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Folate Pathways Mediating the Effects of Ethanol in Tumorigenesis

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Abstract

Folate and alcohol are dietary factors affecting the risk of cancer development in humans. The interaction between folate status and alcohol consumption in carcinogenesis involves multiple mechanisms. Alcoholism is typically associated with folate deficiency due to reduced dietary folate intake. Heavy alcohol consumption also decreases folate absorption, enhances urinary folate excretion and inhibits enzymes pivotal for one-carbon metabolism. While folate metabolism is involved in several key biochemical pathways, aberrant DNA methylation, due to the deficiency of methyl donors, is considered as a common downstream target of the folate-mediated effects of ethanol. The negative effects of low intakes of nutrients that provide dietary methyl groups, with high intakes of alcohol are additive in general. For example, low methionine, low-folate diets coupled with alcohol consumption could increase the risk for colorectal cancer in men. To counteract the negative effects of alcohol consumption, increased intake of nutrients, such as folate, providing dietary methyl groups is generally recommended. Here mechanisms involving dietary folate and folate metabolism in cancer disease, as well as links between these mechanisms and alcohol effects, are discussed. These mechanisms include direct effects on folate pathways and indirect mediation by oxidative stress, hypoxia, and microRNAs.

Keywords

folate metabolism; alcohol consumption; tumorigenesis; oxidative stress; microRNAs; folate enzymes

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

Folate and alcohol are dietary factors affecting the risk of cancer development in humans [1–4]. This conclusion is primarily based on numerous epidemiological studies; precise molecular mechanisms underlying the link between alcohol consumption or folate metabolism and cancer initiation and progression remain largely unknown. The assessment of the combined effect of these two dietary components is obviously more intricate and is a challenging task at molecular, cellular, organism and population levels [5]. The problem is exacerbated by the fact that effects of both folate intake and alcohol consumption are cancer type-specific and can be also modified by other dietary components as well as the personal genetic and epigenetic landscape [6–9]. Thus, though alcohol consumption has been investigated as a potential risk factor for numerous cancers, epidemiological studies have linked it more strongly to the increased risk of breast cancer, cancers of digestive tract and upper respiratory tract [10, 11]. Even with regard to these cancer types, the relationship between alcohol and cancer is not simple. For example, the study of 2812 breast cancer cases from the French E3N-EPIC cohort concluded that there were no association between high alcohol consumption and increased risk of breast cancer among premenopausal women but found a positive linear correlation among post-menopausal women [12]. Of note, this study also indicated that low folate intake increased alcohol-associated breast cancer risk [12]. Some reports also imply that moderate alcohol consumption could be associated with decreased cancer risk especially in the context of specific diets like Mediterranean diet [13–15]. Nevertheless, the prevalent view in the literature is that alcohol consumption is associated with the increased risk of several cancers while folate supplementation can reduce this risk [11, 16, 17]. Accordingly, this review considers potential mechanisms underlying such effects (schematically depicted in Fig. 1).

2. Role of folate in tumorigenesis and malignancy progression

Several mechanisms for ethanol's effect on carcinogenesis have been proposed, including the induction of oxidative stress, acetaldehyde-associated mutagenesis, perturbation of estrogen metabolism, and via folate metabolism (reviewed in [5, 18, 19]). Folate is an important dietary component because humans cannot synthesize it [20]. In the cell, folate functions as a coenzyme in numerous reactions of one-carbon transfer, which are required for the *de novo* purine and TMP biosynthesis, NADPH generation, and for metabolism of several amino acids, including re-methylation of homocysteine to methionine [21–23]. The latter reaction is linked to the biosynthesis of S-adenosylmethionine, the universal methyl donor involved in more than 100 methylation reactions in the cell [24]. Importantly, it has been recently reported that 5-methyltetrahydrofolate, the coenzyme remethylating homocysteine, can directly methylate mitochondrial tRNA, an important step in mitochondrial protein translation [25]. Another reaction important for the mitochondrial protein biosynthesis is the formylation of Met-tRNA by 10-formyltetrahydrofolate [21]. At a more general level, folate metabolism regulates such key biological processes as nucleic acid biosynthesis, mitochondrial protein biosynthesis, methylation of DNA, RNA, proteins and small molecules, DNA repair, and amino acid biogenesis (the role of folate in the cell is schematically depicted in Fig. 2) [21, 23, 26]. Accordingly, dietary folate deficiency or

insufficient folate intake have been associated with several diseases including neural tube defects, cardiovascular diseases and cancer [23, 27, 28].

