
Review

Biochemical mechanisms associating alcohol use disorders with cancers.

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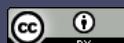
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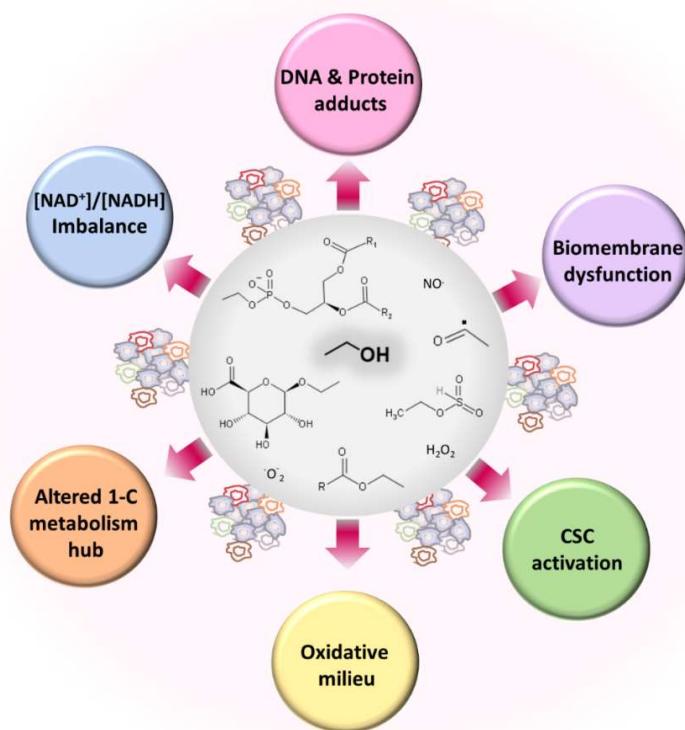
Simple Summary: Of all deaths yearly attributable to alcohol consumption globally, approximately 12 % are due to cancers, representing approximately 0,4 million deceased individuals. Ethanol metabolism disturbs cell biochemistry by targeting the structure and function of essential biomolecules (proteins, nucleic acids, lipids) and provoking alterations in cell programming that lead to cancer development and cancer malignancy. A better understanding of the metabolic and cell signaling realm affected by ethanol is paramount to design effective treatments and preventive actions tailored to specific neoplasias.

Abstract: The World Health Organization identifies alcohol as a cause in several neoplasias of the oropharynx cavity, esophagus, gastrointestinal tract, larynx, liver, or female breast. This study reviews ethanol's nonoxidative and oxidative metabolism and one-carbon metabolism that encompasses both redox and transfer reactions that influence crucial cell proliferation machinery. Ethanol favors the uncontrolled production and action of free radicals that interfere with the maintenance of essential cellular functions. We focus on the generation of protein, DNA, and lipid adducts that interfere with the cellular processes related to growth and differentiation. Ethanol's effects on stem cells responsible for building and repairing tissues are reviewed. Cancer stem cells (CSC) of different origins suffer disturbances related to the expression of cell surface markers, enzymes, and transcription factors after ethanol exposure with consequent dysregulation of mechanisms related to cancer metastasis or resistance to treatments. Our analysis aims to underlie and discuss potential targets that show more sensitivity to ethanol's action and identify specific metabolic routes and metabolic realms that may be corrected to recover metabolic homeostasis after pharmacological intervention. Specifically, research should pay attention to reestablish metabolic fluxes by fine-tuning the functioning of specific pathways related to one-carbon metabolism and antioxidant processes.

Keywords: alcohol use disorders (AUD); cancer, ethanol oxidative and nonoxidative metabolism, acetaldehyde, reactive oxygen species (ROS), DNA adducts, protein damage, cancer stem cells (CSC), epigenetic changes.



Graphical abstract



1. Introduction

Alcohol Use Disorders (AUDs) are chronic diseases where imbibers show compulsive alcohol seeking and drinking behavior accompanied by negative emotional states occurring during abstinence periods. The DSM-5 (Diagnostic and Statistical Manual of mental disorders, fifth edition) establishes that this diagnosis should meet specific criteria [1]. Excessive alcohol drinking causes diseases and incapacities. The World Health Organization (WHO) reports that harmful alcohol drinking is responsible for around 3 million deaths yearly and globally. Moreover, ethanol is to blame for approximately 133 million disability-adjusted life years (DALYs), including premature mortality and morbidity [2]. In 2016, of all deaths attributable to alcohol consumption globally, 12.6% were due to cancers, representing approximately 0.4 million deceased individuals.

Furthermore, of the 244 million DALYs attributed to malignant neoplasms, 10.3 million corresponded to cancers attributable to alcohol use [2]. AUDs have a start pattern of binge consumption. After chronic and intense abuse, the brain's reward and stress control systems malfunction, withdrawal, negative emotions, and craving behavior appear. The brain uses its neurochemical circuitry to adapt and tackle the presence of alcohol [3-6].

Influential work by Hanahan and Weinberg [7, 8] establishes a conceptual configuration to understand cancer development by defining different hallmarks, for example, induction of angiogenesis, invasion, and metastasis, resistance to cell death, changes in metabolism, or evasion of immune attack. Alcohol abuse in humans may disturb genetic stability and induce inflammation events that eventually promote cancer in different forms and locations.

This review describes possible mechanisms linking ethanol ingestion with cancer development in different tissues. It analyzes ethanol effects from its entrance through the digestive tube to its metabolism and its influence on the intermediary and one-carbon units' metabolisms. Also, it evaluates the implication of genetic variants of essential enzymes and other proteins on the damaging action of ethanol. Another section focuses on the generation of protein, lipid, and DNA addition compounds, in the presence of acetaldehyde and other oxidative metabolites to ascertain their impact on cancer development. The last section analyzes how ethanol may alter stem cell capabilities in repairing cells and tissues and turn into uncontrolled proliferative pathways. All the molecular changes induced by ethanol on different targets may trigger cancer development, cancer progression, and treatment resistance. Identifying relevant proteinaceous and non-proteinaceous targets will lead to pharmacological interventions to ameliorate or impede the progression of malignant events where harmful alcohol drinking plays a decisive.

2. The route of alcohol through the gastrointestinal tract in humans.

The dominant alcohol component of alcoholic beverages is usually ethyl alcohol. Besides, beverages contain other alcohols (such as methanol or 1-propanol) and non-alcoholic congeners (for example, acetone, tannins, resveratrol) present in different amounts in recorded and unrecorded alcoholic preparations with potential benefit or trouble locally and after metabolic transformation. The accompanying substances may exert a co-adjuvant or independent role of alcohol itself [9-11]. The heterogeneous compositions of alcoholic drinks add complexity to study effects in human health only attributable to ethanol.

Alcohol enters the oral cavity and descends through the esophagus and the gastrointestinal tract contacting gut epithelia and microbiomes before reaching cells in all organs and tissues. It exerts an irritant effect on the mucosa, and resident microorganisms absorb and metabolize the substance with consequences *in situ* and systemically [12]. In oral human carcinoma samples, Marttila et al. show an increase in the expression of mutated tumor suppressor P53 associated with augmented acetaldehyde production by the microbiome [13]. Alcohol and tobacco alter the composition of the commensal and pathogenic microbiome resident in the oral cavity and gastrointestinal tract, contributing to cancer [14]. Besides, ethanol and its metabolites and the imbalance of the microbiome

populations may affect gut permeability, permitting the pass of bacterial metabolites and endotoxins to the general circulation and inducing inflammation locally and in distant organs [15]. As a representative example, *Fusobacterium nucleatum*, a bacteria resident in the oral cavity, secretes immune modulators, virulence factors, and microRNAs linked to the initiation and progression of the oral cavity [16, 17], esophagus [18], or colorectal [19, 20], cancer. In biopsies from patients suffering colorectal cancer, the expanded bacteria population significantly correlated with alcohol consumption [20]. *F. nucleatum* may also influence tumor growth and metastatic progression in tissues outside the gut, such as the breast. In an *in vivo* experiment, mice inoculated with lectin Fap-2 expressing *F. nucleatum* colonize mammary tumors and promote growth and metastasis by blocking the buildup of T cells. The observed effect disappears with antibiotics [21].

The relationship between heavy episodic alcohol drinking (HED) and cancer development depends on covariates (age, diet, smoking, genetic background, environmental conditions, nutrition state, exercise routine, microbiome, microenvironment), and different mechanisms may confound the impact of a single factor [22-27]. The difficulties pile up due to the apparent restrictions of experiments on humans. Untangling biochemical routes directly compromised by alcohol and its metabolites is necessary for effective prevention and therapy endeavors. Epidemiological and data mining studies and animal experiments are also valuable to the purpose [27-30].

3. Ethanol induces metabolic alterations that may cause or facilitate cancer development

One link that associates chronic alcohol consumption with cancer development is the formation of metabolic products that may induce direct cell dysfunction or cell damage. On the other hand, the metabolic transformation of ethanol stresses many metabolic pathways that, in turn, may lead to metabolic deficiencies with consequent harmful effects. Next, we review ethanol's metabolic pathways, emphasizing its metabolites' role in altering cell function causing cancer.

3.1. Oxidative and nonoxidative metabolism of ethanol

The ingestion of ethanol activates metabolic pathways that move electrons across metabolites (oxidative metabolism) or incorporate ethyl alcohol into other chemical structures (nonoxidative metabolism). Figure 1 shows the principal pathways of ethanol metabolism in humans. Due to the low lipid: water partition coefficient of ethanol and its capacity to passively diffuse through biological membranes (determined by the concentration gradient), it reaches an equilibrium concentration influenced by the tissues' water content, the mass, and the blood flux supply [31].

