives used in laboratories and hospitals, and smoking are likely the main sources of formaldehyde in the environment [17]. The World Health Organization (WHO) has largely documented this issue, establishing an indoor guideline of 0.1 mg/m^3 for a 30-min formaldehyde exposure [18]. Smoking can generate up to 150 μg of formaldehyde-releasing compounds per cigarette, and the indoor concentration can reach more than 0.2 mg/m^3 in a room where somebody is smoking. E-cigarettes might release substantial quantities of formaldehyde when used on a high vaping power [19]. Despite the potential risk, exogenous formaldehyde-induced DNA adducts are not detected beyond the respiratory epithelium [20]. Therefore, the consequences of formaldehyde inhalation are likely to be limited to local effects.

Table 1 Formaldehyde in blood.

Organism	Blood formaldehyde	Method	Reference
Human	~87 μM	Pentafluorophenylhydrazine derivatization	[16]
Rat	~75 μM	Pentafluorophenylhydrazine derivatization	[16]
Human	~15 μM	Dimedone derivatization	[13]
Monkey	~62 μM	Pentafluorophenylhydrazine derivatization	[11]
Human	~10 μM	Diethoxymethane quantitation	[15]
Human	~45 μM	Ampicillin derivatization	[12]
Rat	~77 μM	Dinitrophenylhydrazine derivatization	[14]

2.1.2. Diet

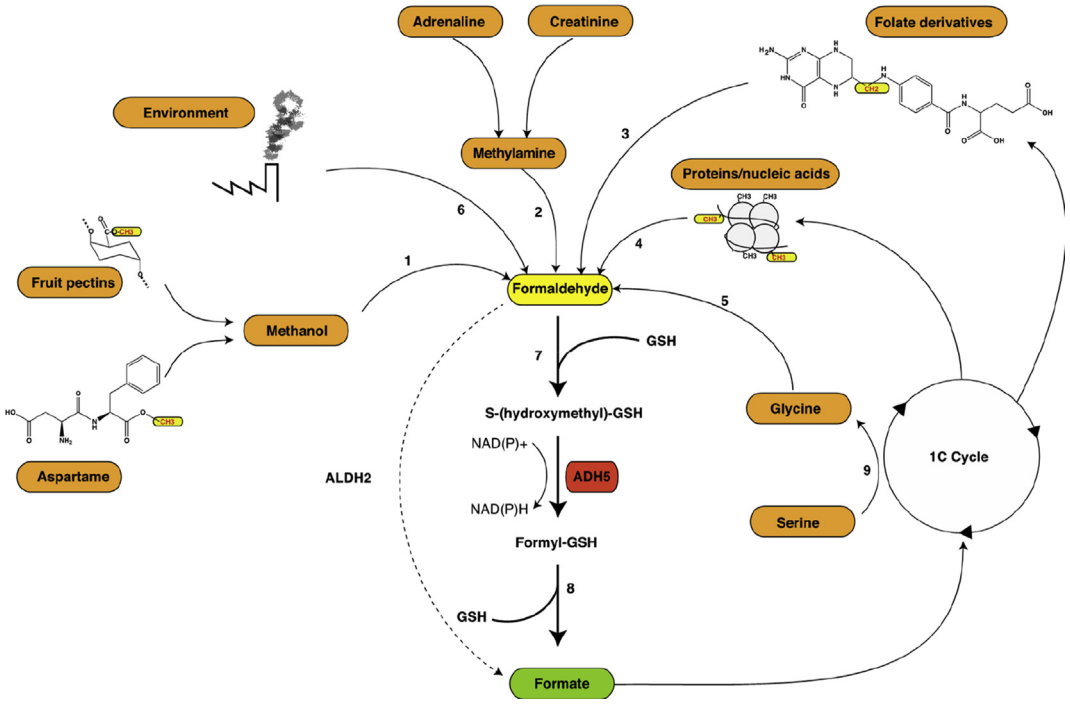
The diet can be a significant source of formaldehyde. It can be present in foods and also produced by cooking fat-containing products [17]. Methanol, the simplest alcohol, is generated by gut bacteria from methyl-esters present in fruit and vegetable pectins [21]. This alcohol is rapidly absorbed in the body and metabolized into formaldehyde (Fig. 2) [17]. Several xenobiotics and chemical compounds are also absorbed in the gastrointestinal tract and metabolized into methanol and/or formaldehyde. For instance, the sweetener aspartame is cleaved to aspartate, phenylalanine and methanol in the small intestine. When rats were given [^{14}C]-aspartame, where the carbon atom that gives rise to methanol is labeled, the radioactivity could be traced to DNA, RNA and proteins [22]. Although the latter study might question the safeness of diet sodas, the amount of aspartame used in those experiments was four times higher than the acceptable daily intake of 50 milligrams per kilogram (mg/kg) of body weight (Food and Drug Administration guideline).