The link between folate metabolism and the malignant transformation, as well as tumor progression, is however, not so simple though. Epidemiological studies provide ample data that dietary folate supplementation inversely correlates with the risk of several cancer types [2, 3, 29, 30]. At the same time, cancer cells critically depend on folate supplementation to support active nucleotide biosynthesis which is linked to the increased demand for nucleic acids during the period of rapid proliferation. Studies of the effect of folate on proliferation in cell culture and animal models provided experimental support for such mechanism [31–34]. The importance of folate for cancer cells provided the basis for cancer treatment using folate antimetabolites [35–38]. These compounds are structural analogs of folate but function as inhibitors of folate metabolizing enzymes. One of the first antifolates methotrexate, had been effectively used as chemotherapeutic since late 1940s while newer such drugs have been developed recently and approved for the treatment of different types of malignant tumors [36, 39]. Overall, folate has opposite effects on tumorigenesis versus the effect on cancer cell proliferation, which partially explains inconsistency of epidemiological data. To add to this complexity, the effect of folate on cancer metastasis is even less clear. For example, in *in vivo* models of tumorigenesis, folate deficiency suppressed proliferation but enhanced metastatic potential likely through the effect on epithelial-mesenchymal transition [40]. Of note, a promoting effect of folate on metastasis were also observed [33].

3. Folate transport and ethanol-induced folate deficiency

Folate was one of the factors intensively investigated with regard to the effect of alcohol consumption (reviewed in [41–43]). Studies from the early 1960s demonstrated that folate deficiency is common among alcoholics and that the positive hematopoietic response to the folate intake in these patients could be completely suppressed by excessive alcohol amounts [44, 45]. Recent studies in animals have confirmed these findings. Thus, rats subjected to chronic ethanol ingestion had decreased levels of folate in serum and red blood cells [46, 47]. Among other mechanisms, folate malabsorption could be one of the main causes of ethanol effect. Folate cannot pass through the cellular membrane on its own. Transport is carried out by three transporters, reduce folate carrier (RFC) [48, 49], proton-coupled folate transporter (PCFT) [50] and folate receptor alpha (FRα or FOLR1) [51]. PCFT and RFC are folate transporters responsible for folate uptake by enterocytes [52] so the effect of ethanol on intestinal folate absorption proceeds through regulation of these proteins [53]. Several mechanisms of such effect have been demonstrated. Ethanol decreases the expression of PCFT and RFC [54–57] most likely through the regulation of gene methylation [58]. Of note, methylation of CpG sites in genes encoding all three folate transporters has been demonstrated [59]. Chronic alcoholism can also affect the kinetics of folate absorption, which could be associated with altered lipid composition and mis-localization of transporters within specific lipid domains in the plasma membrane [46, 60]. Renal excretion is also one of the major factors contributing to ethanol-induced folate deficiency, due to reduced re-uptake of folate by kidneys caused by decreased expression of RFC and FRa [61, 62]. All three folate transporters are abundantly expressed in cancer cells [63, 64]. The effect of ethanol on the folate uptake by tumors is not clear though it has been reported that lower

expression of FRα in pancreatic ductal adenocarcinoma was associated with alcohol consumption [65]. Interestingly, in this study, high FRα expression in surgically removed tumors was significantly associated with favorable prognosis. The mechanism of such effect is not clear, and in many cases the opposite phenomenon, a beneficial effect of the FRα overexpression on cancer development was reported [64].