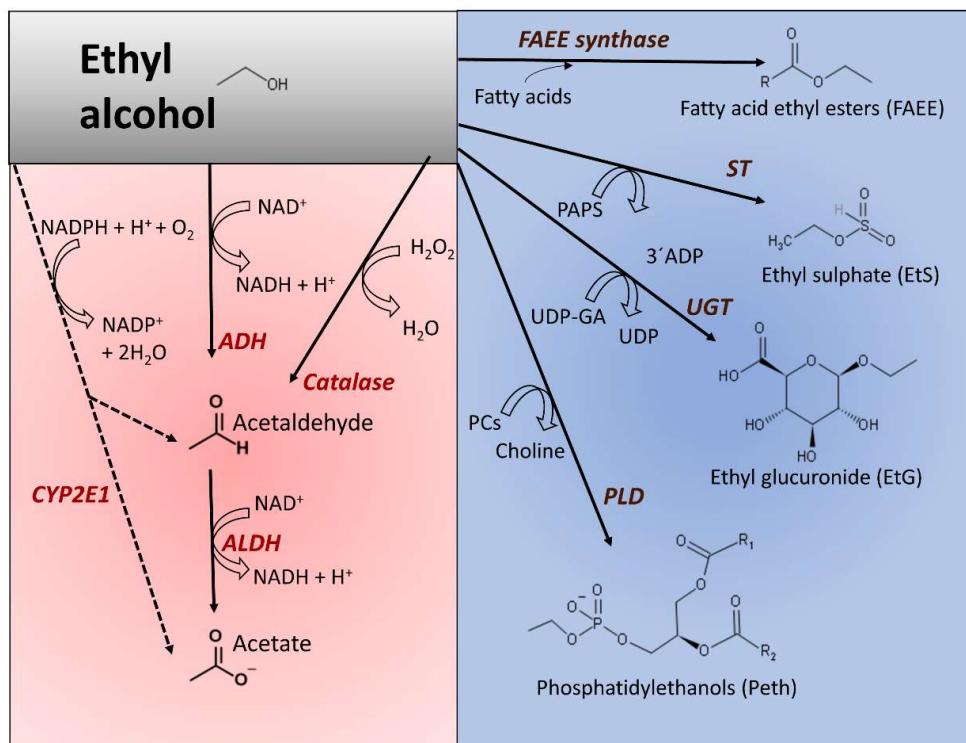


Figure 1. Schematic representation of ethanol oxidative (pink area) and nonoxidative (blue area) metabolism, including metabolites, principal enzymes catalyzing the transformations, and essential coenzymes. ADH (alcohol dehydrogenase, EC 1.1.1.1); ALDH (aldehyde dehydrogenase 2, EC 1.2.1.3); CYP2E11 (cytochrome P450 2E1, EC 1.14.14.1); FAEE synthase (fatty acid ethyl ester synthase, EC 3.1.1.67); PLD (phospholipase D, EC 3.1.1.4); UGT (UDP-glucuronyl transferase, EC 2.4.1.17); ST (sulfotransferase, EC 2.8.2.2); PCs (phosphatidylcholines); PAPS (3' phosphoadenosine 5'phosphosulphate); UDP-GA (uridine diphosphate-glucuronic acid); NAD⁺ (an oxidized form of nicotinamide adenine dinucleotide); NADH (a reduced form of nicotinamide adenine dinucleotide); NADP (an oxidized form of nicotine adenine dinucleotide phosphate); NADPH (a reduced form of nicotine adenine dinucleotide phosphate). Ethanol is oxidized to acetaldehyde by the action of different enzymes. Acetaldehyde is oxidized to acetate by ALDH2 mainly. The dashed arrows indicate that CYP2E1 also oxidizes acetaldehyde to acetate. Some of the reactions shown are reversible *in vitro*; however, we emphasize the movement of *in vivo* ethanol's metabolic transformation [31-47].

Oxidative metabolism of ethanol predominates over nonoxidative conversions. Ethanol oxidizes to acetate in a two-step process sequentially catalyzed by alcohol dehydrogenase (ADH, EC 1.1.1.1) and aldehyde dehydrogenase (ALDH, EC 1.2.1.3). The final product is acetate (Figure 1). The main enzyme responsible for converting ethanol into acetaldehyde is ADH. The reaction uses NAD⁺ as a coenzyme that reduces to NADH, while ethanol oxidizes to acetaldehyde. ADH is widely present in nature, from bacteria and thermophilic archaea [48] to eukaryote [49]. In mammals, ADH is a family of cytosolic enzymes that shows broad substrate specificity and is present in many tissues [50]. The

reaction catalyzed by mammalian ADH requires zinc to stabilize the enzyme's active center's essential amino acid residues. Once ingested, gastric ADH oxidizes some alcohol and, depending on several factors (sex, enzyme variants, empty stomach, or accompanying medication), the proportion of alcohol oxidized may vary. From the stomach and the small intestine, alcohol is absorbed into the blood and distributed into different tissues. The oxidation of ethanol to produce acetaldehyde occurs mainly in hepatocytes. The reaction consumes the redox coenzyme NAD⁺ and therefore, the NADH/NAD⁺ proportion increases.

The fraction of acetaldehyde obtained by other enzymes' catalytic activity, namely catalase (EC 1.11.1.21) and CYP2E1 (cytochrome P450 2E1, EC 1.14.14.1), represents a small fraction of the total. Catalase is a peroxidase that works in the presence of hydrogen peroxide and ethanol to give acetaldehyde and water (Figure 1). Although this heme-containing enzyme is present in many tissues, it does not represent the main route for alcohol elimination [51, 52]; however, its role in brain tissue is quite relevant [47]. CYP2E1 belongs to the MEOS (microsomal ethanol oxidizing system) [53]. It also localizes in mitochondria [35]. Where oxygen is present, the enzyme oxidizes ethanol to acetaldehyde and reduces oxygen to water [53]. CYP2E1 has a heme pocket whose polarity plays an essential role in its mechanistic adaptation to oxidate alcohol when the concentration increases [54]. The catalytic efficiency of CYP2E1 is very low, showing a higher value for Km compared with ADH. This enzyme also acts on other xenobiotic chemicals, such as anesthetics and halogenated hydrocarbons [55, 56]. Besides, CYP2E1 oxidizes acetaldehyde to acetate with a greater kcat/Km value than the observed in ethanol's oxidation to acetaldehyde [57]. One consequence of the activation of CYP2E1 by ethanol is the accelerated retinol inactivation, eventually affecting cell proliferation [58].

Two molibdo-flavoproteins, xanthine oxidoreductase (EC 1.17.3.2) and aldehyde oxidase (EC 1.2.3.1) may also oxidize acetaldehyde and propagate reactive oxygen species [59].

Acetaldehyde rapidly converts into acetate, where active ALDH is available. This reaction also reduces NAD⁺ to NADH and increases the index NADH/NAD⁺ (Figure 1). Human ALDHs are a family of enzymes with different preferred substrates and subcellular locations [60]. The isozyme ALDH2 is abundant in liver cells, localizes in mitochondria, and is responsible for acetaldehyde oxidation with a Km value in the lower micromolar range [34]. Besides its contribution to ethanol removal, ALDH2 also participates in other detoxifying pathways, including eliminating endogenous aldehydes and other metabolites [60, 61]. The liver feeds the acetate to other tissues, where it converts to acetyl-CoA, which eventually fully oxidates to carbon dioxide through the citric acid cycle.

Acetaldehyde is not only a metabolite of alcohol oxidation but is also present in alcoholic beverages, viands, and tobacco smoke and is also a chemical resulting from alcoholic fermentation [62]. Its electrophilic character facilitates reactions with different molecules to give adducts or secondary products such as salsolinol when condensates with dopamine [63] (Figure 2). Salsolinol may cause DNA damage through reactive oxygen species [64]. The formation of protein adducts by acetaldehyde reacting with amino groups (for example, ε-amino groups of Lysine residues) and forming Schiff bases alters many proteins' structures and functions, including histones of the nucleosome core [65]. Acetaldehyde also interferes with retinoic acid metabolism and disrupts retinoic acid signaling with consequent alteration of gene expression and cell differentiation processes [66, 67]. Acetaldehyde may form DNA adducts that impair proper DNA function if not eliminated or repaired [68-70] (Figure 2). *In vitro* studies with human lung, fibroblasts indicate that acetaldehyde induces clastogenic effects with detected DNA breaks at telomeric regions, arresting cells at the G2/M phase and negatively affecting cell viability [71]. The increase of acetate units resulting from ethanol's active oxidative metabolism, accompanied by food intake restriction, depleted glycogen reserves, and increased NADH concentrations, favors ketone bodies' synthesis from acetate.

Acetaldehyde depletes GSH (glutathione) and hence intracellular redox eucrasia. Different mechanisms may participate: sequestering of GSH pools by non-enzymatic

binding [72], reduction of GSH peroxidase (EC 1.11.1.9) activity [73], conjugation with GSH metabolites such as cysteinyl glycine [74, 75], or disruption of the transsulfuration pathway [76]. However, in a murine experimental model of forced GSH depletion obtained by disrupting a glutamate-cysteine ligase modifier (GCLM) gene, Chen et al. [77] showed that low levels of GSH protected liver tissue against the insult of ethanol by adapting the metabolic flux of several compounds to resist alcohol insult. Hence, the availability of GSH needs precise modulation to attend to volatile metabolic environments.

Among the agents classified by the IARC (International Agency for Research of Cancer), monographs, ethanol, and acetaldehyde appear in group 1 (carcinogenic to humans) [78].

