Chapter 10
ALDH1L1 and ALDH1L2 Folate Regulatory Enzymes in Cancer

Sergey A. Krupenko and Natalia I. Krupenko

Abstract Epidemiological studies implicate excess ethanol ingestion as a risk factor for several cancers and support the concept of a synergistic effect of chronic alcohol consumption and folate deficiency on carcinogenesis. Alcohol consumption affects folate-related genes and enzymes including two major folate-metabolizing enzymes, ALDH1L1 and ALDH1L2. ALDH1L1 (cytosolic 10-formyltetrahydrofolate dehydrogenase) is a regulatory enzyme in folate metabolism that controls the overall flux of one-carbon groups in folate-dependent biosynthetic pathways. It is strongly and ubiquitously down-regulated in malignant tumors via promoter methylation, and recent studies underscored this enzyme as a candidate tumor suppressor and potential marker of aggressive cancers. A related enzyme, ALDH1L2, is the mitochondrial homolog of ALDH1L1 encoded by a separate gene. In contrast to its cytosolic counterpart, ALDH1L2 is expressed in malignant tumors and cancer cell lines and was implicated in metastasis regulation. This review discusses the link between folate and cancer, modifying effects of alcohol consumption on folate-associated carcinogenesis, and putative roles of ALDH1L1 and ALDH1L2 in this process.

Keywords Folate · Cancer · Alcohol · ALDH1L1 · ALDH1L2 · Methylation · SNPs · Tumor suppressor

10.1 Introduction

Epidemiological studies implicate excess ethanol ingestion as a risk factor for several cancers and support the concept of a synergistic effect of chronic alcohol consumption and folate deficiency on carcinogenesis [1]. Alcohol consumption

S. A. Krupenko (✉) · N. I. Krupenko
Department of Nutrition, University of North Carolina, Chapel Hill, NC, USA

UNC Nutrition Research Institute, Chapel Hill, NC, USA
e-mail: sergey_krupenko@unc.edu

V. Vasiliou et al. (eds.), *Alcohol and Cancer*, Advances in Experimental Medicine and Biology 1032, https://doi.org/10.1007/978-3-319-98788-0_10

itself impairs folate metabolism through the enhanced coenzyme degradation or the inhibition of absorption, as well as through the influence on folate-related genes and enzymes [1, 2]. Among these targets, two major folate-metabolizing enzymes, ALDH1L1 and ALDH1L2, were considered. This review discusses the link between folate and cancer, modifying effects of alcohol consumption on folate-associated carcinogenesis, and putative role of ALDH1L1 and ALDH1L2 in this process.

10.2 Folate: Overview

Folate coenzymes are vital for cellular homeostasis due to their key role in transferring one-carbon groups in reactions of *de novo* nucleotide biosynthesis, metabolism of serine, glycine and histidine, and the regeneration of methionine from homocysteine [3]. The methionine biosynthesis is linked to the production of S-adenosylmethionine, a universal methyl donor in more than a hundred methylation reactions in the cell [4]. Folates also participate in the clearance of formate as CO_2 [5] and the formylation of methionyl-tRNA [3]; the latter process is essential for translation initiation in eukaryotic mitochondria [6]. Humans are unable to synthesize this coenzyme and must obtain it from the diet. Insufficient folate intake has dramatic consequences for the cell, including: deregulation of methylation processes [7]; altered protein expression [8]; and decreased DNA repair capability and accumulation of DNA damage leading to increased chromosomal aberrations and fragility [9, 10]. These mechanisms underlie reduced growth rate and impaired cell division caused by folate deficiency. Low folate status has been linked to increased risk for several types of cancer, neural tube defects, and cardiovascular diseases [7] though the association between folate and carcinogenesis, as well as cardiovascular diseases, is inconclusive at present. For the reason of the prevention of neural tube defects, in 1996 the FDA approved a mandatory fortification of several types of grain foods in the US with a synthetic form of the vitamin, folic acid. Though the overall importance of folate for human health was known for long time, the underlying molecular mechanisms are not fully understood and continue to emerge. This is exemplified by recent studies, which have underscored the significance of folate metabolism for ES cells [11], the contribution of folate-dependent carbon oxidation into the cellular energy balance [12, 13], and the role of folate enzymes in cancer progression and metastasis [14–19]. To further complicate the picture, a concept that parental folate intake or folate status can modify disease risk in offspring later in life has been recently proposed [20].

10.3 Interactions Between Alcohol Consumption and Dietary Folate: Implication for Cancer

The link between folate and cancer has been investigated for decades but this issue is complicated by the phenomenon that while in general folate intake protects against tumorigenesis, it also can promote the proliferation of existing neoplastic lesions [21]. This adverse effect is primarily associated with the increased demand of rapidly proliferating cancer cells for folate coenzymes to support enhanced nucleotide biosynthesis towards unlimited DNA replication. Thus, there is a dilemma that folate intake above basal requirements may increase the incidence of malignancies and cancer-related death, which has been increasingly recognized by the experts in folate field [22]. The tumorigenic response to dietary folate depends on numerous factors, including cancer subtypes, the timing or duration of vitamin administration, its dose and ingested form (synthetic folic acid *vs*. natural folate) [4, 21]. End-point effects of the vitamin could be further modified by other factors such as age, the status of vitamins B_6/B_{12}, and individual genotypic features including polymorphisms in folate enzymes [4, 20]. One of the factors known to affect folate metabolism is chronic alcohol consumption [1, 2].

Alcoholism is typically associated with folate deficiency due to reduced dietary folate intake [2]. Heavy alcohol consumption also decreases folate absorption, enhances urinary folate excretion and inhibits enzymes pivotal for one-carbon metabolism [1, 2]. While folate metabolism is involved in numerous key biochemical pathways (Fig. 10.1), the aberrant DNA methylation, due to the deficiency of methyl donors, was widely considered as a common downstream target of the folate-mediated effect of ethanol [23]. The negative effects of low intakes of nutrients, which provide dietary methyl groups, with high intakes of alcohol are additive in general [24]. In support of such association, it has been reported that the low methionine, low-folate diets and alcohol consumption increase the risk for colorectal cancer in men [25]. Therefore, to counteract the negative effects of alcohol consumption, the increased intake of nutrients providing dietary methyl groups is recommended [24].

In agreement with this notion, a protective effect of folate on alcohol-impaired processes has been demonstrated in experiments with cultured mouse embryos, where addition of the vitamin, in the form of folic acid, blocked ethanol-induced teratogenesis [26]. The microarray profiling further indicated that the effect of prenatal ethanol exposure on teratogenesis in mice, and associated mental retardation, were induced through alterations in the expression pattern of several micro RNAs in fetal brain. In line with this mechanism, increased folic acid prevented micro RNAs changes in response to ethanol. Though it is not clear whether a similar mechanism mediating the interaction between dietary folate and alcohol consumption could be activated in carcinogenesis, SNPs (single nucleotide polymorphisms) in the micro RNA bindings sites of thymidylate synthase were associated with gastric cancer risk and patient survival [27]. Perhaps the interaction between folate status and alcohol consumption in carcinogenesis involves multiple mechanisms and is likely cancer-type specific. Four main alcohol-associated cancers are liver, colon, breast