4. Folate degradation

Reduced folates are unstable *in vitro* and rapidly undergo oxidative degradation but they are protected from degradation in the cell through binding to numerous folate enzymes [66]. Despite of such protection, *in vivo* folate catabolism is an active process [67–70]. The degradation of folate can be non-enzymatic but is also catalyzed by ferritin [71]. As alcohol consumption induces folate deficiency, the question has been asked of whether ethanol contributes to enhanced folate catabolism [72]. In fact, it has been shown that *in vitro* ethanol metabolism can induce folate degradation [73]. Major enzymatic pathways of ethanol metabolism via catalase, alcohol dehydrogenase or CYP450 lead to the formation of acetaldehyde, which is further metabolized to acetate by several aldehyde dehydrogenases [74, 75]. The oxidation of acetaldehyde can also occur in the reaction catalyzed the ubiquitous enzyme xanthine oxidase, which produces superoxide radicals [73]. Superoxide radicals in turn cause cleavage of folates with 5-methyltetrahydrofolate being much more susceptible to this degradation than folic acid [73].

While it is not clear whether this mechanism takes place in vivo, it has been recently shown that spontaneous folate decomposition produces formaldehyde, a cytotoxic metabolite which can damage DNA [76]. Formaldehyde is converted to formic acid by a pathway including as an intermediate step the catalysis by the alcohol dehydrogenase 5 (ADH5) enzyme [77]. Interestingly, it has been shown that ethanol exposure of zebrafish embryos reduces ADH5 mRNA [78]. Of note, the final step of formaldehyde detoxification in the proposed mechanism, which is the clearance of formic acid, requires tetrahydrofolate [76]. In fact, this folate-dependent pathway is the main mechanism of formate clearance and methanol detoxification in humans, and it requires two folate metabolizing enzymes, MTHFD1 and ALDH1L1 [79, 80]. Another recent report underscored the enhanced folate degradation associated with the accumulation of specific reduced folate, THF, in the cytosol [81]. This study also highlighted the role of folate metabolizing enzyme ALDH1L1 in the prevention of THF degradation. The binding of THF was proposed as a likely mechanism for such protection. 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 [82, 83]. Interestingly, ALDH1L1 is one of the most down-regulated proteins in several cancers and it has been suggested as putative tumor suppressor (reviewed in [84]).

5. Effect of ethanol on folate metabolizing enzymes

Reactions constituting folate metabolism are carried out by about two dozen of specific enzymes [21]. The functions of many of these enzymes have been linked to tumorigenesis and malignancy progression [20, 84–86]. Several of these enzymes are well-known targets

of ethanol [42]. Thus, ethanol has been shown to produce inhibitory effect on the activities of MTHFR and MTR in an animal model [87]. This mechanism can contribute to carcinogenesis by affecting the liver S-adenosylmethionine pool thus altering methylation capacity of the cell [88]. Ethanol also decreases thymidylate synthase mRNA levels in regenerating liver after partial hepatectomy [89], which could inhibit DNA biosynthesis and diminish the DNA repair capability. Two folate enzymes involved in the metabolism of 10-formyltetrahydrofolate, ALDH1L1 and ALDH1L2, were also investigated as targets of ethanol and in response mechanisms to alcohol consumption (reviewed recently in [42]). An OMICS-type study has also reported that prenatal ethanol exposure of mouse embryos leads to the decreased DHFR expression [90]. Though the mechanism of this effect is not clear, it could have a far-reaching effect on carcinogenesis since DHFR is a key enzyme incorporating dietary folic acid into the reduced folate pool [91, 92]. FPGS, the enzymes conjugating folate to glutamate, was downregulated in the intestine and kidney of rats fed ethanol for 3 month [58]. This effect was likely the result of the *FPGS* gene hypermethylation, observed in this study. The FPGS-catalyzed reaction is crucial for folate retention inside the cell and the loss of the enzyme in mice is embryonically lethal [93]. Therefore, the decrease of FPGS activity in response to alcohol consumption could be a contributor to folate-mediated ethanol toxicity and a factor playing a role in carcinogenesis.