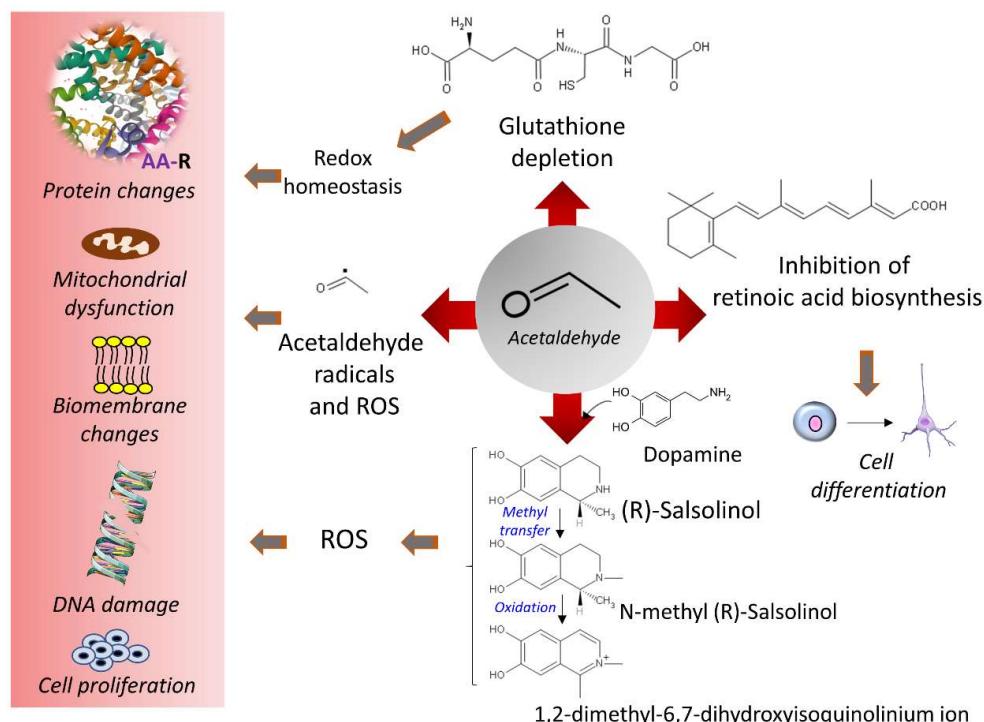


Figure 2. Mechanisms of acetaldehyde cell damage. Due to its reactivity, acetaldehyde covalently alters lipids, DNA, and proteins (for example, histones) by forming adducts. Subsequently, protein damage and DNA damage occur. Also, acetaldehyde interferes with the metabolism of other compounds such as retinoic acid, hampering cell differentiation. It facilitates the formation of toxic metabolites, including salsolinol and its products, that may damage DNA structure by forming ROS (reactive oxygen species). The figure includes representations of a human nucleosome (Protein data bank, code 3AFA). Pyramidal cell drawing: doi.org/10.5281/zenodo.3926221 and DNA representation: doi.org/10.5281/zenodo.4012404. [59, 62-67, 79-85].

Several enzymes catalyze ethanol's nonoxidative incorporation into different molecules, including glucuronic acid, sulfate, phosphatidylcholine, or fatty acids (Figure 1, blue color panel). These reactions quantitatively represent a minority compared to the oxidative pathways but may have pathological significance due to the modification of metabolism homeostasis [37]. Furthermore, these alcohol metabolites' determination in different tissues may help ascertain alcohol consumption and unveil unreported alcohol drinking [86].

A transphosphatidylation reaction, prevailing over a hydrolytic activity, uses phospholipids, preferentially phosphatidylcholine, and ethanol to give phosphatidyl ethanol (Peth). The phospholipid forms after alcohol exposure [33, 36] by the intervention of

phospholipase D (PLD, EC 3.1.4.4) [36, 39]. Consequently, Peth, an anionic phospholipid, interferes with phosphatidic acid (PA) synthesis, and its buildup in cell membranes induces changes that may affect membrane-bonded events (cell adhesion, cell signaling, cell trafficking, or cell proliferation) [87, 88].

Enzymatic esterification of ethanol and fatty acids generates fatty acid ethyl esters (FAEE) in different tissues after alcohol exposure [46, 89]. Two catalysts participate in this synthesis: FAEE synthase (EC 3.1.1.67) conjugates ethanol with free fatty acids, and AEAT (acyl-CoA ethanol-O-acyltransferase, EC 2.3.1.84) esterifies acyl chains from acyl-CoA to ethanol [40, 89, 90]. CEL's (carboxyl ester lipase, EC 3.1.1.3) acting on triglycerides and ethanol is another source of FAEE following an "ethanolysis" (instead of hydrolysis) reaction mechanism [41, 42]. In tissues where the oxidative capacity is scarce, the formation of nonoxidative products, including FAEE, can be relevant, as it may amass in mitochondrial membranes and alter their function [91]. Accumulation of FAEE may also change the activity of key enzyme activities. For example, although it may not appear as the only mechanism, it disrupts the work of adenosine monophosphate-activated protein kinase (AMPK α), a sensor, and a keeper of energy equilibrium [92]. In human pancreatic acinar cells, FAEE leads to a deterioration of cell bioenergetics and causes cell damage since the activation of AMPK α with AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) attenuated FAEE formation and improved mitochondrial bioenergetics, and alleviated inflammatory responses [93].

Broadly expressed UDP-glucuronosyltransferases (EC 2.4.1.17) catalyze the conjugation of ethanol with glucuronic acid by using 5'-uridine diphosphate (5'-UDP-glucuronic acid) as substrate donor to generate ethyl glucuronide (EtG) as an endproduct [94]. Sulfotransferases (ST, EC 2.8.2.2) activate the sulfonation of ethanol with PAPS (3'-phospho-adenosine-5'-phosphosulfate) to give ethyl sulfate [95]. Some reports establish a putative biological role of EtG and other glucuronide conjugates in the activation of Toll-like receptor proteins [38] or the *in vitro* association of EtG with increased oxidant stress in red blood cells ([96]. However, we lack *in vivo* evidence that both chemicals may have salient biological significance [37]. Because they are water-soluble excretion metabolites, they may serve as biomarkers of alcohol consumption and abstinence vigilance due to their detection after ethanol blood concentrations reach zero value [43, 97, 98].

3.2. Imbalanced proportion [free NAD $^+$]/[free NADH]

Tunneling ethanol through oxidation pathways leads to a depletion of oxidized NAD at the expense of increasing its reduced form (NADH). Therefore, the ratio [free NAD $^+$]/[free NADH] falls.

Hundreds of metabolic reactions (glycolysis, pyruvate fermentation, oxidation of pyruvate, citric acid cycle reactions, mitochondrial electron transport chain reactions, oxidation of amino acids, and fatty acids oxidations) use NAD $^+$ /NADH as redox coenzymes. Besides, NAD $^+$ is a substrate in other metabolic reactions such as deacetylation of histones, polymerization of nucleotides, post-translational modifications of proteins, synthesis of cADP-ribose, or synthesis of NADP $^+$ [45, 99, 100]. Therefore, NAD $^+$ -coupled enzymes influence the coenzyme's bioavailability and energy metabolism [101] (Figure 3). The imbalance of the redox couple concentrations can have consequences that globally affect cell function. An acute outcome is that gluconeogenesis from lactate, serine, and alanine is inhibited [102], and carbohydrate metabolism is significantly compromised. Besides, alcohol helps switch the metabolism of acetate units to fatty acids storage deposits, aided by the malic enzyme (EC 1.1.1.40) that oxidizes malate to pyruvate and increases reducing equivalents in the form of NADPH [103]. What is more, the altered homeostasis of nicotinamide adenine dinucleotide coenzymes impacts the utilization of nutrients by tumor cells [100].

Depletion of NAD $^+$ affects ADP-ribosylation of different protein substrates and histones' deacetylation by sirtuins (EC 3.5.1.98; EC 2.4.2.31) with consequent cellular stress.

Sirtuins are sensors that link energy metabolism with transcriptional regulation and, depending on the context, may behave as mitochondrial tumor suppressors or tumor-promoting agents, as is the case for sirtuin Sirt 4 [104]. Deficits in sirtuin Sirt1 deacetylase activity disrupt lipid metabolism and alter specific transcriptional factors, favoring alcohol liver damage progression [105].

The enzymes poly(ADP-ribose) polymerases (PARP, EC 2.4.2.30) also depend on NAD⁺ availability. In experimental models of alcohol-induced steatohepatitis, Mukhopadhyay et al. [106] reported that PARP inhibition restored Sirt1 activity and ameliorated the induced inflammatory and oxidative stress responses. The results associate PARP and Sirt1 actions through the utilization of NAD⁺ in their reactions.

The free AMP concentration also regulates the enzyme AMPK. This enzyme promotes ATP synthesis by increasing ATP catabolic production and inhibiting ATP anabolic needs. It also regulates several metabolic pathways that keep a state of metabolic homeostasis and adequate cell function. One consequence of ethanol oxidation is the augmented [free NADH]/[free NAD⁺] proportion and the cell's energy state. Consequently, free AMP concentrations decay, and AMPK activation is blocked. Therefore, the metabolic activities depending on AMPK's proper functioning are affected [44]. Given the essential role of AMPK in anabolic metabolism, cell growth, proliferation, autophagy, and DNA repair, it has a central role in carcinogenesis control [107].

NAD⁺ is a chemical beacon regulating many enzyme activities responsible for essential metabolic control and disease resilience [108]. Alcohol ingestion may trouble cell functioning, among other mechanisms, by disabling the delicate balance of [free NAD⁺]/[free NADH] and the energy state of the cell [109] (Figure 3).