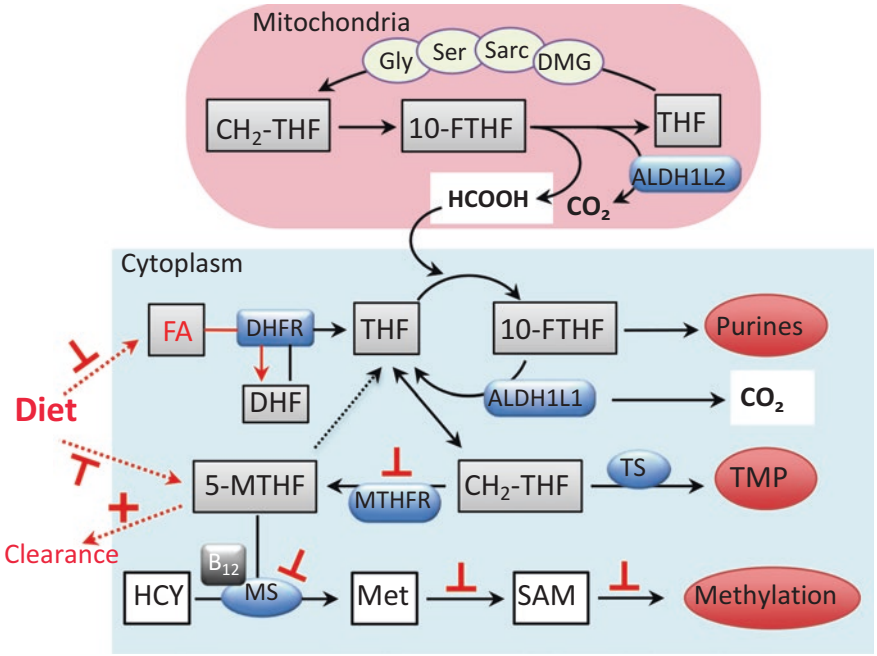

Fig. 10.1 ***Folate metabolism.*** Folate is taken up by the cell as folic acid (FA, supplements or fortified foods) or 5-methyl-THF (5-MTHF, natural diet). In the cell, FA is sequentially converted to dihydrofolate (DHF) and the active form of the coenzyme, tetrahydrofolate (THF) in reactions catalyzed by DHFR (dihydrofolate reductase). Acceptance of a one-carbon group (comes from serine, glycine, histidine or formate) converts THF to coenzymes directly participating in biosynthetic reactions (10-FTHF, 10-formyl-THF; CH_2-THF, 5,10-methylene-THF). HCY, homocysteine; SAM, S-adenosylmethionine; MS, methionine synthase; TS, thymidylate synthase; MTHFR, methylenetetrahydrofolate reductase. Reaction catalyzed by MS converts 5-MTHF to THF (*dotted arrow*). Overall, folate coenzymes provide one-carbon groups for three biosynthetic pathways: (i) methionine production; (ii) *de novo* purine generation; (iii) TMP synthesis. Mitochondrial folate metabolism provides one-carbon groups, derived from the degradation of serine, glycine, sarcosine (Sarc) or dimethylglycine (DMG), to the cytosolic folate pathways in the form of formate. Processes inhibited by ethanol are indicated by (⊥). Degradation of 5-methyl-THF is accelerated by ethanol (indicated by "+")

and upper aerodigestive tract [23]. In agreement with such etiology, recent prospective cohort study indicated that the folate pathway is likely to be involved in alcohol-related colorectal cancer development [28]. Higher folate intake can also ameliorate the effect of alcohol consumption on the development of HCC (hepatocellular carcinoma) [29] and the risk of breast cancer [30]. A prospective study of alcohol consumption and the risk of colorectal cancer before and after folic acid fortification in the US showed that fortification may attenuate this risk [31]. Another case-control study indicated that folate-related enzyme polymorphisms modify the association between drinking habit and pancreatic cancer risk [32]. Studies of other cancer types did not provide a clear association between folate status, alcohol consumption and cancer risk [33, 34].

The effect of ethanol on folate metabolism could be direct, through the enhanced coenzyme degradation or the inhibition of absorption, as well as indirect, through the influence on folate-related genes and enzymes. The intracellular folate pool consists of several major forms of the coenzyme, which differ in the oxidation level of the bound one-carbon group and are interconvertible through multiple reactions catalyzed by more than a dozen enzymes (Fig. 10.1). Enzymes of folate metabolism bring one-carbon groups to the folate pool, oxidize/reduce the folate-bound groups, or utilize these groups in biosynthetic reactions. The role of folate enzymes in cancer is well established and some of them, including DHFR and thymidylate synthase, are canonical chemotherapeutic targets [35]. An additional association between folate enzymes and cancer is provided by epidemiologic studies, which linked SNPs in the *MTHFR* gene with the risk of several cancer types [23]. The combination of folate intake and SNPs in genes associated with methionine biosynthesis may contribute to breast [36] and gastric [37] cancer risk, indicating that folate intake-associated cancer risk can be further modified by gene-nutrient interactions. Towards this line, a cross-sectional analysis of 19 human studies indicated a role for folate enzymes and their SNPs in response to alcohol consumption [38]. The direct inhibitory effect of ethanol on the activities of MTHFR and MTR in an animal model was demonstrated as well [39]. As a likely cause of decreased liver SAM and reduced methylation capacity, this mechanism can contribute to carcinogenesis [23]. Of note, ethanol also decreases thymidylate synthase mRNA levels in regenerating liver after partial hepatectomy [40], the effect which could be translated into the impaired DNA synthesis and repair.

10.4 ALDH1L1 Role in Cancer

One of the most abundant folate enzymes is cytosolic 10-formyltetrahydrofolate dehydrogenase (FDH, ALDH1L1) [41]. Levels of this enzyme can reach about 1.2% of the total protein in rat liver cytosol [42, 43], suggesting an important role (proposed functions for the enzyme are summarized in Fig. 10.2). ALDH1L1 converts 10-formyl-THF to THF (tetrahydrofolate) and carbon dioxide in a $NADP^+$-dependent reaction (Fig. 10.2). This reaction clears one-carbon groups (in the form of CO_2) from the cell thus limiting their flux toward folate-dependent biosynthetic reactions (Fig. 10.1) [44, 45]. It is also important for replenishing the pool of THF [46], which is the only folate coenzyme capable of accepting one-carbon groups and thus is central to folate metabolism [47]. In agreement with such function of ALDH1L1, genome-wide association studies revealed that SNPs in this gene are associated with serine to glycine ratio in serum [48] (THF is required for the reaction of the conversion of serine to glycine, Fig. 10.1). Furthermore, ALDH1L1 might regulate *de novo* purine biosynthesis [44, 49], formate degradation [5] and methylation status of the cell [45]. Another function originally proposed for this enzyme is to serve as the folate depot, though this hypothesis is primarily based on the phenomenon that the protein was purified in complex with THF [42].

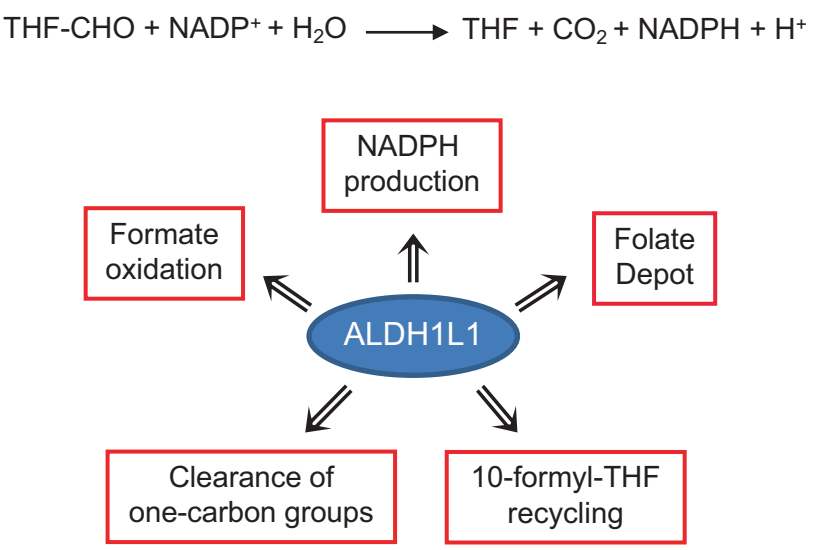

Fig. 10.2 Reaction catalyzed by ALDH1L1 and ALDH1L2 and proposed biological roles for the enzymes. *THF* tetrahydrofolate; *THF-CHO* 10-formyl-THF