Folate-metabolizing enzymes themselves could also mediate effects of ethanol on the cell. In support of this notion, studies indicated that single nucleotide polymorphisms in enzymes of folate pathways could modify cancer risk associated with alcohol consumption [94–99]. Several studies demonstrated, in a more direct way, that enzymes of folate metabolism are involved in cellular response to the ethanol exposure. For example, in a zebrafish model, exposure of embryos to ethanol led to the up-regulation of ALDH1L1 (10-formyltetrahydrofolate dehydrogenase), which alleviated ethanol-induced oxidative stress [83]. In another study, mice with mild MTHFR deficiency (heterozygous disruption of *Mthfr* mimicking the *Mthfr* 677C→T SNP in humans [100]) had lower capacity to repair DNA and displayed more neuronal damage in the brain in response to the ethanol feeding [101]. Paradoxically, the *MTHFR* 677TT genotype has been shown to play a protective role against alcohol dependence [102]. Furthermore, subjects with the *MTHFR* 677TT genotype constituted a subgroup of alcoholic patients with a decreased risk for developing hepatic toxicity [102]. Overall, the mechanistic studies on the interaction between ethanol and folate enzyme are limited.

6. Molecular mechanisms underlying effects of ethanol on folate homeostasis

The interaction between alcohol consumption and dietary folate intake is relevant not only to cancer but also to liver diseases and disorders of embryonic development. Indeed, studies in micropigs have shown that folate deficiency enhances perturbations in hepatic methionine metabolism, decreases S-adenosylmethionine and glutathione, and increases DNA damage and lipid oxidation while promoting alcoholic liver injury [103, 104]. As well, both alcohol consumption and dietary folate deficiency have a teratogenic effect. Dietary folate deficiency has long been known as a cause of neural tube defects (NTDs) with most common such

defect being spina bifida [105]. For the reason of the NTDs prevention, in 1996 the FDA mandated the supplementation of grain foods in the US with the synthetic form of the vitamin, folic acid. Prenatal exposure to maternal consumption of the ethanol is a common cause of developmental abnormalities, known as fetal alcohol spectrum disorder (FASD), associated with neurological, behavioral, and cognitive deficits [106–108]. In general, there are many common mechanisms regulating embryonic development and tumorigenesis [109–112]. For example, FASD are linked to an impaired immune system which consequently leads to an elevated risk of cancer and other diseases [113]. It has been recently shown that the transcriptional repressor Snai2, which is involved in the induction of epithelial-mesenchymal transition in cancer and development, is deregulated in response to ethanol thus causing apoptosis in avian neural crest progenitors [114]. Of note, folate metabolism is also involved in the regulation of proliferation, apoptosis and epithelial-mesenchymal transition [33, 81, 115–117]. Furthermore, DNA methylation, which is intrinsically linked to folate metabolism and plays roles in the regulation of embryonic development and in tumorigenesis, is also deregulated by alcohol [88, 118–123]. Thus, analysis of cellular responses to ethanol and folate in developmental processes can provide clues for mechanistic links between these nutrients and the malignant transformation. Several examples of such links are discussed below.