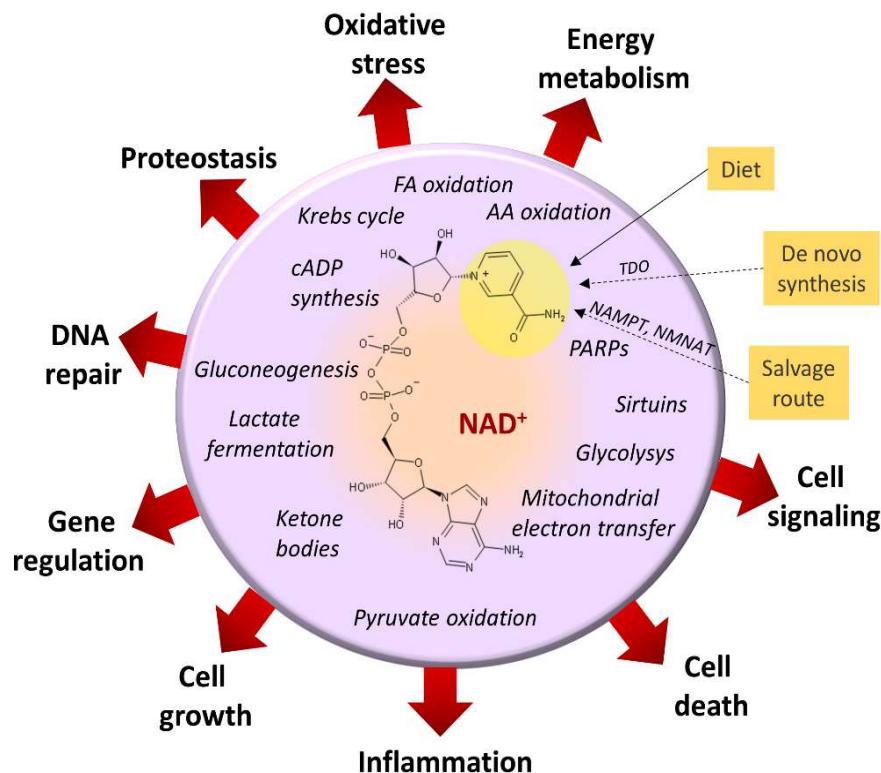


Figure 3. Representation of the metabolic routes affected by an imbalance in the ratio of free coenzymes NAD⁺/NADH. This imbalance provokes alterations in cell function related to depleted energy state, alteration of DNA repair mechanisms, and derangement of cell signaling and cell growth with consequent cell death or cell transformation. Dotted arrows indicate several reactions in a metabolic pathway. AA (amino acid); FA (fatty acid); NAMPT (nicotinamide

phosphoribosyltransferase, EC 2.4.2.12); NMNAT (nicotinamide mononucleotide adenylyltransferase, EC 2.7.7.1); PARPs (poly(ADP)-ribosyl polymerases, EC 2.4.2.30); TDO (tryptophan 2,3-dioxygenase, EC 1.13.11.11) [45, 99-102, 110, 111].

3.3 Ethanol and metabolism of c1-units

The term C1 metabolism refers to the circuitry of metabolic pathways (Figure 4) essential for cell proliferation and endurance (nucleotide synthesis, Ser Gly and Met metabolism, methylation reactions, synthesis of polyamines, redox reactions, and transsulfuration pathway) that manage the provision of one-carbon modules (methyl groups) and connects with the control of the cellular redox state [76, 112-116]. Folate (pteroyl-L-glutamate) metabolism distributes one-carbon components through redox reactions. It also couples with metabolic routes where a carbon atom moves between different substrates by transfer reactions essential for cellular proliferation and epigenetic regulation [112, 114-116]. Many excellent reports analyze valuable information concerning the role of one-carbon metabolism in cell proliferation, differentiation, and growth [112, 113, 116-121].

Several studies report that chronic ingestion of alcohol affects folate availability and metabolism, not restored after folate's additional dietary supply [122]. In humans, many mechanisms contribute, including reduced intestinal absorption [122-124], augmented renal excretion [125], and oxidative disruption of the molecule, possibly by the effect of acetaldehyde or free radicals derived from its oxidation [126]. Sustained alcohol consumption impairs an intestinal γ -glutamate carboxypeptidase (GCP, EC 3.4.17.11) that hydrolyzes polyglutamate forms of folate to absorbable forms. It also reduces folate binding proteins' action, also essential for absorption [124, 127]. Besides, ethanol may interfere with metabolic pathways involving the movement of one-carbon units (see Figure 4) by affecting essential enzyme activities such as MS (methionine synthase, EC 2.1.1.13). It also is influenced by GSH since homocysteine is a source for the synthesis of GSH by the transsulfuration route [76, 128]. Ethanol-treated micropigs during 14 weeks showed reduced liver methionine synthase activity, lowered SAM (S-adenosyl methionine) and GSH, and elevated plasma concentrations of MDA (malondialdehyde). These findings correlated with detecting acetaldehyde adducts, DNA damage, and liver injury [124]. The methionine deficiency affects the levels of other metabolites' pools, including the methyl donor SAM, thus negatively impacting essential methylation reactions [129]. Besides, 5-methyl-THF accumulates in a trapped pool that cannot convert into other folate forms, given that methyleneTHF reductase (EC 1.5.1.20) catalyzes an irreversible reaction (see Figure 4). This effect has consequences on different reactions responsible for DNA synthesis and DNA defect repairing [122, 130, 131]. However, the evidence obtained points to variable impact, depending on the organ exposed. For example, experimental chronic alcohol treatment in rats differentially affects one-carbon metabolism in liver and brain tissue [132].

The relationship of ethyl alcohol with carcinogenesis and tumor progression is complex and manifold. The influence of alcohol on folate metabolism plays a prominent and not yet well-understood role. The altered metabolism may induce malignant transformation, but, on the other hand, cell proliferation in tumors requires complete folate metabolism to support the synthetic demands of the transformed cells [26, 27, 81, 133-136]. Consequently, chemicals designed to target folate metabolism's crucial steps are essential tools when treating or preventing cancer, whether ethanol or other known aetiological factors play their part.

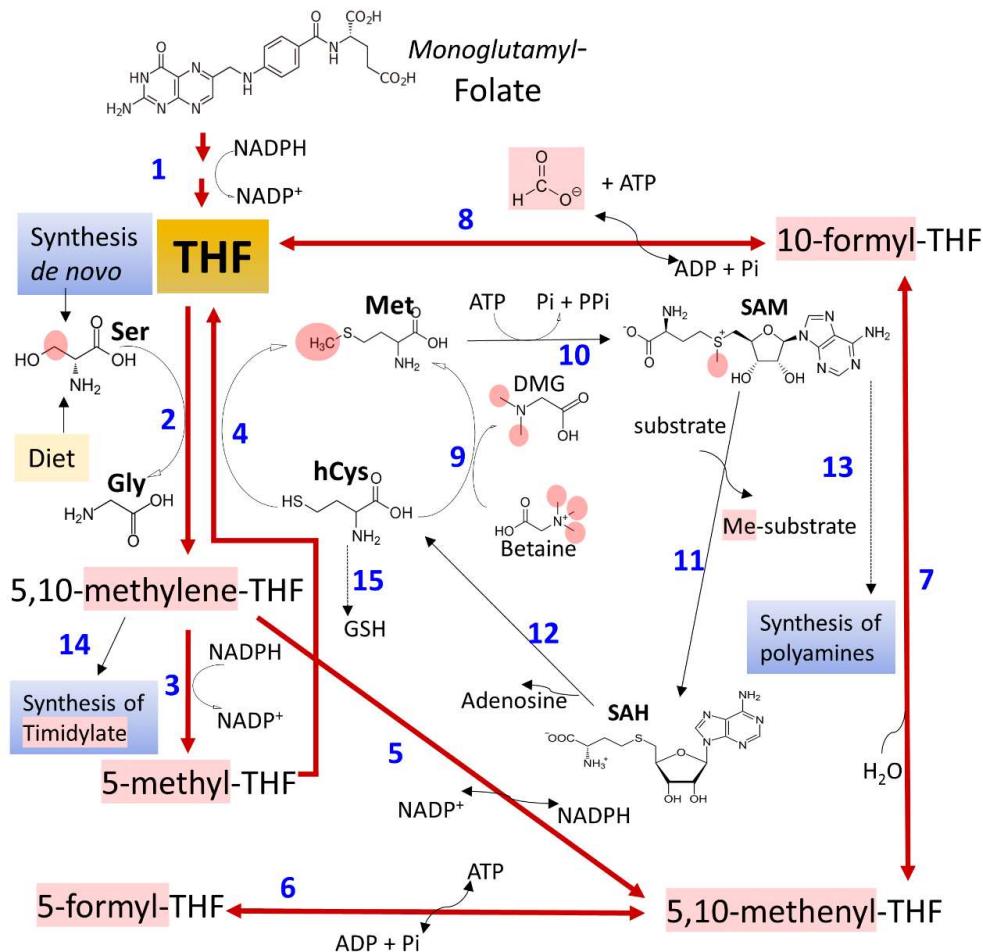


Figure 4. The hub of one-carbon metabolism pathways. The figure depicts the main routes involved in transferring one-carbon modules (highlighted red) from one metabolite to another. Homocysteine also serves as a substrate for the synthesis of GSH (reduced glutathione) through the transsulfuration pathway. THF (tetrahydrofolate); hCys (homocysteine); SAM (S-adenosylmethionine); SAH (S-adenosyl homocysteine); DMG (dimethylglycine); Me-substrate (methylated substrate). Numbers in blue color indicate enzyme activities: 1 (dihydrofolate reductase, EC 1.5.1.3); 2 (Ser-hydroxymethyl transferase, EC 2.1.2.1); 3 (methylene THF reductase, EC 1.5.1.20); 4 (MS: Met synthase, EC 2.1.1.13); 5 (methylenetetrahydrofolate reductase, EC 1.5.1.20); 6 (5-formyltetrahydrofolate cyclo-ligase, EC 6.3.3.2); 7 (methyltetrahydrofolate cyclohydrolase EC 3.5.4.9); 8 (formate-tetrahydrofolate ligase, EC 6.3.4.3); 9 (betaine: homocysteine methyltransferase, EC 2.1.1.5); 10 (Met adenosyltransferase, EC 2.5.1.6); 11 (methyltransferases, EC 2.1.1...); 12 (S-adenosylhomocysteine hydrolase, EC 3.3.1.1); 13 (SAM decarboxylase and other enzymes); 14 (thymidylate synthase, EC 2.1.1.45); 15 (indicates the transsulfuration pathway where several enzymes participate) [76, 117, 124, 128, 130, 136-139].

3.4 Ethanol and oxidative stress

Oxidative stress refers to a state characterized by increased production of highly reactive species. Two reactive species classes [140] are, on one hand, radicals or short half-life molecules with unpaired electrons in their atoms' outer orbitals (examples are superoxide, oxygen radical, hydroxyl, alkoxy radical, peroxy radical, or nitric oxide). On the other hand, non-radical molecules (for example, hydrogen peroxide, singlet oxygen, or nitrosyl cation) can easily give rise to radicals (Figure 5). The balance of these molecules' concentration is paramount to serve cell function since reactive species' production does not always associate with cell damage, and essential activities depend on these molecules'

action [141-143]. These compounds can be generated intracellularly or may have an exogenous origin [140]. Mitochondrial enzymatic activities carried out by the mitochondrial electron transfer chain, monoamine oxidases, and several dehydrogenases are a primary source of reactive oxygen species (ROS) [144-146]. Reactive oxygen and nitrogen species (RONS) derive from nitric oxide synthase and NADPH oxidase enzymatic reactions [147, 148].