ALDH1L1 is not ubiquitously expressed in human tissues: highest levels of its mRNA were detected in liver, kidney and pancreas while the levels in several tissues including placenta, spleen, thymus, small intestine, leukocytes, testis, and ovary were undetectable [44, 50]. Interestingly, ALDH1L1 is also differentially expressed in central nervous system during development: most quiescent cells in developing mouse brain are ALDH1L1 positive while proliferating cells do not express this protein [51]. Curiously, levels of this protein also significantly fluctuate (up to about seven-fold change) in the liver of golden-mantled ground squirrel depending on seasonal stages [52]. In further support of highly regulated expression of this protein, its levels were decreased in rat liver by clofibrate, a peroxisome proliferator [53] and increased in zebrafish embryos exposed to ethanol [54].

Perhaps most striking example of the ALDH1L1 regulation is its silencing in malignant tumors [44], which is achieved through methylation of the CpG island within the *ALDH1L1* promoter [55]. It contains 96 CpG pairs and covers the region between −525 and + 918 bp of the *ALDH1L1* gene including the promoter, the entire exon 1, and a part of intron 1 immediately downstream of the exon. Bisulfite sequencing analysis revealed extensive methylation of the island (76%–95% of CpGs) in cancer cell lines. Analysis of the samples from patients with lung adenocarcinomas demonstrated methylation of the *ALDH1L1* CpG island in tumor samples and a total lack of methylation in respective normal tissues. The same phenomenon was observed in liver tissues: the CpG island was methylation free in DNA extracted from normal hepatocytes but was extensively methylated in a hepatocellular carcinoma. Levels of *ALDH1L1* mRNA and protein correlated with the methylation status of the island, with tumor samples demonstrating down-

regulation of expression or even complete silencing of the gene. The down-regulation of *ALDH1L1* mRNA in NSCLC (non-small cell lung cancer) [56], cervical cancer [57] and renal cell carcinoma [58] associated with the gene methylation was also demonstrated by microarray assays. The regulation of *ALDH1L1* through the promoter methylation could also be a common cellular response to the environmental conditions. Thus, it has been reported that the prolonged exposure to isoflavone through dietary supplementation significantly reduces *Aldh1l1* promoter methylation in rat mammary tissue [59]. In addition, the methylation of *ALDH1L1* could be responsible for the individual variation in the protein expression. For example, higher CpG methylation in the body of the *ALDH1L1* gene was significantly correlated with its lower transcript expression in normal breast tissue in women [60].

In agreement with the phenomenon that ALDH1L1 is down-regulated in proliferating tumors, re-expression of the protein in cancer cells produces drastic antiproliferative effects including cell cycle arrest and apoptosis [44, 49, 61–63]. These findings indicated that ALDH1L1 is a key regulator of proliferation and an implication has been made in the literature that this protein is a candidate tumor suppressor [44, 55, 57, 58, 64]. Furthermore, under-expression of this gene could be a marker of a more aggressive tumor phenotype. Thus, decreased expression of ALDH1L1 was associated with aggressive subtypes of sporadic pilocytic astrocytoma [64], poor prognosis in hepatocellular carcinoma [65], and low overall survival in neuroblastoma [66], while high expression of *ALDH1L1* mRNA correlates with better overall survival in breast cancer patients [67]. It should be mentioned that the association between decreased ALDH1L1 expression and malignant tumor progression could be cancer type-specific [68]. For example, though decreased expression of ALDH1L1 was demonstrated in NSCLC [55, 56], cervical cancer [57], renal cell carcinoma [58] and peripheral cholangiocarcinoma [69], the extent of its expression in other cancers is not clear. In line with the idea that ALDH1L1 prognostic role could be cancer type-specific, SNPs in the *ALDH1L1* gene were significantly associated with altered risk of breast cancer [70] and increased risk of hepatocellular carcinoma [71] and non-Hodgkin lymphoma [72–74] but no SNPs were associated with the risk of prostate cancer [75].

10.5 Role of Mitochondrial ALDH1L2 Enzyme in Cancer

Folate pathways are compartmentalized within the cell, mainly between cytoplasm and mitochondria [3, 76], though the compartmentalization was recently extended to the nucleus, where folate-dependent TMP biosynthesis takes place [77]. It has been suggested that the mitochondrial pathways mainly serve to provide one-carbon groups, in the form of formate, for incorporation into the cytosolic folate pool where they are utilized for biosynthetic purposes [3]. While some folate-dependent reactions are unique to cytoplasm or mitochondria, several of them take place in both compartments and are catalyzed by homologous enzymes, which are products of distinct genes [3, 78]. The oxidation of 10-formyl-THF to THF and CO_2 is one of

such reactions. Mitochondrial 10-fTHF dehydrogenase is encoded by the *ALDH1L2* gene, which originated via the duplication of the *ALDH1L1* gene and acquired a mitochondrial leader sequence [50]. Accordingly, two proteins share about 72% identity of the amino acid sequence and are close structurally and enzymatically [50, 79]. Their biological roles, however, could be quite different. While cytosolic ALDH1L1 is involved in the regulation of cellular proliferation, through the control of folate pools, ALDH1L2 is the key enzyme to provide reduced NADPH in mitochondria [12]. NADPH produced in this mitochondrial reaction is required for the reduction of oxidized glutathione, and the loss of ALDH1L2 shifts the ratio of GSH/GSSG. This in turn decreases the capacity of mitochondria to eliminate reactive oxygen species leading to oxidative stress [19].

The *ALDH1L2* gene was discovered relatively recently and its studies are limited so far. Of note, it can be up-regulated by certain drugs, though mechanism of this response were not studied. For example, *ALDH1L2* mRNA levels are strongly increased (up to 6.8-fold) in immortalized human B cells treated with ER stress inducers thapsigargin or tunicamycin [80]. *ALDH1L2* mRNA was also significantly up-regulated in human adrenocortical NCI-H295R cells treated with mitotane, an adrenolytic drug extensively used in combination with other cytotoxic drugs and as an adjuvant monotherapy in the treatment of adrenocortical carcinoma [81]. This effect, however, is hard to correlate with the pharmacological action of the drug. *ALDH1L2* mRNA was also up-regulated more than three-fold in mouse neonatal ovaries exposed to 3-methylcholanthrene, a potent ovotoxicant [82]. The question of whether the regulatory effects of these drugs on the *ALDH1L2* gene are associated with the cellular response to oxidative stress awaits further investigation. Curiously, the *ALDH1L2* gene expression was lost in CCL-131 Neuro-2a malignant neuroblastoma cells at acidic pH [83]. Likewise, levels of the ALDH1L2 protein were dramatically decreased in nonalcoholic steatohepatitis in rats fed fat-rich diet [84]. Another study has reported a different effect for ALDH1L2: the protein was elevated about two-fold in fibroblasts of the patient with short-chain acyl-CoA dehydrogenase deficiency [85]. Thus, it appears that levels of ALDH1L2 inversely correlate with fatty acid oxidation. It has been also suggested that both acidic pH and fatty acid oxidation deficiency induce metabolic reprogramming, driving the switch to OXPHOS and less glucose utilization in the former case and to biosynthetic processes in the latter case. In this regard, ALDH1L2 could be differentially regulated depending on the cellular demand for the energy production. Alternatively, the regulation could be driven by ROS levels as well as the ratio of reduced/oxidized glutathione but precise mechanisms controlling ALDH1L2 expression remain elusive.