2.2. Endogenous sources

2.2.1. Folate-derivatives breakdown

Whereas the diet may contribute to blood-circulating formaldehyde, it is still possible that cellular metabolism generates a significant amount of this toxic metabolite. In cells, formaldehyde might originate as an intermediate in the one-carbon (1C) cycle after enzymatic cleavage of serine to generate glycine. This formaldehyde molecule is however quickly condensed with tetrahydrofolate (THF) -the active form of the cofactor folate (vitamin B9), to generate 5,10-methylene-THF. This can subsequently be converted to other forms of folate to deliver 1C units to several biosynthetic pathways and methylation reactions [23]. Alternative, 5,10-methylene-THF might dissociate spontaneously, thereby releasing formaldehyde and THF. However, it is unclear whether this dissociation occurs *in vivo* [8]. It was recently reported that the oxidative decomposition of certain folate derivatives can be a metabolic source of formaldehyde (Fig. 2) [8]. In an

Fig. 2



Formaldehyde metabolism. The scheme represents the main formaldehyde sources and catabolic reactions discussed in the text. ADH5 is depicted in a red box. Formaldehyde and methyl-groups that give rise to formaldehyde are shown in yellow boxes. 1: Alcohol dehydrogenase 1 (ADH1) and Catalase. 2: Semicarbazide-sensitive amine oxidase. 3: Oxidative breakdown. 4: Protein and nucleic acid demethylases (Jumonji, LSD1 and AlkB family). 5: Myeloperoxidase. 6: Direct assimilation/cytochrome P450. 7: Spontaneous reaction. 8: S-formylglutathione hydrolase. 9: Serine hydroxymethyltransferase 1 and 2. GSH: Reduced glutathione.

oxidative environment, the folate backbone spontaneously degrades into two main components, a pterine moiety and p-aminobenzoylglutamate (pABG), while the methylene bridge that connects these two units is released as formaldehyde. Consequently, certain folate-derivatives are genotoxic to cells that cannot counteract formaldehyde such as those deficient in *Adh5* or in the FA DNA repair pathway [8].

2.2.2. Protein and nucleic acid demethylations

Histone demethylation could be another source of endogenous formaldehyde. Two well-characterized families of histone demethylases can generate formaldehyde. The first family consists of the FAD-dependent amine-oxidase LSD1 (also known as KDM1A) and catalyzes the demethylation of lysine 4 residues in the histone H3 (H3K4me1/2), releasing formaldehyde [24]. The second family consists of a mechanistically different class of histone demethylases: the Jumonji-C/JmjC family. These proteins work through a Fe(II)/2-oxoglutarate (2-OG) mechanism. An oxygen atom is inserted into a C—H substrate forming an unstable intermediate that degrades, thereby releasing formaldehyde [10].

In addition to histone demethylases, the ALKB family of Fe(II)/2-OG-dependent oxygenases can release, among others, formaldehyde from methylated nucleic acid substrates [9]. AlkB was initially characterized in bacteria as a 1-methyladenine (1-meA) and 3-methylcytosine (3-meC) demethylase [25]. Subsequently, nine different ALKB-like enzymes were identified in mammals (ALKBH1-8 and FTO (fat and obesity associated protein)) [9]. For some of these proteins, the methylated substrates have been characterized and indeed, they release formaldehyde as well (recently discussed by Fedeles BI et al.) [9]. It remains to be investigated whether formaldehyde produced *in vivo* by histone demethylation could damage proteins and/or nucleic acids.

2.2.3. Other metabolic sources

In addition to protein and nucleic acid demethylation reactions, endogenous formaldehyde may be also generated by other metabolic reactions (Fig. 2). For instance, the metabolism of creatinine or the hormone adrenaline produces methylamine. This molecule can be deaminated to release formaldehyde by the enzyme semicarbazide-sensitive amine oxidase (SSAO) [26,27].

Inflammation might be another physiological condition associated to the generation of endogenous formaldehyde. Activated neutrophils and monocytes release the enzyme myeloperoxidase (MPO), which is able to generate formaldehyde from glycine [28]. The mitochondrial enzymes dimethylglycine dehydrogenase (DMGDH) and sarcosine dehydrogenase also generate formaldehyde from their respective substrates [29], which is quickly condensed with THF to enter the 1C cycle. Furthermore, N-demethylation of methylamines and xenobiotics by the cytochrome P450 yields formaldehyde [30]. The fate and physiological relevance of these formaldehyde molecules remain to be studied.