The escalation of acetaldehyde concentration brings together oxidative activities that can produce ROS. Both acetaldehyde and ROS contribute to carcinogenesis by covalently modifying DNA, proteins, and lipids, leading to function losses [149, 150]. A few examples below illustrate the assertion. In alcoholics, the catalytic hemoprotein CYP2E1 is a ROS source [35, 55, 151]. Epithelial gastric cells increased ROS formation after direct exposure to 0.1 % (v/v) acetaldehyde [82]. Human neurons treated with ethanol showed an elevated synthesis of RONS linked to the activation of NADPH oxidase (NOX, EC 1.6.3.1), xanthine oxidase (XOX, EC 1.17.3.2), and inducible nitric oxide synthase (iNOS, EC 1.14.13.39) via acetaldehyde [152]. In neuroblastoma SH-SY5Y cells, acetaldehyde provoked mitochondrial fragmentation and cell damage in a ROS formation and calcium-dependent manner by phosphorylating Drp1 (dynamin-related protein1), a key regulator of mitochondrial fission [84]. In neurovascular tissues, acetaldehyde induces oxidant production enzymes, NADPH oxidase, and iNOS [153]. Synaptosomal membranes isolated from chronically treated rats showed reduced activity of SOD (superoxide dismutase, EC 1.15.1.1), GPx (Glutathione peroxidase, EC 1.11.1.9), and catalase, accompanied by changes in lipid composition that altered membrane-bound enzyme function; vitamin E annihilated the observed changes [154]. Alcohol produced increased ROS and triggered apoptosis in gastric epithelial cells by downregulating mitogen-activated protein kinase cascades. Theaflavins, polyphenols with antioxidant properties, alleviated the fluctuations [155]. With ROS formation after ethanol exposure, iron accumulates and may contribute to the oxidative milieu for its ready participation in one-electron transfer reactions [156].

Antioxidant enzymes depict a paradoxical role and may benefit or derange redox homeostasis [157]. They encompass specialized enzymes, reductive compounds, or chelates. For example, the enzyme SOD converts superoxide anion (O_2^-) into hydrogen peroxide and water. Catalase reduces two hydrogen peroxide molecules to water and molecular oxygen (see Figure 5). Glutathione peroxidases reduce many substrates, including hydrogen peroxide, by concomitant oxidation of reduced glutathione to oxidized glutathione (GSSG). Peroxiredoxins (EC 1.11.1.15) oxidize their N-terminal Cys residue to reduce hydrogen peroxide [157, 158].

Dysregulation of antioxidant barriers may also account for the harmful effect of acetaldehyde. The authors found a diminished serum antioxidant activity in rats treated with alcohol (an oral diet containing 15% v/v) for two months [159]. Direct exposure of endothelial cells of human origin to alcohol and acetaldehyde increases RONS production and augments SOD and catalase activities [160]. Many factors play a part in gastric and colon cancer; the generation of ROS caused by the suppression of enzymes with antioxidant capacity contributes significantly [161]. Chronic but not acute ethanol exposure induces an oxidative milieu that may facilitate the progression from chronic hepatitis to cirrhosis and hepatocellular carcinoma [162]. Many studies report contradictory results regarding how and to what extent alcohol influences the cells' antioxidant barrier status [163-167]. Different results may reflect the different experimental approaches (mostly related to the amount and pattern of exposure and the experimental specimen under analysis).

Another aspect worth considering is that ethanol can promote cancer development in different tissues and contribute to cancer cell survival. In malignant colon cells, ethanol promotes cell survival. It favors a more malignant phenotype, in an oxidative environment, by activating Nrf2/HO-1(nuclear factor erythroid 2-related factor 2/heme oxygenase 1) recruitment to the nucleus that eventually provokes the activation of antioxidant enzymes and bolsters malignant cell survival [168].

Besides, the failure of complete oxidation by ethanol metabolizing enzymes may generate acetaldehyde radicals (ethoxy, hydroxymethyl, or acetyl) with potential toxic effects [59, 169].

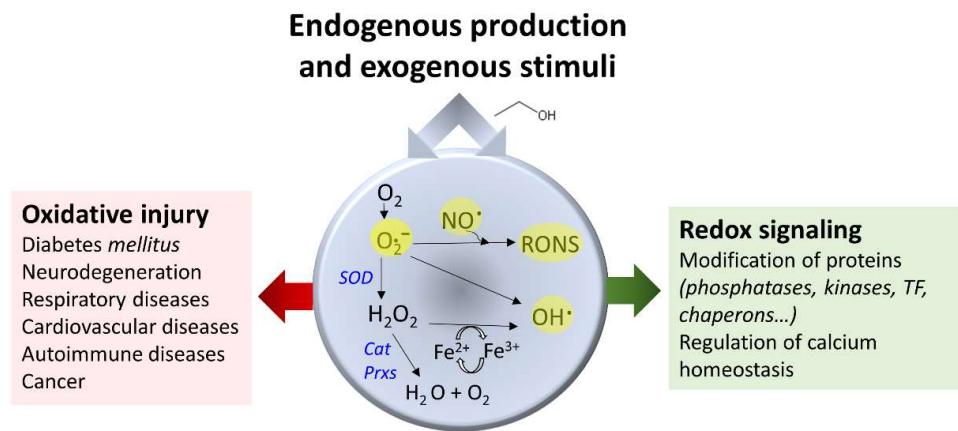


Figure 5. Exogenous agents (for example, ethyl alcohol) and endogenous mechanisms lead to reactive species formation. These species contribute both to physiological signaling and cell damage if the balance breaks. Essential enzymes, including Cat (catalase, EC 1.11.1.21), Prxs (peroxiredoxins, EC 1.11.1.15), and SOD (EC 1.15.1.1), support antioxidant defense activity. TF (transcription factors) RONS (reactive oxygen and nitrogen species) [70, 140-142, 147, 157].

3.5 Gene variants

Another origin of metabolic changes is genetic variants of enzymes that participate directly in ethanol elimination, exhibit an antioxidant task, or are key in different metabolic routes that maintain cell function. Gene variants relate to sensitivity to alcohol and its metabolites [170-173].

When analyzing ethanol's influence as a risk or causal factor of certain types of cancer, one should consider that some gene polymorphisms linked to alcohol metabolism may contribute to maintaining harmful drinking behavior that sustains and prolongs damage. Also, the expression of some genes and variants may be affected by alcohol or its metabolites. Other genes or variants not influenced by alcohol can contribute as primary risk elements independently or in an additive or synergistic manner combined with alcohol drinking. Therefore, the dissection of specific mechanisms accountable for direct or selected damage is challenging; however, establishing relationship patterns may clear these interactions and their relevance in delineating prevention and treatment strategies.

Gene variations of two ethanol metabolizing enzymes, ADH and ALDH, may facilitate acetaldehyde accumulation. Also, some polymorphisms of these two enzymes are associated with imbibers' enhanced or attenuated drinking behavior. The distribution of these polymorphisms varies among ethnic and geographical groups, adding complexity to the unveiling of their impact on pathologies, including cancer [174-180]. Cancer cells of alcohol metabolizing organs of the gastrointestinal system show activated ADH and attenuated ALDH activities, compared to healthy tissues. This observation relates to different isoenzymes acting in cancer cells [177]. Furthermore, evaluating enzyme polymorphisms as a risk for the development and progression of malignancies needs attention within the context of other factors (nutrition, smoking habit, sex, age, diabetes, obesity) that may also contribute.

Human alcohol dehydrogenases (ADHs) arrange into five classes. Class I include ADH1A, ADH1B, and ADH1C isoenzymes [181] that may form homodimers or heterodimers and are responsible for almost all ethanol oxidation in the liver [50, 182]. SNPs (single nucleotide polymorphisms) in coding and noncoding regions influence the function or the expression of the corresponding protein, affecting its overall performance [50, 183]. ADBH1B allele variations ADH1B*2 (rs1229984, Arg48His), ADH1B*3 (rs2066702,

Arg370Cys), and ADH1C (rs698, Ile350Val, and rs1693482, Arg272Gln) manifest higher activity compared with normally functioning allele, thus accelerating ethanol's oxidation to acetaldehyde [174, 184]. However, this effect may disappear if a robust form of ALDH acts on mounting acetaldehyde [50].

Human ALDHs form a family of nineteen members. Only three of them, ALDH1A1, ALDH1B1, and ALDH2, are relevant for acetaldehyde oxidation to acetate [50, 185]. Drinking patterns and alcohol metabolism are affected by the allele variation rs671 (Glu487Lys) of isoenzyme ALDH2, ALDH2*2, observed mainly in oriental populations. The amino acid change (acidic to basic) blocks the enzyme, and, consequently, acetaldehyde accumulates. The variation may protect the carrier from excessive alcohol ingestion to avoid the unpleasant effects caused by acetaldehyde [186, 187].

The combination of more effective ADH variants and deficient ALDH activities favors the exposure of cells to acetaldehyde. The epidemiological analysis of specific human communities relates to these gene variants with a higher risk of gastrointestinal tract cancer [188-192]. Besides, polymorphisms of ethanol metabolizing enzymes and gastric colonization by bacteria (*Helicobacter pylori* and others) contribute to augmented acetaldehyde concentrations in the stomach and colon [161].

Cytochrome CYP2E11 belongs to the Cytochrome P450 subfamily of enzymes. SNV (single nucleotide variations) of the enzyme CYP2E11, rs2031920 (associates with colorectal cancer risk) [193]. Polymorphisms rs2031920, rs6413432 associate with PTGS2 (Prostaglandin G/H synthase 2) polymorphisms for lung cancer risk in specific human groups [194] (Table1). Two variants, rs72559710 (Arg76His) and rs55897648 (Val389Ile) [195] may affect the function of the enzyme, although its relationship with cancer risk is not well defined and needs more in-depth analysis [55].