Of note, ALDH1L2 has a different tissue-expression pattern than ALDH1L1 and in contrast to the cytosolic enzyme is highly expressed in cancer cell lines [50]. It has been recently reported that ALDH1L2 is up-regulated in human colorectal tumor tissues compared to normal tissues [86]. Furthermore, rates of recurrence-free survival and overall survival in patients with high expression of ALDH1L2 tend to be lower than in patients with low expression of the enzyme, the situation opposite to cytosolic ALDH1L1. Considering that ALDH1L2 is a mitochondrial protein, it should be pointed out that numerous recent studies specifically underscored the

role of mitochondrial folate pathways in cancer with the emphasis on folate-dependent metabolism of serine and glycine [14–16, 87–90]. In this regard, ALDH1L2 might be an important component providing THF for the serine to glycine conversion in mitochondria and for glycine degradation (Fig. 10.1).

Intriguingly, *ALDH1L2* was implicated as a metastasis-regulatory gene [18]. Thus, in a mouse melanoma metastasis model, a striking increase in the expression of this protein in liver, pancreas and lung metastases compared to subcutaneous tumors has been shown [18]. Of note, other folate enzymes tested in this study did not demonstrate such trend. In further support of the metastasis-promoting role of ALDH1L2, the silencing of the gene in melanoma by shRNA significantly reduced the frequency of circulating melanoma cells in blood and overall metastatic burden [18]. Interestingly, the reduced invasion of MDA-MB-435 cells after the treatment with anti-inflammatory agent indomethacin was associated with a significant elevation of *ALDH1L2* mRNA [91]. While the mechanism by which indomethacin leads to *ALDH1L2* gene up-regulation is not clear, it could be a compensatory cellular response to the increased ROS production caused by the drug. The cytosolic isoform, ALDH1L1, could be also associated with the metastatic potential of cancer cells [92]. In contrast to ALDH1L2, however, the cytosolic isoform inhibits cellular migration and invasion, the phenomenon rather associated with the decreased metastasis [93].

10.6 Effect of Ethanol on ALDH1L1/L2 Genes and Proteins

One of the folate-related effects of alcohol consumption could be the interaction of ethanol or its metabolites with folate enzymes [39]. Since the decrease of the ALDH1L1 expression could be associated with tumor promotion, metabolites inhibiting the activity of the enzyme or causing down-regulation of its expression would have pro-tumorigenic effect. Though studies of the effect of ethanol on ALDH1L1 are scarce, a role for the enzyme in mediation of the effect of alcohol intake on oral carcinogenesis has been proposed [94]. In another study, levels of ALDH1L1 were changed after liver transplant in recipients with alcoholic cirrhosis [95], implying the effect of chronic alcohol consumption on the enzyme. Interestingly, a recent study reported that alcohol consumption is associated with differentially methylated CpGs in the *ALDH1L1* gene in breast tissue of healthy women [60]. Furthermore, women carrying an allelic variant of the gene were more likely to have hypermethylated *ALDH1L1*, the phenomenon correlated with lower gene expression. These findings point toward a potential mechanism by which alcohol implements its folate-mediated tumorigenic effect in mammary tissue.

Chronic ethanol ingestion was reported to decrease hepatic ALDH1L1 dehydrogenase activity in rats [96]. The ethanol treatment also affected ALDH1L1 activities in brain and hepatic tissues of chicken embryos [97, 98]. It has been further demonstrated that the ALDH1L1 enzymatic activity is inhibited by acetaldehyde *in vitro* [99], which could be a mechanism of the ethanol effect on the enzyme and one of the mechanisms by which alcohol consumption changes folate status. It should be

noted that ALDH1L1 is capable, at least *in vitro*, to metabolize acetaldehyde to acetic acid [100], which would argue against such inhibitory effect. This reaction still could interfere with the folate-related catalysis of the enzyme thus affecting folate metabolism. ALDH1L1 has been also reported as a target for acetaminophen, which covalently modifies a key cysteine of the enzyme; this effect could contribute to the drug toxicity [101]. Since excessive alcohol consumption is a risk factor for acetaminophen-induced hepatotoxicity [102], ALDH1L1 could be a dual target towards liver damage. Whether this effect would contribute to carcinogenesis is not clear at present. Interestingly, ALDH1L1 can also counteract the effect of ethanol on folate metabolism by protecting THF from degradation [103]. The metabolism of acetaldehyde by xanthine oxidase generates superoxide radicals, which can cleave folates [104]. Of note, 5-methyl-THF, the most common form of natural folate, is highly susceptible to the degradation by superoxide [104]. In agreement with the mechanism of folate protection by ALDH1L1, up-regulation of the *ALDH1L1* gene prevented folate degradation and alleviated the oxidative stress induced by ethanol exposure in zebrafish embryos [54].

The role of ALDH1L2 in alcohol response and ethanol metabolism is even less clear due to the lack of corresponding studies. By analogy with the *ALDH1L1* gene, it can be hypothesized that ALDH1L2 is relevant to the interaction between ethanol and folate metabolism. Indeed, the implication that this gene is a part of alcohol dependence mechanism has been made in the literature [105]. Thus, in the study of genome-wide DNA methylation in discordant sib pairs with alcohol dependence, the deregulation of *ALDH1L2* gene through the promoter hypomethylation was associated with alcohol dependence [105].

10.7 Conclusion

ALDH1L1 and ALDH1L2 are key enzymes in the regulation of folate metabolism as well as downstream processes associated with folate-dependent biochemical reactions. While both enzymes catalyze the same reaction, their compartmentalization leads to the differential effect on overall cellular metabolism, regulating either reduced folate pools and purine biosynthesis (cytosolic ALDH1L1) or NADPH production and oxidative stress (mitochondrial ALDH1L2). Both enzymes were implicated in the proliferation of malignant tumors, though with opposite roles, tumor suppression in the case of the cytosolic enzyme and metastasis promotion in the case of the mitochondrial isoform. These enzymes were also implicated in the cellular response to alcohol consumption. Taking into account that both enzymes have essentially identical structural organization and enzymatic mechanism, it is likely that the direct effect of ethanol or its metabolites on ALDH1L1 and ALDH1L2 would be similar in both cases. However, considering differential regulation of the two isoforms, the overall effect of alcohol consumption on two enzymes would be more complex and not so direct. Clearly, more studies are needed to address the role of ALDH1L1 and ALDH1L2 in biology of malignant tumors and in potential mediation of the alcohol effect.