Exposure to ethanol produces a pleiotropic effect on the cell with alcohol consumption causing genetic abnormalities, epigenetic dysregulation, induction of cell signaling, and metabolic abnormalities, global events activating whole arrays of downstream cellular responses [5]. In support of such a wide-spread effect, OMICs studies have shown that exposure to ethanol causes dramatic alterations in the overall gene expression [124–128]. Interestingly, in one of these studies, a significant number of affected targets were ribosomal genes [124]. Inactivating or deleterious mutations of some of these genes cause Diamond-Blackfan anemia, which are conditions characterized by macrocytic anemia and cancer predisposition, and representative of a class of disorders known as ribosomopathies [129]. Importantly, it has been recently reported that ribosomal proteins are commonly deleted in human cancers and that this phenomenon is often associated with p53 mutations [130]. One of the ribosomal proteins involved in the response to ethanol was rps3a [90, 124]. Curiously, this protein physically interacts with mitochondrial folate metabolizing enzymes, MTHFD2 [131]. While this enzyme is a resident of mitochondria, it can translocate to the nucleus which is likely a mechanism for the regulation of cellular proliferation [132]. In fact, numerous reports linked MTHFD2 expression to enhanced cellular proliferation and highlighted upregulation of the enzyme as a cancer trait [132–138]. These findings raise the question of whether MTHFD2 could be a mediator of the effect of alcohol consumption on malignant transformation or progression of initiated cells.

7. microRNA link between alcohol consumption and dietary folate

Alcohol consumption was also investigated with regard to the role of microRNAs (miRNAs) in the teratogenic, liver damaging and carcinogenic effects of ethanol (reviewed in [139–142]). miRNAs, a diverse class of highly conserved small non-coding RNAs that regulate gene expression, play important role in malignant tumor initiation and in metastasis [143–145]. A recent analysis of RNA-Seq paired-end dataset derived from alcohol-exposed neural

fold-stage chick crania suggested that miRNAs significantly contribute to gene expression in response to ethanol [127]. Certain dietary components, including folate, can impact tumorigenesis and cancer progression by modulating tissue levels of miRNAs [146]. A growing body of evidence links folate status to the regulation of a large number of miRNAs but also identifies a reverse effect - the regulation of folate metabolizing enzymes by miRNAs (reviewed in [147, 148]). One of the early reports demonstrated that folate deficiency leads to a pronounced but reversible global increase in miRNA expression in human lymphoblastoid cells [149]. In another study, deregulation of miR-122, −23 and −130 was observed in hepatocellular carcinomas developed in rats kept on the folate- and methyl-deficient diet [150]. It has been further shown that miR-122 is significantly downregulated in human primary hepatocellular carcinomas [150]. Interestingly, in a recent study miR-122 protected from ethanol-induced liver disease [151]. Thus, the regulation of miR-122 can be a point of crosstalk between ethanol and folate. Cross-reference of miRNA responding to both the folate status [147] and alcohol consumption or *in vitro* ethanol exposure identified several potential links including miR-21 [152–156], miR-222 [149, 157, 158] and miR- 34a [159–161] all of which were implemented in cancer disease [162–164].

While numerous reports link folate and ethanol to the regulation of microRNAs, it is not clear yet how the cross-talk between these dietary components regulates progression of known pathologies. One study that linked ethanol-induced birth defects to the up-regulation of miR-10a/miR-10b and associated down-regulation of transcription factor Hoxa1 also demonstrated that folic acid prevented ethanol-induced miR-10a elevation and reduced developmental abnormalities [165]. Of note, miR-10a could also have a role in carcinogenesis [166]. For example, levels of miR-10a/b were significantly increased in peripheral blood mononuclear cells derived from patients with acute myeloid leukemia compared with cells derived from healthy donors [167]. Furthermore, miR-10a/b expression promoted proliferation and inhibited differentiation of HL-60 cells [167]. miR-10 was also suggested as an oncogene involved in breast cancer initiation and progression, with one of the downstream mechanisms being modulation of *HOXA1* gene expression [168]. Another mechanism of miR-10b in tumor promotion is associated with Rho GTPase up-regulation leading to Rho-kinase-associated cytoskeleton activation and enhanced tumor cell invasion [169, 170]. In this regard, the role of folate in metastasis promotion through the activation of Rho GTPase-dependent cytoskeleton rearrangement has been reported [33, 171].