Table 1. Representative examples of enzyme variants liaised to cancer risk, participating in alcohol metabolism, or other metabolic pathways related to alcohol metabolism. The EC four digits represent the nomenclature given by the Enzyme Commission (EC) of the International Union of Biochemistry and Molecular Biology (IUBMB) [196] (accessed the 1st April 2021). The nomenclature rs (RefSNP) refers to gene variants named after The Single Nucleotide Polymorphism Database (dbSNP) [197] (accessed the 21st March 2021). HSD17B13, hydroxysteroid 17-beta dehydrogenase; MS, Methionine synthase; MTHFR, methylenetetrahydrofolate reductase; MTRR, Methionine synthase reductase; PNPLA3, patatin-like phospholipase domain-containing protein 3 or adiponutrin; GSH (reduced glutathione); TM6SF2, transmembrane 6 superfamily member 2; SNV, single nucleotide variants. The asterisk * indicates that SNP (single nucleotide polymorphism is a single variant, SNV, appearing in the population with a 1% frequency or higher).

ENZYME	SNVs*	GENE VARIANTS & CANCER RISK (References)
ADH, EC 1.1.1.1	rs1229984, rs2066702, rs698, rs1693482	[25, 50, 175-177, 180, 189, 198-200]
ALDH, EC 1.2.1.3	rs671	[50, 175, 177, 180, 188, 191, 198, 200-204]
CYP2E11, EC 1.14.14.1	rs2031920, rs6413432	[55, 176, 193, 205]
HSD17B13, EC 1.1.1.51	rs 4607179	[206]
SOD, EC 1.15.1.1	rs4998557, rs4880	[207-209]
PNPLA3, EC 2.3.1.51	rs738409	[69, 69, 206, 210, 211, 211, 212, 212, 213]
MTHFR, EC 1.5.1.20	rs 2184227, rs868014	[174, 179, 214]
MS, EC 2.1.1.13	rs1805087	[215]
MTRR, EC 1.16.1.8	rs162036, rs1532268	[213, 215]
TM6SF2	Rs58542926	[213]

Additional enzyme variants may associate with cancer risk. Compared with the most common genotype, the homozygous rs1801133 (Ala222Val) variant of the enzyme MTHFR (methylenetetrahydrofolate reductase) shows reduced activity. Many studies analyze the link between excessive alcohol drinking and this variant of MTHFR with cancer risk of head and neck, gastrointestinal tract, or lung in different human populations [174, 198, 214, 216-222]. SOD variants rs 4998557 and rs4880 (Ala16Val), Helicobacter pylori infection history, and alcohol drinking correlate with gastric cancer risk [209]. The SOD rs4880 variant is associated with EGFR (epidermal growth factor receptor) Leu858Arg mutation in patients with non-small-cell lung cancer and primary brain tumors [208] (Table 1).

Lipid metabolism is also affected by alcohol. In liver tissue, fat accumulates, leading to liver steatosis and fibrosis [223]. An enzyme associated with these processes is PNPLA3 (patatin-like phospholipase domain-containing 3 or adiponutrin, EC 2.3.1.51), a protein that catalyzes coenzyme A (CoA)-dependent acylation of 1-acyl-sn-glycerol 3-phosphate to produce phosphatidic acid (PA). Besides, it shows triacylglycerol lipase (EC 3.1.1.3) and CoA-independent acylglycerol transacylase (2.3.1.147) activities [224, 225]. Genetic variation of PNPLA rs738409 is associated with steatosis and fibrosis in individuals with alcoholic liver disease [69, 211, 212]. The occurrence of single nucleotide variants rs738409 in PNPLA and rs58542926 in transmembrane 6 superfamily member 2 (TM6SF2) associate with the risk of hepatocellular carcinoma, whereas variant rs4607179 of hydroxysteroid 17-beta dehydrogenase (HSD17B13) reduces the risk [213]. In a genome-wide association study, variants rs738409 of PNPLA and rs4607179 of HSD17B13 show significant association with the appearance of alcohol-associated liver cirrhosis, and rs374702773 of Fas-associated factor family member 2 (FASF2) shows a protective association [206].

Additional gene variants of proteins (phosphatases, phospholipases, kinases, receptors, DNA-repair enzymes) are statistically associated with developing different types of cancer in the context of alcohol drinking [178, 210, 226-228].

Polymorphism studies are relevant to ascertain cancer risk in certain tissues and specific populations. Also, the analysis of polymorphisms in selected alcoholic cohorts provides essential information. Nevertheless, we need broader analysis and studies that link these relationships with experimental evidence at the molecular level. The task is not easy but is necessary. Alcohol may represent an independent risk factor that may act in an additive or synergistic manner with the polymorphic background of certain enzymes found in selected human communities. In this regard, genome-wide association studies

(GWAS) and gene-environment-wide interaction studies (GWiS) [178] may serve, together with biochemical analysis, to offer a clearer picture.

3.6. Ethanol and cancer development

Humans usually ingest alcohol *per os* and may exert a direct irritant impact on mucoses. Besides, resident oral and gut microbiota populations destabilize and metabolize the substance locally to generate acetaldehyde. Local effects of ethanol include changes in the permeability of the intestinal wall and the pass of bacterial endotoxins and metabolites that may induce inflammation. Once ethanol reaches the general circulation, it arrives at cells in different organs, but the liver is the central station of arrival. Cells may metabolize ethanol through oxidative and nonoxidative pathways producing noncommon molecules that alter the intermediary metabolism, break the proportion of essential coenzymes NAD⁺ and NADH, detour energy production mechanisms, alter substrate fluxes in one-carbon unit pathways, and generate free radicals. These transformations may enhance oncogenic transformation by damaging DNA. To the modifications mentioned above, gene variants affecting a diversity of enzymes and proteins add complexity to the effects of ethanol on human health. The elements contributing to the described framework of alcohol capacities may facilitate cell, tissue, and organ suffering leading to disease. Poblational studies identify alcohol and its metabolites as necessary candidates in cancer development. This association receives support from basic research using *in vivo* and *in vitro* models analyzing the impact of ethanol on specific targets. Unfortunately, we cannot precisely define ethanol as a specific agent leading to carcinogenesis, but indirect evidence is overwhelming as we intend to relate in this review. According to the defining hallmarks of cancer [8], alcohol metabolism may fire carcinogenesis directly or accompanied by other agents and mechanisms endorsed by its capacity to induce inflammation, DNA damage with subsequent oncogenic activation, and protein/enzyme malfunction.

4. Damage of DNA and proteins and epigenetic shifts

Direct or indirect alcohol metabolism products may react with proteins, lipids, and DNA, affecting their architecture and function with consequences on the activation of cell proliferation or inhibition of tumor suppressor mechanisms [26, 27, 62, 68, 79, 83, 150, 229-231]. One of the metabolites that outstand is acetaldehyde. Besides, reactive oxygen and nitrogen species, lipid peroxidation products [68], and folate and estrogens' altered metabolism play a significant role [26].

Acetaldehyde is an electrophile that reacts with nucleophiles to generate covalent adducts with lipids, proteins, and nucleic acids (Figure 6).

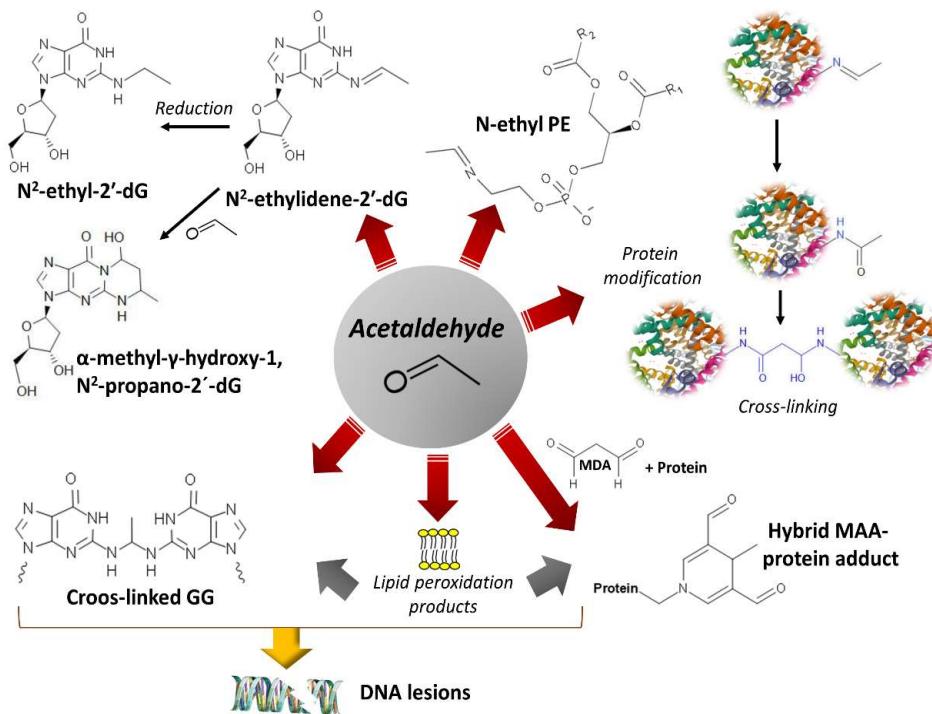


Figure 6. Protein, DNA, and phospholipid adducts are generated by the reaction of electrophilic acetaldehyde with nucleophilic groups. Additional secondary transformations may take place. dG, deoxyguanosine; GG, two contiguous deoxyguanosine on a DNA strand; MDA, malondialdehyde; MAA, malondialdehyde acetaldehyde; PE, phosphatidylethanolamine. The figure includes colored representations of a human nucleosome (Protein data bank code 3AFA). DNA figure: doi.org/10.5281/zenodo.4012404 [26, 62, 80, 82, 83, 85, 149, 229, 231].