References

1. Mason JB, Choi SW (2005) Effects of alcohol on folate metabolism: implications for carcinogenesis. Alcohol 35(3):235–241. https://doi.org/10.1016/j.alcohol.2005.03.012
2. Medici V, Halsted CH (2013) Folate, alcohol, and liver disease. Mol Nutr Food Res 57(4):596–606. https://doi.org/10.1002/mnfr.201200077
3. Tibbetts AS, Appling DR (2010) Compartmentalization of mammalian folate-mediated one-carbon metabolism. Annu Rev Nutr 30:57–81. https://doi.org/10.1146/annurev.nutr.012809.104810
4. Strickland KC, Krupenko NI, Krupenko SA (2013) Molecular mechanisms underlying the potentially adverse effects of folate. Clin Chem Lab Med 51(3):607–616. https://doi.org/10.1515/cclm-2012-0561
5. Brosnan ME, MacMillan L, Stevens JR, Brosnan JT (2015) Division of labour: how does folate metabolism partition between one-carbon metabolism and amino acid oxidation? Biochem J 472(2):135–146. https://doi.org/10.1042/BJ20150837
6. Tucker EJ, Hershman SG, Kohrer C, Belcher-Timme CA, Patel J, Goldberger OA, Christodoulou J, Silberstein JM, McKenzie M, Ryan MT, Compton AG, Jaffe JD, Carr SA, Calvo SE, Rajbhandary UL, Thorburn DR, Mootha VK (2011) Mutations in MTFMT underlie a human disorder of formylation causing impaired mitochondrial translation. Cell Metab 14(3):428–434. https://doi.org/10.1016/j.cmet.2011.07.010
7. Crider KS, Yang TP, Berry RJ, Bailey LB (2012) Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. Adv Nutr 3(1):21–38. https://doi.org/10.3945/an.111.000992
8. Jhaveri MS, Wagner C, Trepel JB (2001) Impact of extracellular folate levels on global gene expression. Mol Pharmacol 60(6):1288–1295
9. Blount BC, Mack MM, Wehr CM, MacGregor JT, Hiatt RA, Wang G, Wickramasinghe SN, Everson RB, Ames BN (1997) Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proc Natl Acad Sci USA 94(7):3290–3295
10. Choi SW, Mason JB (2000) Folate and carcinogenesis: an integrated scheme. J Nutr 130(2):129–132
11. Wang J, Alexander P, Wu L, Hammer R, Cleaver O, McKnight SL (2009) Dependence of mouse embryonic stem cells on threonine catabolism. Science 325(5939):435–439. https://doi.org/10.1126/science.1173288
12. Fan J, Ye J, Kamphorst JJ, Shlomi T, Thompson CB, Rabinowitz JD (2014) Quantitative flux analysis reveals folate-dependent NADPH production. Nature 510(7504):298–302. https://doi.org/10.1038/nature13236
13. Liu L, Shah S, Fan J, Park JO, Wellen KE, Rabinowitz JD (2016) Malic enzyme tracers reveal hypoxia-induced switch in adipocyte NADPH pathway usage. Nat Chem Biol 12(5):345–352. https://doi.org/10.1038/nchembio.2047
14. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK (2012) Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. Science 336(6084):1040–1044. https://doi.org/10.1126/science.1218595
15. Zhang WC, Shyh-Chang N, Yang H, Rai A, Umashankar S, Ma S, Soh BS, Sun LL, Tai BC, Nga ME, Bhakoo KK, Jayapal SR, Nichane M, Yu Q, Ahmed DA, Tan C, Sing WP, Tam J, Thirugananam A, Noghabi MS, Pang YH, Ang HS, Mitchell W, Robson P, Kaldis P, Soo RA, Swarup S, Lim EH, Lim B (2012) Glycine decarboxylase activity drives non-small cell lung cancer tumor-initiating cells and tumorigenesis. Cell 148(1–2):259–272. https://doi.org/10.1016/j.cell.2011.11.050
16. Nilsson R, Jain M, Madhusudhan N, Sheppard NG, Strittmatter L, Kampf C, Huang J, Asplund A, Mootha VK (2014) Metabolic enzyme expression highlights a key role for

MTHFD2 and the mitochondrial folate pathway in cancer. Nat Commun 5:3128. https://doi.org/10.1038/ncomms4128
17. Locasale JW (2013) Serine, glycine and one-carbon units: cancer metabolism in full circle. Nat Rev Cancer 13(8):572–583. https://doi.org/10.1038/nrc3557
18. Piskounova E, Agathocleous M, Murphy MM, Hu Z, Huddlestun SE, Zhao Z, Leitch AM, Johnson TM, DeBerardinis RJ, Morrison SJ (2015) Oxidative stress inhibits distant metastasis by human melanoma cells. Nature 527:186–191. https://doi.org/10.1038/nature15726
19. Ducker GS, Chen L, Morscher RJ, Ghergurovich JM, Esposito M, Teng X, Kang Y, Rabinowitz JD (2016) Reversal of cytosolic one-carbon flux compensates for loss of the mitochondrial folate pathway. Cell Metab. https://doi.org/10.1016/j.cmet.2016.04.016
20. Mason JB, Tang SY (2016) Folate status and colorectal cancer risk: a 2016 update. Mol Asp Med 53:73–79. https://doi.org/10.1016/j.mam.2016.11.010
21. Miller JW, Ulrich CM (2013) Folic acid and cancer–where are we today? Lancet 381(9871):974–976. https://doi.org/10.1016/S0140-6736(13)60110-5
22. Boyles AL, Yetley EA, Thayer KA, Coates PM (2016) Safe use of high intakes of folic acid: research challenges and paths forward. Nutr Rev 74(7):469–474. https://doi.org/10.1093/nutrit/nuw015
23. Varela-Rey M, Woodhoo A, Martinez-Chantar ML, Mato JM, Lu SC (2013) Alcohol, DNA methylation, and cancer. Alcohol Res 35(1):25–35
24. Bailey LB (2003) Folate, methyl-related nutrients, alcohol, and the MTHFR 677C–>T polymorphism affect cancer risk: intake recommendations. J Nutr 133(11 Suppl 1):3748S–3753S
25. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC (1995) Alcohol, low-methionine--low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst 87(4):265–273
26. Wang LL, Zhang Z, Li Q, Yang R, Pei X, Xu Y, Wang J, Zhou SF, Li Y (2009) Ethanol exposure induces differential microRNA and target gene expression and teratogenic effects which can be suppressed by folic acid supplementation. Hum Reprod 24(3):562–579. https://doi.org/10.1093/humrep/den439
27. Shen R, Liu H, Wen J, Liu Z, Wang LE, Wang Q, Tan D, Ajani JA, Wei Q (2015) Genetic polymorphisms in the microRNA binding-sites of the thymidylate synthase gene predict risk and survival in gastric cancer. Mol Carcinog 54(9):880–888. https://doi.org/10.1002/mc.22160
28. Svensson T, Yamaji T, Budhathoki S, Hidaka A, Iwasaki M, Sawada N, Inoue M, Sasazuki S, Shimazu T, Tsugane S (2016) Alcohol consumption, genetic variants in the alcohol- and folate metabolic pathways and colorectal cancer risk: the JPHC study. Sci Rep 6:36607. https://doi.org/10.1038/srep36607
29. Persson EC, Schwartz LM, Park Y, Trabert B, Hollenbeck AR, Graubard BI, Freedman ND, McGlynn KA (2013) Alcohol consumption, folate intake, hepatocellular carcinoma, and liver disease mortality. Cancer Epidemiol Biomark Prev 22(3):415–421. https://doi.org/10.1158/1055-9965.EPI-12-1169
30. Islam T, Ito H, Sueta A, Hosono S, Hirose K, Watanabe M, Iwata H, Tajima K, Tanaka H, Matsuo K (2013) Alcohol and dietary folate intake and the risk of breast cancer: a case-control study in Japan. Eur J Cancer Prev 22(4):358–366. https://doi.org/10.1097/CEJ.0b013e32835b6a60
31. Nan H, Lee JE, Rimm EB, Fuchs CS, Giovannucci EL, Cho E (2013) Prospective study of alcohol consumption and the risk of colorectal cancer before and after folic acid fortification in the United States. Ann Epidemiol 23(9):558–563. https://doi.org/10.1016/j.annepidem.2013.04.011
32. Suzuki T, Matsuo K, Sawaki A, Mizuno N, Hiraki A, Kawase T, Watanabe M, Nakamura T, Yamao K, Tajima K, Tanaka H (2008) Alcohol drinking and one-carbon metabolism-related gene polymorphisms on pancreatic cancer risk. Cancer Epidemiol Biomark Prev 17(10):2742–2747. https://doi.org/10.1158/1055-9965.EPI-08-0470