8. Folate, ethanol and oxidative stress

Folate can alleviate oxidative stress [172, 173] while ethanol is a known inducer of such stress [174–176]. Ethanol metabolism generates reactive oxygen species and depletes the antioxidant molecule glutathione (GSH) which leads to oxidative stress and lipid and protein damage and then to growth retardation and neurotoxicity [177, 178]. The relationship between alcohol consumption and folate intake is a two-way street: ethanol can decrease folate-dependent antioxidative capacity while folate can alleviate ethanol-induced oxidative stress [177, 179]. In support of this notion, it has been reported that folic acid protects offspring against oxidative stress in the case of ethanol feeding to pregnant rats [180]. The effect of folate in this study was observed in liver and pancreas and was attributed to either the direct quenching of reactive oxygen species or scavenging capacity toward acetaldehyde.

These findings are especially important taking into consideration that prenatal folate supplementation can affect the cancer risk later in life [181–186]. While in fact the scavenging behavior of folate *in vitro* has been reported [187], it is unclear whether the direct reduction of reactive oxygen species by folate takes place *in vivo* [172]. Instead, the antioxidant effect of folate *in vivo* is primarily associated with the ability to lower Hcy and thus to alleviate hyperhomocysteinemia-induced effects [188, 189]. It has been shown that folic acid supplementation attenuates xanthine oxidase activity, restores SOD activity and effectively antagonizes oxidative stress in the kidneys of hyperhomocysteinemic rats [190]. In *in vitro* experiments in this study, incubation of tubular cells with 5-methyltetrahydrofolate abolished Hcy-induced NADPH oxidase activation and reduced the intracellular level of superoxide anion, and also reduced the mRNA levels of NOX4 and $p22^{phox}$ [190]. Of note, the study indicated that the folate effect on oxidative stress can either be associated with Hcy re-methylation or proceed through Hcy-independent mechanisms.

Alcohol consumption has been linked to the induction of hypoxia [191, 192], a state leading to increased generation of reactive oxygen species [193]. Several reports have also addressed the effect of folate on hypoxia. Thus, folic acid has been shown to protect cultured endothelial cells from hypoxia by decreasing both ROS levels and apoptosis linked to the ERK1/2 and NOX4 pathways [194]. The protective mechanism of folate in hypoxia is primarily associated with the induction of nitric oxide production by endothelial NO synthase (eNOS) [195]. This mechanism is linked to the upregulation of DHFR in response to folate administration, which enhances BH4 recycling thus promoting eNOS recoupling [196, 197]. Since eNOS uncoupling is linked to cardiopulmonary disorders [198], the eNOS-related mechanism of folate was mainly investigated in endothelial cells as a potential therapeutic approach to prevent cardiovascular disease [195]. However, solid malignant tumors typically grow under hypoxic conditions and to survive and proliferate in a hypoxic environment, cancer cells undergo genetic and adaptive changes that contribute to the malignant phenotype and to aggressive tumor behavior [199–203]. Interestingly, it has been shown that ubiquitously expressed folate enzymes are downregulated under severe hypoxia [204], which suggests folate metabolism as one of the components of such adaptive response. In support of the role of folate pathways in this response, the suppression of MTHFD2 folate enzyme disturbs NADPH and redox homeostasis and accelerates cell death under hypoxia-induced oxidative stress [205]. Furthermore, it has been recently shown that folic acid supplementation represses hypoxia- induced inflammatory response in promyelomonocytic cells via the elimination of ROS and inhibition of the JAK2/STAT3/NF-κB pathway [206].

9. Summary

Mountains of literature link alcohol consumption and folate intake to the risk of cancer development. While alcohol consumption has positive correlation with the risk of several types of cancer, numerous studies support the idea that increased dietary folate has inverse correlation with tumorigenesis. However, precise molecular mechanisms underlying the effects of ethanol and folate in this respect are diverse and not completely understood. Several of these mechanisms involve the effect of ethanol on folate metabolism and it is likely that ethanol-induced folate deficiency contributes to tumorigenesis. The obvious

conclusion here would be that increased folate intake could alleviate effects of alcohol, and numerous studies support such a connection. Ethanol produces folate-dependent as well as folate independent effects, and there are also some cellular nodes which are targeted by both ethanol and folate independently. Thus, the overall response to the combined effect of ethanol and folate will create an intricate circuit, the outcomes of with will further depend on other dietary components, genetic and epigenetic modalities, the sites of interaction, and numerous other factors. It should be also emphasized that the effect of both these dietary constituents is likely different in tumor initiation versus tumor progression and metastasis [19, 20, 207–209]. The role of ethanol and folate in tumor progression and metastasis, however, is much less investigated and awaits future studies.