3. ADH5, a central player in formaldehyde biology

3.1. The role of ADH5 in formaldehyde catabolism

Formaldehyde catabolism initiates with the spontaneous reaction between the aldehyde and glutathione to form *S*-hydroxymethylglutathione (HMGSH). The enzyme ADH5 oxidizes HMGSH to *S*-formylglutathione (FGSH) using $NAD(P)^+$ as a cofactor [31]. FGSH is further metabolized by S-formylglutathione hydrolase (FGH) yielding formate and regenerating reduced glutathione [32]. Deletion of *Adh5* in mice leads to increased levels of formaldehyde-induced DNA adducts in the liver, kidney and bone marrow [5]. Additionally, *Adh5*-deficient mice as well as *Adh5*-knockout cell lines are highly sensitive to formaldehyde, overall indicating a central role of ADH5 in formaldehyde metabolism [5,6,33]. In addition to ADH5, formaldehyde can also be catabolized by the enzyme aldehyde dehydrogenase 2 (ALDH2) [34], although the physiological relevance of ALDH2 in formaldehyde biology is less understood (Fig. 2).

3.2. The formaldehyde cycle

Remarkably, ADH5 not only prevents formaldehyde toxicity but also supports essential metabolism by providing 1C units for nucleotide biosynthesis [8]. 1C units are produced primarily by the enzymatic cleavage of serine, which generates glycine and formaldehyde; this formaldehyde rapidly reacts with tetrahydrofolate (THF) entering the 1C cycle. Formate is also an intermediary that can be incorporated into THF, feeding the 1C cycle [23]. Consequently, human cells deficient in serine catabolism have a severe growth defect in the absence of the nucleotide precursors hypoxanthine and thymidine (HT) and formate. Growth is further impaired in the *ADH5*-deficient background, suggesting that conversion of endogenous formaldehyde into formate provides 1C units for nucleotide synthesis. Moreover, cells with defective serine catabolism can obtain 1C units from exogenous formaldehyde, which completely depends on ADH5, or formate and incorporate these units into nucleotides [8]. Therefore, the recycling of endogenous formaldehyde into 1C units defines a formaldehyde cycle that fuels biosynthetic reactions through ADH5.

3.3. ADH5 and nitric oxide

In addition to its function in formaldehyde detoxification, ADH5 reduces S-nitrosoglutathione (GSNO), which is formed upon the reaction of nitric oxide with glutathione [31]. Nitric oxide is a reactive molecule that nitrosylates proteins and causes DNA damage [35]. It is also an essential signaling molecule in several physiological processes such as generation of cyclic GMP and activation of certain kinases by posttranslational modifications [36]. Liu and colleagues reported that *Adh5*-deficient mice present higher mortality in inflammatory conditions such as an endotoxic shock with bacterial lipopolysaccharide (LPS) or pulmonary infection by *Klebsiella pneumoniae*, as well as elevated hepatocellular carcinoma predisposition, due to a substantial dysregulation of S-nitrosylation [37,38]. It is still unknown how formaldehyde detoxification and GSNO reduction by ADH5 are coordinated *in vivo*.

4. Formaldehyde and human health

4.1. Fanconi Anemia (FA)

Formaldehyde is a source of cellular damage posing a threat to human health. In fact, genetic defects in several DNA repair mechanisms reduce cellular tolerance to formaldehyde. For instance, vertebrate cells deficient in the FA DNA repair pathway are exquisitely sensitive to formaldehyde [5,6]. The FA DNA repair pathway has been characterized as a complex machinery dedicated to repair ICLs [2]. Mutations in genes coding for the FA DNA repair pathway lead to the genetic disease FA, a human disorder characterized by the development of bone marrow failure, congenital malformations, sterility, and predisposition to develop certain types of cancer [39].