33. Matejcic M, de Batlle J, Ricci C, Biessy C, Perrier F, Huybrechts I, Weiderpass E, Ruault BM, Cadeau C, His M, Cox DG, Boeing H, Fortner RT, Kaaks R, Lagiou P, Trichopoulou A, Benetou V, Tumino R, Panico S, Sieri S, Palli D, Ricceri F, Bueno-De-Mesquita HB, Skeie G, Amiano P, Sanchez MJ, Chirlaque MD, Barricarte A, Quiros JR, Buckland G, van Gils CH, Peeters PH, Key TJ, Riboli E, Gylling B, Zeleniuch-Jacquotte A, Gunter MJ, Romieu I, Chajes V (2016) Biomarkers of folate and vitamin B12 and breast cancer risk: report from the EPIC cohort. Int J Cancer 140(6):1246–1259. https://doi.org/10.1002/ijc.30536
34. Schouten LJ, Deckers IA, van den Brandt PA, Baldewijns MM, van Engeland M (2016) Alcohol and dietary folate intake and promoter CpG Island methylation in clear-cell renal cell Cancer. Nutr Cancer 68(7):1097–1107. https://doi.org/10.1080/01635581.2016.1187283
35. Goldman ID, Chattopadhyay S, Zhao R, Moran R (2010) The antifolates: evolution, new agents in the clinic, and how targeting delivery via specific membrane transporters is driving the development of a next generation of folate analogs. Curr Opin Investig Drugs 11(12):1409–1423
36. Luo WP, Li B, Lin FY, Yan B, Du YF, Mo XF, Wang L, Zhang CX (2016) Joint effects of folate intake and one-carbon-metabolizing genetic polymorphisms on breast cancer risk: a case-control study in China. Sci Rep 6:29555. https://doi.org/10.1038/srep29555
37. Kim W, Woo HD, Lee J, Choi IJ, Kim YW, Sung J, Kim J (2016) Dietary folate, one-carbon metabolism-related genes, and gastric cancer risk in Korea. Mol Nutr Food Res 60(2):337–345. https://doi.org/10.1002/mnfr.201500384
38. Wang LL, Li Y, Zhou SF (2009) Prediction of deleterious non-synonymous single nucleotide polymorphisms of genes related to ethanol-induced toxicity. Toxicol Lett 187(2):99–114. https://doi.org/10.1016/j.toxlet.2009.02.007
39. Villanueva JA, Halsted CH (2004) Hepatic transmethylation reactions in micropigs with alcoholic liver disease. Hepatology 39(5):1303–1310. https://doi.org/10.1002/hep.20168
40. Yoshida Y, Komatsu M, Ozeki A, Nango R, Tsukamoto I (1997) Ethanol represses thymidylate synthase and thymidine kinase at mRNA level in regenerating rat liver after partial hepatectomy. Biochim Biophys Acta 1336(2):180–186
41. Krupenko SA (2009) FDH: an aldehyde dehydrogenase fusion enzyme in folate metabolism. Chem Biol Interact 178(1–3):84–93
42. Cook RJ, Wagner C (1982) Purification and partial characterization of rat liver folate binding protein: cytosol I. Biochemistry 21(18):4427–4434
43. Kisliuk RL (1999) Folate biochemistry in relation to antifolate selectivity. In: Jackman AL (ed) Antifolate drugs in cancer therapy. Humana Press, Totowa, pp 13–36
44. Krupenko SA, Oleinik NV (2002) 10-formyltetrahydrofolate dehydrogenase, one of the major folate enzymes, is down-regulated in tumor tissues and possesses suppressor effects on cancer cells. Cell Growth Differ 13(5):227–236
45. Anguera MC, Field MS, Perry C, Ghandour H, Chiang EP, Selhub J, Shane B, Stover PJ (2006) Regulation of folate-mediated one-carbon metabolism by 10-Formyltetrahydrofolate dehydrogenase. J Biol Chem 281(27):18335–18342
46. Champion KM, Cook RJ, Tollaksen SL, Giometti CS (1994) Identification of a heritable deficiency of the folate-dependent enzyme 10-formyltetrahydrofolate dehydrogenase in mice. Proc Natl Acad Sci USA 91(24):11338–11342
47. Wagner C (1995) Biochemical role of folate in cellular metabolism. In: Bailey LB (ed) Folate in health and disease. Marcel Dekker, Inc., New York, pp 23–42
48. Dharuri H, Henneman P, Demirkan A, van Klinken JB, Mook-Kanamori DO, Wang-Sattler R, Gieger C, Adamski J, Hettne K, Roos M, Suhre K, Van Duijn CM, Consortia E, van Dijk KW, Hoen PA (2013) Automated workflow-based exploitation of pathway databases provides new insights into genetic associations of metabolite profiles. BMC Genomics 14:865. https://doi.org/10.1186/1471-2164-14-865
49. Oleinik NV, Krupenko NI, Priest DG, Krupenko SA (2005) Cancer cells activate p53 in response to 10-formyltetrahydrofolate dehydrogenase expression. Biochem J 391(Pt 3):503–511