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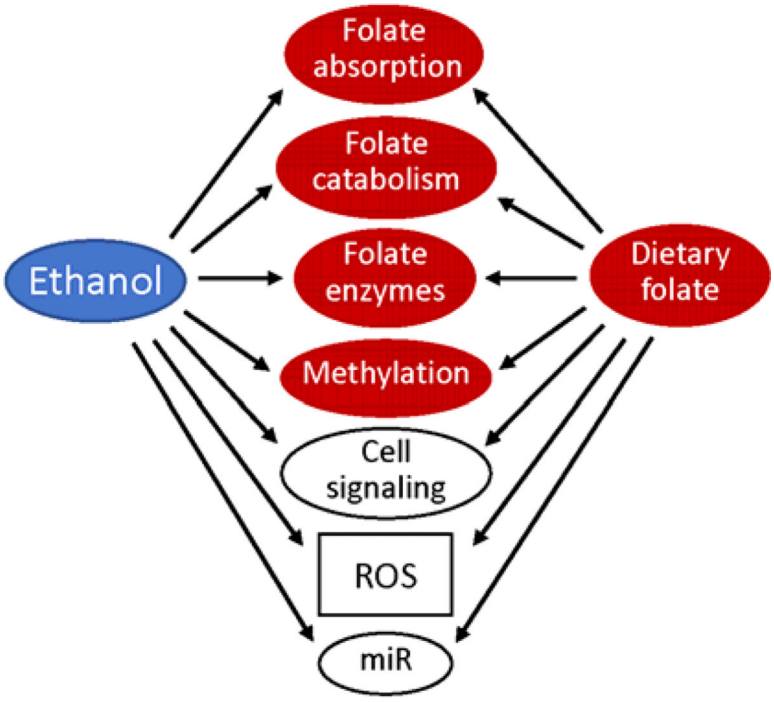

Fig. 1.

Ethanol suppresses key biological processes directly relevant to folate metabolism *(red shapes*); this effect can be alleviated by dietary folate. Several pathways outside of folate metabolism are affected by both ethanol and folate *(open shapes).*

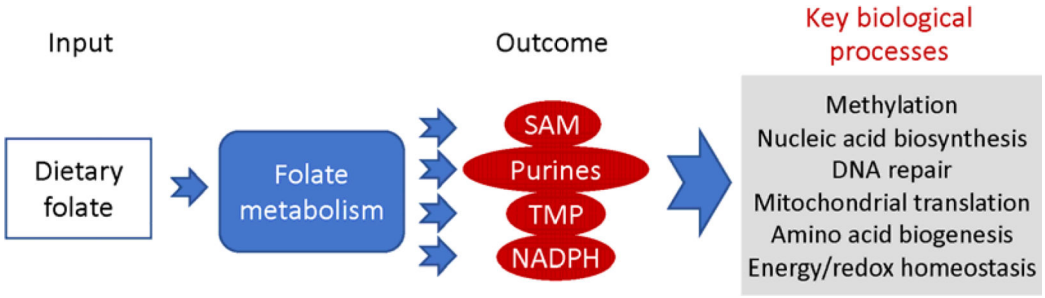

Fig. 2.

Role of folate in the cell. Folate taken up from the diet *(Input)* functions as a coenzyme in reactions of one-carbon transfer *(Folate metabolism).* These reactions are important for the biosynthesis of several essential molecules *(Outcome),* which are required for key biological processes.