Although acetaldehyde rapidly oxidizes to acetate by ALDH, its concentration can reach significant levels in individuals carrying ALDH2 poorly active variants and facilitate the formation of adducts [65, 232], and augment cancer risk [200]. Experimentally increased acetaldehyde concentrations obtained in ALDH knockout mice exposed to ethanol elicited an increase of acetaldehyde-DNA adducts [233]. Furthermore, the disruption of DNA repair mechanisms, such as the tumor suppressor OVCA2 [234] or tumor suppressor p53 [235], dramatically influences acetaldehyde tolerance. The aldehyde reacts with amino groups in proteins (ϵ -amino of Lysines and α -amino of the amino acids at the N-terminus). Firstly, unstable, reversible Schiff base forms, and later, stable adducts may derive in intrachain and interchain crosslinked structures [83].

Acetaldehyde also forms DNA adducts by reacting with nucleophilic amino groups. Reaction with guanine's purine ring gives N²-ethylidenedeoxyguanosine that converts to the reduced, more stable adduct, N²-ethyldeoxyguanosine [65, 70, 151, 236] (Figure 6). Besides, acetaldehyde can generate intrastrand crosslinked structures between two adjacent guanines and significantly disturb the double helix's topography [237]. Another DNA adduct, α -methyl- γ -hydroxy-1, N²-propane-2'-deoxyguanosine (detected as an open aldehyde or closed-ring form), is the product of the reaction of acetaldehyde with the guanine ring taking place in a basic environment (e.g., arginine and lysine basic groups on the neighbor histones) [68, 238] (Figure 6). This guanosine adduct also appears after the nucleophilic attack of prop-2-enal (a lipid peroxidation product) [239].

High concentrations of ethanol and chronic consumption activate CYP2E11 with consequent local accumulations of ROS [55], causing lipid peroxidation of biomembranes that yields reactive aldehydes, 4-hydroxynonenal, prop-2-enal, 4-oxo-2-nonenal, and malondialdehyde, and their epoxides, from oxidized lipids containing polyunsaturated fatty acids (PUFAs) [68, 240, 241]. These compounds non-enzymatically react with proteins through Michael additions and Schiff base formation and generate lipid and DNA adducts (Figure 7) [241, 242].

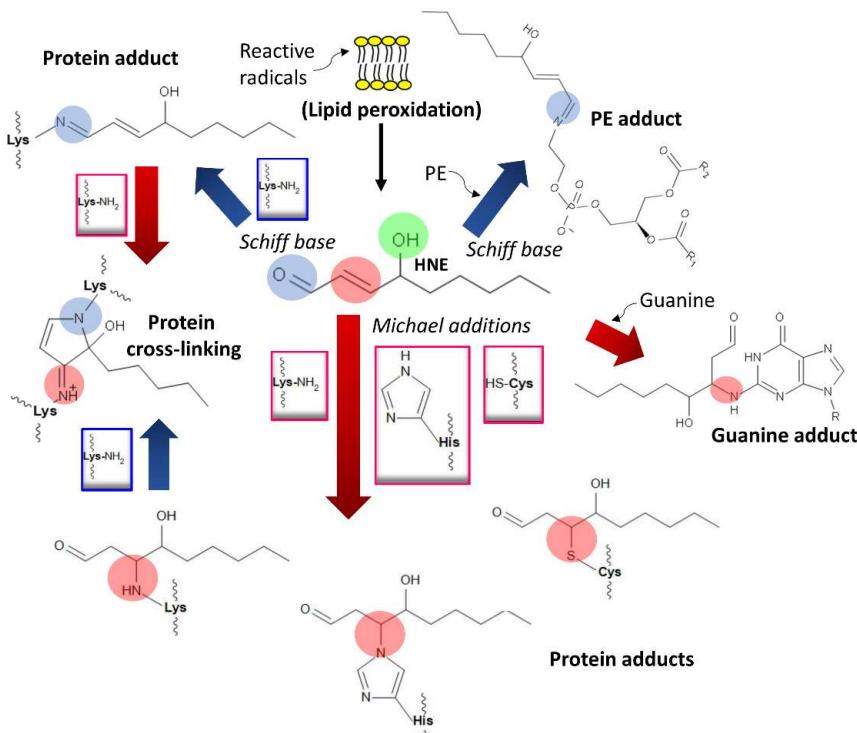


Figure 7. Protein adducts are generated by the reaction of amino, imidazole, and thiol groups of amino acids with reactive carbons of HNE (4-Hydroxy-2-trans-nonenal) Schiff base formation or Michael additions to the C2=C3 double bond. Also, HNE may react with lipids and DNA to generate adducts. Additional secondary reactions may occur between the carbonyl and the hydroxyl groups. Colored circles represent reactive groups within HNE that undergo different redox reactions. PE, phosphatidylethanolamine [79, 151, 230, 241-243].

They also form adducts with membrane lipids, such as phosphatidylethanolamine or phosphatidylserine, to give phospholipids exhibiting modified solubility that influences the membrane's biophysical properties [81, 244] (Figure 7). Besides, acetaldehyde and malondialdehyde (a lipid peroxidation product) may generate malondialdehyde-acetaldehyde (MAA) protein hybrid adducts [83, 245, 246].

Adducted proteins, covalently modified after reacting with aldehydes, are many and involve numerous activities [65]. Covalent modifications may alter function (often by inactivation), depending on the protein's targeted amino acid(s). Moreover, these modifications block enzymes involved in ethanol metabolism. In this situation, they serve as a control mechanism to regulate ROS and acetaldehyde accumulation and modify drinking behavior [65, 80, 247]. Protein adducts may trigger an immune response directed against specifically modified epitopes (adduct epitopes) acting as neoantigens [245, 248-250]. This phenomenon affects immunity responses essential for controlling cell damage and extracellular milieu homeostasis.

DNA modifications lead to secondary reactions carried out by exposed carbonyl or hydroxyl groups that result in intrastrand and interstrand crosslinks and DNA-protein structures crosslinked that obstruct proper function. DNA lesions, if not repaired,

propagate as mutations after DNA replication. Specific mutations in genes that code for tumor suppressor proteins, transcription factors, or proteins responsible for cell cycle surveillance may lead to cell decline or uncontrolled cell proliferation, cell transformation, and malignancy [229, 230, 235]. Furthermore, the cell's difficulties repairing damage by canonical mechanisms amplify damage [68, 243]. Analytical assessment of these adducts represents a valuable tool, combined with other biomarkers analysis, to better monitor AUD patients and predict reliable disease risk profiles [65].

As a consequence of DNA damage, mutations of oncogenic routes located at the so-called fragile sites accumulate and enhance their activity. Their mutated products compromise DNA repair and trigger the onset of cell transformation by different pathways. Specific oncogenic routes associate with several cancer types and define mutational signatures [251]. Specifically, among these signatures, *TP53* (tumor suppressor p53), *CUL3* (cullin 3), and *NSD* (nuclear receptor binding SET domain protein 1) contribute to profiles related to alcohol consumption by cancer patients [251]. Examples of population studies observe the activation of oncogenic routes such as *KRAS* (Kirsten rat sarcoma viral oncogene homolog gene)[252], tumor suppressor genes *APC* (Adenomatous polyposis coli) and *TP53* [13, 253], *CCND-1* (Cyclin D1), or *MMP2* (Matrix metalloprotease 2) [254], in different cancers types influenced, at least in part, by alcohol consumption [255]. In some types of cancer, the association is not clear [253].

Epigenetic mechanisms (dependent on noncoding RNA signaling and chromatin modifications) play a significant role in cancer development by silencing tumor suppressor genes or facilitating unstable genomes [256]. Observed modifications (described previously) induced by ethanol in one-carbon metabolism, antioxidant barriers, NADH concentration, noncoding RNAs regulatory function, or altered autophagy mechanisms may affect DNA regulation histone architecture and compromise gene expression [138, 257-264]. Other intrinsic and extrinsic factors may determine these epigenetic shifts in a scenario where alcohol may synergize in the injuring process [265-267].

This review deals with the influence of ethanol on different signaling pathways leading to transformation in cancer stem cells (CSC) (see section 5).

Table 2 summarizes some targets that may show different sensitivity to ethanol and its metabolites in the context of cancer development. Research efforts should address ethanol's direct impact on specific biomolecules and the altered metabolic environments arising after ethanol exposure.

Table 2. Representative targets of ethanol and its metabolites deserving further research to establish ethanol's participation in cancer development and progression and design new pharmacological tools.

TARGET	MECHANISM	EFFECT	REFER-ENCES
ADH	Increased demand by substrate presence	[NAD ⁺]/[NADH] imbalance	[48-50]
ALDH	Increased demand by substrate presence	[NAD ⁺]/[NADH] imbalance	[60]
Catalase	Increased demand by substrate presence	ROS production	[51, 201]
CYP2E	Increased demand by substrate presence	ROS production	[53]
FAEE (Fatty acid ethyl ester) synthase and CEL (carboxyl ester lipase)	Increased demand by substrate presence	Accumulation of fatty acid ethyl esters (biomarkers of alcohol consumption). It alters AMPK α (AMP kinase)activity	[41, 46, 89, 93]
ST (Sulfotransferase)	Increased demand by substrate presence	Accumulation of ethyl sulfate (a biomarker of alcohol consumption)	[95]

UGT	Increased demand by substrate presence	Ethyl glucuronide (a biomarker of alcohol consumption) accumulates. It activates Toll-like receptor proteins	[38, 94]
PLD	Increased demand by substrate presence	Phosphatidylethanol (a biomarker of alcohol consumption) accumulates. It produces changes in membranes and alters the phosphatidic acid synthesis	[33, 36]
PARP (poly (ADP-ribose) polymerases)	[NAD ⁺]/[NADH] imbalance	Defects in DNA repair	[106]
Sirtuins	[NAD ⁺]/[NADH] imbalance	Loss of histone deacetylation	[105]
AMPK	[NAD ⁺]/[NADH] imbalance	Alteration of energy equilibrium and anabolic metabolism, cell growth, proliferation, autophagy, and DNA repair	[107]
MS	Inhibition by acetaldehyde	Downregulation of the conversion of methyltetrahydrofolate to tetrahydrofolate and synthesis of methionine	[268]
NADPH oxidase and iNOS (inducible nitric oxide synthase)	Activation by acetaldehyde	ROS formation	[152, 153]
SOD (Superoxide dismutase)	Downregulation/ up-regulation by ethanol and acetaldehyde	Imbalance of ROS	[160, 161]
Lipids, proteins, and DNA	Formation of adducts with acetaldehyde, ROS, and HNE	Lipid peroxidation, dysregulation of protein function, and disruption of gene expression	[62, 80, 82, 83, 149, 229, 231]

5. Alcohol, cancer stem cells theories and therapeutic strategies

Stem/progenitor cells play a pivotal role in the development of organs and response to tissue injuries. The study on the harmful actions mediated by ethanol and its metabolites (e.g., acetaldehyde, acetate) opens a new and essential research line on the changes operated on stem/progenitor cells [269]. A small number of tumorigenic stem cells (tumor-initiating cells) drive the growth of tumors. Hence, in-depth knowledge of alcohol's actions on cancer stem cells' biology could lead to new therapeutic strategies to counteract the occurrence of tumors induced by alcohol [270].