50. Krupenko NI, Dubard ME, Strickland KC, Moxley KM, Oleinik NV, Krupenko SA (2010) ALDH1L2 is the mitochondrial homolog of 10-formyltetrahydrofolate dehydrogenase. J Biol Chem 285(30):23056–23063. 10.74/jbc.M110.128843
51. Anthony TE, Heintz N (2007) The folate metabolic enzyme ALDH1L1 is restricted to the midline of the early CNS, suggesting a role in human neural tube defects. J Comp Neurol 500(2):368–383
52. Epperson LE, Dahl TA, Martin SL (2004) Quantitative analysis of liver protein expression during hibernation in the golden-mantled ground squirrel. Mol Cell Proteomics 3(9):920–933
53. Leonard JF, Courcol M, Mariet C, Charbonnier A, Boitier E, Duchesne M, Parker F, Genet B, Supatto F, Roberts R, Gautier JC (2006) Proteomic characterization of the effects of clofibrate on protein expression in rat liver. Proteomics 6(6):1915–1933
54. Hsiao TH, Lin CJ, Chung YS, Lee GH, Kao TT, Chang WN, Chen BH, Hung JJ, Fu TF (2014) Ethanol-induced upregulation of 10-formyltetrahydrofolate dehydrogenase helps relieve ethanol-induced oxidative stress. Mol Cell Biol 34(3):498–509. https://doi.org/10.1128/MCB.01427-13
55. Oleinik NV, Krupenko NI, Krupenko SA (2011) Epigenetic silencing of ALDH1L1, a metabolic regulator of cellular proliferation, in cancers. Genes Cancer 2(2):130–139
56. Dmitriev AA, Kashuba VI, Haraldson K, Senchenko VN, Pavlova TV, Kudryavtseva AV, Anedchenko EA, Krasnov GS, Pronina IV, Loginov VI, Kondratieva TT, Kazubskaya TP, Braga EA, Yenamandra SP, Ignatjev I, Ernberg I, Klein G, Lerman MI, Zabarovsky ER (2012) Genetic and epigenetic analysis of non-small cell lung cancer with NotI-microarrays. Epigenetics 7(5):502–513. https://doi.org/10.4161/epi.19801
57. Senchenko VN, Kisseljova NP, Ivanova TA, Dmitriev AA, Krasnov GS, Kudryavtseva AV, Panasenko GV, Tsitrin EB, Lerman MI, Kisseljov FL, Kashuba VI, Zabarovsky ER (2013) Novel tumor suppressor candidates on chromosome 3 revealed by NotI-microarrays in cervical cancer. Epigenetics 8(4):409–420. https://doi.org/10.4161/epi.24233
58. Dmitriev AA, Rudenko EE, Kudryavtseva AV, Krasnov GS, Gordiyuk VV, Melnikova NV, Stakhovsky EO, Kononenko OA, Pavlova LS, Kondratieva TT, Alekseev BY, Braga EA, Senchenko VN, Kashuba VI (2014) Epigenetic alterations of chromosome 3 revealed by NotI-microarrays in clear cell renal cell carcinoma. Biomed Res Int 2014:735292. https://doi.org/10.1155/2014/735292
59. Blei T, Soukup ST, Schmalbach K, Pudenz M, Moller FJ, Egert B, Wortz N, Kurrat A, Muller D, Vollmer G, Gerhauser C, Lehmann L, Kulling SE, Diel P (2015) Dose-dependent effects of isoflavone exposure during early lifetime on the rat mammary gland: studies on estrogen sensitivity, isoflavone metabolism, and DNA methylation. Mol Nutr Food Res 59(2):270–283. https://doi.org/10.1002/mnfr.201400480
60. Song MA, Brasky TM, Marian C, Weng DY, Taslim C, Llanos AA, Dumitrescu RG, Liu Z, Mason JB, Spear SL, Kallakury BV, Freudenheim JL, Shields PG (2016) Genetic variation in one-carbon metabolism in relation to genome-wide DNA methylation in breast tissue from heathy women. Carcinogenesis 37:471–480. https://doi.org/10.1093/carcin/bgw030
61. Ghose S, Oleinik NV, Krupenko NI, Krupenko SA (2009) 10-formyltetrahydrofolate dehydrogenase-induced c-Jun-NH2-kinase pathways diverge at the c-Jun-NH2-kinase substrate level in cells with different p53 status. Mol Cancer Res 7(1):99–107
62. Oleinik NV, Krupenko NI, Krupenko SA (2007) Cooperation between JNK1 and JNK2 in activation of p53 apoptotic pathway. Oncogene 26(51):7222–7230
63. Oleinik NV, Krupenko SA (2003) Ectopic expression of 10-formyltetrahydrofolate dehydrogenase in a549 cells induces g(1) cell cycle arrest and apoptosis. Mol Cancer Res 1(8):577–588
64. Rodriguez FJ, Giannini C, Asmann YW, Sharma MK, Perry A, Tibbetts KM, Jenkins RB, Scheithauer BW, Anant S, Jenkins S, Eberhart CG, Sarkaria JN, Gutmann DH (2008) Gene expression profiling of NF-1-associated and sporadic pilocytic astrocytoma identifies aldehyde dehydrogenase 1 family member L1 (ALDH1L1) as an underexpressed candidate biomarker in aggressive subtypes. J Neuropathol Exp Neurol 67(12):1194–1204

65. Chen XQ, He JR, Wang HY (2011) Decreased expression of ALDH1L1 is associated with a poor prognosis in hepatocellular carcinoma. Med Oncol 29(3):1843–1849. https://doi.org/10.1007/s12032-011-0075-x
66. Hartomo TB, Van Huyen PT, Yamamoto N, Hirase S, Hasegawa D, Kosaka Y, Matsuo M, Hayakawa A, Takeshima Y, Iijima K, Nishio H, Nishimura N (2015) Involvement of aldehyde dehydrogenase 1A2 in the regulation of cancer stem cell properties in neuroblastoma. Int J Oncol 46(3):1089–1098. https://doi.org/10.3892/ijo.2014.2801
67. Wu S, Xue W, Huang X, Yu X, Luo M, Huang Y, Liu Y, Bi Z, Qiu X, Bai S (2015) Distinct prognostic values of ALDH1 isoenzymes in breast cancer. Tumour Biol 36(4):2421–2426. https://doi.org/10.1007/s13277-014-2852-6
68. Shen JX, Liu J, Li GW, Huang YT, Wu HT (2016) Mining distinct aldehyde dehydrogenase 1 (ALDH1) isoenzymes in gastric cancer. Oncotarget 7(18):25340–25349. https://doi.org/10.18632/oncotarget.8294
69. Darby IA, Vuillier-Devillers K, Pinault E, Sarrazy V, Lepreux S, Balabaud C, Bioulac-Sage P, Desmouliere A (2010) Proteomic analysis of differentially expressed proteins in peripheral cholangiocarcinoma. Cancer Microenviron 4(1):73–91. https://doi.org/10.1007/s12307-010-0047-2
70. Stevens VL, McCullough ML, Pavluck AL, Talbot JT, Feigelson HS, Thun MJ, Calle EE (2007) Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence. Cancer Epidemiol Biomark Prev 16(6):1140–1147. https://doi.org/10.1158/1055-9965.EPI-06-1037
71. Zhang H, Liu C, Han YC, Ma Z, Zhang H, Ma Y, Liu X (2015) Genetic variations in the one-carbon metabolism pathway genes and susceptibility to hepatocellular carcinoma risk: a case-control study. Tumour Biol 36(2):997–1002. https://doi.org/10.1007/s13277-014-2725-z
72. Lim U, Wang SS, Hartge P, Cozen W, Kelemen LE, Chanock S, Davis S, Blair A, Schenk M, Rothman N, Lan Q (2007) Gene-nutrient interactions among determinants of folate and one-carbon metabolism on the risk of non-Hodgkin lymphoma: NCI-SEER case-control study. Blood 109(7):3050–3059. https://doi.org/10.1182/blood-2006-07-034330
73. Lee KM, Lan Q, Kricker A, Purdue MP, Grulich AE, Vajdic CM, Turner J, Whitby D, Kang D, Chanock S, Rothman N, Armstrong BK (2007) One-carbon metabolism gene polymorphisms and risk of non-Hodgkin lymphoma in Australia. Hum Genet 122(5):525–533. https://doi.org/10.1007/s00439-007-0431-2
74. Wu L, Lu X, Guo J, Zhang T, Wang F, Bao Y (2016) Association between ALDH1L1 gene polymorphism and neural tube defects in the Chinese Han population. Neurol Sci 37(7):1049–1054. https://doi.org/10.1007/s10072-016-2527-8
75. Stevens VL, Rodriguez C, Sun J, Talbot JT, Thun MJ, Calle EE (2008) No association of single nucleotide polymorphisms in one-carbon metabolism genes with prostate cancer risk. Cancer Epidemiol Biomark Prev 17(12):3612–3614. https://doi.org/10.1158/1055-9965.EPI-08-0789
76. Fox JT, Stover PJ (2008) Folate-mediated one-carbon metabolism. Vitam Horm 79:1–44. https://doi.org/10.1016/S0083-6729(08)00401-9
77. MacFarlane AJ, Anderson DD, Flodby P, Perry CA, Allen RH, Stabler SP, Stover PJ (2011) Nuclear localization of de novo thymidylate biosynthesis pathway is required to prevent uracil accumulation in DNA. J Biol Chem 286(51):44015–44022. https://doi.org/10.1074/jbc.M111.307629
78. Strickland KC, Holmes RS, Oleinik NV, Krupenko NI, Krupenko SA (2011) Phylogeny and evolution of aldehyde dehydrogenase-homologous folate enzymes. Chem Biol Interact 191(1–3):122–128. https://doi.org/10.1016/j.cbi.2010.12.025
79. Strickland KC, Krupenko NI, Dubard ME, Hu CJ, Tsybovsky Y, Krupenko SA (2011) Enzymatic properties of ALDH1L2, a mitochondrial 10-formyltetrahydrofolate dehydrogenase. Chem Biol Interact 191(1–3):129–136. 10.16/j.cbi.2011.01.008