The endogenous source of DNA damage in FA patients is still controversial. However, over the last years, strong genetic evidence has emerged supporting endogenous aldehydes as a source of DNA damage in FA [5,40,41]. The inactivation of the FA DNA repair pathway in chicken-lymphoma B cells deficient in *ADH5* causes cell death [6]. Furthermore, mice deficient in both formaldehyde detoxification (*Adh5*) and the FA DNA repair pathway (*Fancd2*) recapitulate the main aspects of the human disease. These double-knockout animals (*Adh5* -/- *Fancd2* -/-) lack hematopoietic stem cells and develop severe bone marrow failure, liver and kidney dysfunction, dying soon after birth. Bone marrow transplantation using cells from a wild type donor restores the hematopoietic function. However, transplanted mice succumb to cancer, mainly liver cancer

and acute T-lymphoblastic leukemia, which originates from remaining *Adh5* -/- *Fancd2* -/- double-knockout hematopoietic cells [5]. Liver and kidney dysfunction are not features of FA but they are observed in other DNA crosslink repair deficiencies in humans [42]. Therefore, the phenotypes observed in *Adh5* -/- *Fancd2* -/- mice suggest that endogenous formaldehyde might be one of the drivers of not only FA but also of other DNA repair disorders.

4.2. Ruijs-Aalfs syndrome

It is also well established that formaldehyde can cause DNA-protein crosslinks (DPCs). Several pathways carry out DPC repair, a field that has already been extensively revised [3]. However, it is worth mentioning the recent finding of the involvement of the yeast DNA-dependent protease Wss1 and its mammalian orthologue SPRTN (also called DVC1) in DPC repair [43]. Deleting *SPRTN* in mammalian cells results in lethality, whereas *SPRTN*-knockdown cells are viable and show high sensitivity to formaldehyde as well as to other DPCs-inducing agents [44]. In humans, mutations in *SPRTN* lead to the Ruijs-Aalfs syndrome, which is characterized by progeria, hepatocellular carcinoma and genome instability [45]. SPRTN has been shown to participate in the repair of naturally occurring Top1-DPCs [46]. However, it remains to be established to what extent DPCs generated *in vivo* by endogenous formaldehyde are repaired by SPRTN. Inactivation of *Adh5* in *Sprtn*-hypomorphic mice could help to understand the physiological role of this protease in the repair of DPCs generated by endogenous formaldehyde, and therefore elucidate the impact of this genotoxic metabolite on the Ruijs-Aalfs syndrome.

4.3. Carcinogenesis

Endogenous formaldehyde is a carcinogen to animals deficient in formaldehyde detoxification and DNA crosslink repair. In addition, exogenous formaldehyde has also been catalogued as a carcinogen to humans by the IARC. In fact, formaldehyde exposure can activate the DNA-damage response kinase ATM and the tumor suppressor P53 in human cells [47]. In addition to direct DNA damage, it has recently been reported that formaldehyde promotes BRCA2 degradation [48]. BRCA2 (a.k.a FANCD1) is a tumor suppressor involved in DNA repair by error-free homologous recombination [49]. The reduction in BRCA2 levels is particularly threatening for individuals carrying heterozygous *BRCA2* mutations and might lead to carcinogenesis. Cells harboring heterozygous truncating-BRCA2 mutations show reduced expression of wild type BRCA2. In these cells, formaldehyde exposure induces BRCA2 haploinsufficiency causing genome instability. BRCA2 depletion can be reverted by blocking the proteasome, but the molecular aspects underlying BRCA2 degradation are still not well understood [48].

5. Conclusions

Several genetic disorders have been associated to failures in the repair of lesions that can be caused by formaldehyde. Thus, manipulating endogenous formaldehyde metabolism could lead to alternative treatments of those human conditions. For instance, metformin appears to be a promising drug for treatment of FA, likely because of its capability to quench formaldehyde [50]. On the other hand, increasing the concentration of cellular formaldehyde might be considered as a therapeutic approach to inhibit cancer growth. Cancer cells deficient in homologous recombination-dependent DNA repair (*BRCA1* and *BRCA2*) are highly sensitive to formaldehyde [8]. Therefore, it is possible that *BRCA1*- and *BRCA2*-deficient tumors are hypersensitive to ADH5-specific inhibitors such as N6022. ADH5 inhibition would increase the endogenous formaldehyde level, selectively killing the cancer cells. A similar approach has been successfully tested by treating *BRCA1*- and *BRCA2*-deficient cells with Disulfiram, which inhibits acetaldehyde detoxification [49]. Disulfiram selectively kills *BRCA1*- and *BRCA2*-deficient cells, likely because of a burden of toxic endogenous acetaldehyde. The combination of N6022 and Disulfiram might be more effective against BRCA-deficient tumors. In conclusion, formaldehyde metabolism emerges as a novel therapeutic target for the treatment of DNA-repair deficient tumors and certain genetic diseases.

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Conflict of interest

The authors declare no conflict of interest.

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Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

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