80. Dombroski BA, Nayak RR, Ewens KG, Ankener W, Cheung VG, Spielman RS (2010) Gene expression and genetic variation in response to endoplasmic reticulum stress in human cells. Am J Hum Genet 86(5):719–729. https://doi.org/10.1016/j.ajhg.2010.03.017
81. Zsippai A, Szabo DR, Tombol Z, Szabo PM, Eder K, Pallinger E, Gaillard RC, Patocs A, Toth S, Falus A, Racz K, Igaz P (2012) Effects of mitotane on gene expression in the adrenocortical cell line NCI-H295R: a microarray study. Pharmacogenomics 13(12):1351–1361. https://doi.org/10.2217/pgs.12.116
82. Sobinoff AP, Nixon B, Roman SD, McLaughlin EA (2012) Staying alive: PI3K pathway promotes primordial follicle activation and survival in response to 3MC-induced ovotoxicity. Toxicol Sci 128(1):258–271. https://doi.org/10.1093/toxsci/kfs137
83. Mazzio EA, Boukli N, Rivera N, Soliman KF (2012) Pericellular pH homeostasis is a primary function of the Warburg effect: inversion of metabolic systems to control lactate steady state in tumor cells. Cancer Sci 103(3):422–432. https://doi.org/10.1111/j.1349-7006.2012.02206.x
84. Li L, Lu DZ, Li YM, Zhang XQ, Zhou XX, Jin X (2014) Proteomic analysis of liver mitochondria from rats with nonalcoholic steatohepatitis. World J Gastroenterol 20(16):4778–4786. https://doi.org/10.3748/wjg.v20.i16.4778
85. Edhager AV, Stenbroen V, Nielsen NS, Bross P, Olsen RK, Gregersen N, Palmfeldt J (2014) Proteomic investigation of cultivated fibroblasts from patients with mitochondrial short-chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab 111(3):360–368. https://doi.org/10.1016/j.ymgme.2014.01.007
86. Miyo M, Konno M, Colvin H, Nishida N, Koseki J, Kawamoto K, Tsunekuni K, Nishimura J, Hata T, Takemasa I, Mizushima T, Doki Y, Mori M, Ishii H (2016) The importance of mitochondrial folate enzymes in human colorectal cancer. Oncol Rep 37:417–425. https://doi.org/10.3892/or.2016.5264
87. Labuschagne CF, van den Broek NJ, Mackay GM, Vousden KH, Maddocks OD (2014) Serine, but not glycine, supports one-carbon metabolism and proliferation of cancer cells. Cell Rep 7(4):1248–1258. https://doi.org/10.1016/j.celrep.2014.04.045
88. Gustafsson Sheppard N, Jarl L, Mahadessian D, Strittmatter L, Schmidt A, Madhusudan N, Tegner J, Lundberg EK, Asplund A, Jain M, Nilsson R (2015) The folate-coupled enzyme MTHFD2 is a nuclear protein and promotes cell proliferation. Sci Rep 5:15029. https://doi.org/10.1038/srep15029
89. Ben-Sahra I, Hoxhaj G, Ricoult SJ, Asara JM, Manning BD (2016) mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle. Science 351(6274):728–733. https://doi.org/10.1126/science.aad0489
90. Mehrmohamadi M, Liu X, Shestov AA, Locasale JW (2014) Characterization of the usage of the serine metabolic network in human cancer. Cell Rep 9(4):1507–1519. https://doi.org/10.1016/j.celrep.2014.10.026
91. Ackerstaff E, Gimi B, Artemov D, Bhujwalla ZM (2007) Anti-inflammatory agent indomethacin reduces invasion and alters metabolism in a human breast cancer cell line. Neoplasia 9(3):222–235
92. Ishiguro T, Nakajima M, Naito M, Muto T, Tsuruo T (1996) Identification of genes differentially expressed in B16 murine melanoma sublines with different metastatic potentials. Cancer Res 56(4):875–879
93. Oleinik NV, Krupenko NI, Krupenko SA (2010) ALDH1L1 inhibits cell motility via dephosphorylation of cofilin by PP1 and PP2A. Oncogene 29(47):6233–6244. https://doi.org/10.1038/onc.2010.356
94. Hwang PH, Lian L, Zavras AI (2012) Alcohol intake and folate antagonism via CYP2E1 and ALDH1: effects on oral carcinogenesis. Med Hypotheses 78(2):197–202. https://doi.org/10.1016/j.mehy.2011.10.023
95. Muffak-Granero K, Olmedo C, Garcia-Alcalde F, Comino A, Villegas T, Villar JM, Garrote D, Blanco A, Bueno P, Ferron JA (2012) Gene network profiling before and after transplantation in alcoholic cirrhosis liver transplant recipients. Transplant Proc 44(6):1493–1495. https://doi.org/10.1016/j.transproceed.2012.05.017

96. Min H, Im ES, Seo JS, Mun JA, Burri BJ (2005) Effects of chronic ethanol ingestion and folate deficiency on the activity of 10-formyltetrahydrofolate dehydrogenase in rat liver. Alcohol Clin Exp Res 29(12):2188–2193
97. Barnett RK, Booms SL, Gura T, Gushrowski M, Miller RR Jr (2009) Exogenous folate ameliorates ethanol-induced brain hyperhomocysteinemia and exogenous ethanol reduces taurine levels in chick embryos. Comp Biochem Physiol C Toxicol Pharmacol 150(1):107–112. https://doi.org/10.1016/j.cbpc.2009.03.005
98. Berlin KN, Cameron LM, Gatt M, Miller RR Jr (2010) Reduced de novo synthesis of 5-methyltetrahydrofolate and reduced taurine levels in ethanol-treated chick brains. Comp Biochem Physiol C Toxicol Pharmacol 152(3):353–359. 10.16/j.cbpc.2010.06.002
99. Mun JA, Doh E, Min H (2008) In vitro inhibition of 10-formyltetrahydrofolate dehydrogenase activity by acetaldehyde. Nutr Res Pract 2(4):195–199. https://doi.org/10.4162/nrp.2008.2.4.195
100. Cook RJ, Lloyd RS, Wagner C (1991) Isolation and characterization of cDNA clones for rat liver 10-formyltetrahydrofolate dehydrogenase. J Biol Chem 266(8):4965–4973
101. Pumford NR, Halmes NC, Martin BM, Cook RJ, Wagner C, Hinson JA (1997) Covalent binding of acetaminophen to N-10-formyltetrahydrofolate dehydrogenase in mice. J Pharmacol Exp Ther 280(1):501–505
102. Stine JG, Chalasani NP (2017) Drug hepatotoxicity: environmental factors. Clin Liver Dis 21(1):103–113. https://doi.org/10.1016/j.cld.2016.08.008
103. Chang WN, Lee GH, Kao TT, Lin CY, Hsiao TH, Tsai JN, Chen BH, Chen YH, Wu HR, Tsai HJ, Fu TF (2014) Knocking down 10-Formyltetrahydrofolate dehydrogenase increased oxidative stress and impeded zebrafish embryogenesis by obstructing morphogenetic movement. Biochim Biophys Acta 1840(7):2340–2350. https://doi.org/10.1016/j.bbagen.2014.04.009
104. Shaw S, Jayatilleke E, Herbert V, Colman N (1989) Cleavage of folates during ethanol metabolism. Role of acetaldehyde/xanthine oxidase-generated superoxide. Biochem J 257(1):277–280
105. Zhao R, Zhang R, Li W, Liao Y, Tang J, Miao Q, Hao W (2013) Genome-wide DNA methylation patterns in discordant sib pairs with alcohol dependence. Asia Pac Psychiatry 5(1):39–50. https://doi.org/10.1111/appy.12010