Alcohol generates ROS responsible for damages in the DNA, biomembranes, and proteins. Besides, it decreases NAD⁺ concentrations (promoting a decrease in differentiation/self-renewal of stem cells) and deranges signal transduction pathways [269, 271]. ROS control the renewal and differentiation of stem cells [272, 273]. The decrease in the intracellular levels of NAD⁺ exerts a negative effect on stem cells [269]. Fully functional ALDH activity counteracts the toxic effect induced by acetaldehyde and is involved in stem cell protection, maintenance, and differentiation [269, 274]. A high level of aldehyde dehydrogenase in tumor-initiating cells relates to cancer stem cells' expansion, although this enzyme is not the only factor contributing [269, 275].

Epigenetic processes control stem cells (self-renewal, differentiation). Alcohol can alter these epigenetic processes by perturbing the expression of those genes involved in the maintenance/proliferation and differentiation of stem/progenitor cells [276-278]. Alcohol decreased the expression of stem cell markers in stem/progenitor cells (e.g., neural, adventitial, and hematopoietic progenitor cells; hepatic, intestinal, and dental pulp stem cells). It also intercepted cell differentiation, induced DNA damage and apoptosis, and promoted phenotypic changes. Alcohol also altered the stem cell niche's

microenvironment and disturbed cell fate determination by dysregulating the extracellular matrix deposition and changing the plasma membrane's fluidity (reviewed in [269]). Fanconi anemia and transforming growth factor β pathways are involved in the maintenance/differentiation of stem cells and alcohol metabolism [15]. The tumor suppressor β 2-spectrin increased the tumor suppression mediated by the transforming growth factor β [279]. Both β 2-spectrin and transforming growth factor β pathways, by controlling the Fanconi anemia DNA repair pathway, are involved in the genomic stability maintenance from genotoxic metabolites. β 2-spectrin keeps this stability after alcohol-induced DNA damage, and inflammation and cancer appeared when a defective transforming growth factor β signaling occurred [279].

Ethanol exerts teratogenic effects and is responsible for both fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASD) [280]. Ethanol promoted a loss of pluripotency in embryonic stem cells; in these cells, a decreased staining for TRA-1-81 and alkaline phosphatase was observed, but no change in other markers, such as TRA-1-60, SSEA4, and Oct4 was found [281]. Alcohol promoted DNA methylation changes in several chromosome regions and altered genes related to oxidative stress/metabolic processes in human embryonic stem cells [282, 283], and induced the differentiation of embryonic stem cells by activating the nuclear transcriptional program controlled by the retinoic acid/retinoic acid receptor gamma complex [280]. During embryogenesis, alcohol exerted a teratogenic effect on neurodevelopment; this could explain, at least in part, the pathology of FASD [284]. Ethanol reduced the level of P2RX3 (purine receptor three associated with pain) in undifferentiated human embryonic stem cells. Still, it increased both P2RX3 mRNA/protein levels in human embryonic stem cell-derived neural precursor cells. Moreover, it altered the Toll-like receptor and JAK-STAT (signal transducer and activator of transcription 3) signaling pathways, autophagy regulation, and ligand-receptor cytokine-cytokine receptor interactions [284].

Alcohol drinking is a risk factor for developing gastrointestinal cancer by facilitating intestinal barrier dysfunction, which occurs even weeks after the cessation of alcohol intake. Ethanol exposure (acute and chronic) promoted intestinal stem cells' dysregulation and favored long-lasting intestinal damage. Intestinal damage stimulates the division of stem cells (to regenerate the damaged epithelium); thus, the stem cells divide more frequently. These divisions can induce mutations leading to the dysfunction and transformation of intestinal stem cells [285]. Chronic alcohol intake reduced Bmi1 expression (a stem cell marker) and dysregulated the β -catenin signaling (a pivotal regulator of its target Lgr5 gene and intestinal stem cell function). In the same study, organoids generated (from small intestine tissue) and *in vitro* exposed to alcohol (0.2%) for seven days exhibited decreased growth and diminished expression of Bmi, p- β -catenin (ser552), and Lgr5[285]. The findings presented above suggest that the dysregulation of the intestinal stem cells is a process by which alcohol (acute/chronic) promotes a long-lasting intestinal injury.

Human dental pulp stem cells are multipotent mesenchymal stem cells that differentiate into osteogenic/odontogenic cells and neuronal cells after a trans-differentiation mechanism [282, 286]. Ethanol promoted transcriptomic changes and affected many human dental pulp stem cells by altering the DNA methylation profiles [286, 287]. During osteogenic/odontogenic differentiation, alcohol inhibited lysine-specific demethylase 6B (KDM6B) activity, and a dysregulation of the mineralization potential occurred [287]. The latter means that alcohol decreases mineral deposition inducing an altered dental development and osteoporosis/osteopenia.

During the early hepatic specification, alcohol decreased hepatic progenitor cells' formation and proliferation of early/mature hepatocyte-like cells [288]. At a mature stage of hepatocyte-like cells, alcohol increased two liver progenitor subsets, promoted an oxidative mitochondrial injury, and induced, in a dose-dependent manner, disease phenotypes in the liver (hepatocellular carcinoma markers, steatosis). It seems that these phenotypes are related to an increase in oxidative stress since an antioxidant treatment reversed some of them. Thus, during the fetal period, it appears that alcohol exposure impaired the generation of progenitor cells (at an early stage of hepatic specification) and decreased fetal

hepatocyte proliferation. In contrast, alcohol contributed to generating disease phenotypes during the post-natal/mature phase [288]. Human-induced pluripotent stem cells differentiate into mature human cell types, including functional hepatocytes [289]. Hepatocyte-like cells obtained from human-induced pluripotent cells (iPSCs) exposed to ethanol *in vitro* showed decreased AFP (alpha-fetoprotein, an early hepatic marker) and apoptosis [290]. The proliferation of more mature hepatic cells diminished, and lipid droplets increased [290]. Alcoholic steatohepatitis accelerates early hepatobiliary tumors (showing molecular characteristics of hepatocellular carcinoma) and increased stemness markers (CD133, Nanog). These markers evidence epithelial-mesenchymal transition, and it appears that the alcoholic microenvironment (e.g., pro-inflammatory molecules) is responsible for the activation of progenitor cells [291].

CSC originate new CSC and more differentiated bulk cancer cells [292, 293]. The CSC number increases after the symmetric division, leading to a high undifferentiated/aggressive state [292, 294, 295]. CSC with differentiation and self-renewal capacity are involved in cancer initiation/progression, invasion/metastasis, recurrence, heterogeneity, and resistance to the conventional therapies used in clinical practice [283, 296]. These cells may maintain a proliferative or quiescent state [292, 294, 295, 297, 298]. When quiescent, it is essential to note that these cells escape from the immune system's attacks and resist anti-cancer treatments (e.g., chemotherapy) [292, 299, 300]. These latter statements mean that these cells are involved in cancer recurrence and exhibit a high invasion/metastasis capacity [292, 301, 302]. It seems that tumors contain CSC responsible for cancer propagation originated, after mutations, from normal stem/progenitor cells or non-cancer stem cells suffering de-differentiation/interconversion processes [303, 304]. Therefore, CSC is a potential target to prevent cancer development. It is important to note that CSC are poorly differentiated or undifferentiated cells that resist standard therapies.

In contrast, differentiated tumor cells (99% of the cells located in the tumors) are more responsive to these therapies [297]. One therapeutic strategy against undifferentiated/poorly differentiated CSC is to promote differentiation to be eliminated by conventional treatments [297]. CSCs dwell in niches controlled by cells (stromal fibroblasts, immune, endothelial and adipose cells) and components of the extracellular matrix, growth factors, chemokines, cytokines, angiogenesis, pH [304]. Hence, some processes (e.g., wound healing, hypoxia, inflammation) can originate carcinogenesis-promoting niches [292]. Alcohol can encourage the de-differentiation of cancer cells into CSC through microenvironment inflammatory mechanisms [292, 305]. ROS generation by alcohol can alter these niches' microenvironment and, hence, CSC functional attributes (e.g., self-renewal, survival, differentiation) [283]. In this line, alcohol altered the extracellular matrix components by modifying the CSC microenvironment [283, 291, 305]. Alcohol augments the CSC population, explaining tumors promoted by ethanol [283]. In tumor suppressor p53-deficient animals, ethanol blocks apoptosis and promotes an early appearance of dysplasia, and hence p53-dependent apoptosis counteracts the tumorigenic action exerted by ethanol [306]. In CSC, alcohol increased the expression of the ErbB1, ErbB2, and ErbB3 epidermal growth factor receptors, and in these cells expressing a low level of ErbB2, the increase in the number of CSC mediated by alcohol was lower when compared to CSC overexpressing ErbB2 [283, 307, 308]. Thus, the proliferative activity of CSC mediated by alcohol appears related to the ErbB2 expression.

CSC, exposed to ROS, activates antioxidant mechanisms and shows a malignant phenotype [303]. However, it is pertinent to note that the generation of ROS associates to pro-survival stimulation pathways controlled by Akt/PI3K and cytokine signalings. It seems that, in CSC, the responses against the generation of ROS can stimulate survival mechanisms, maintaining their characteristics and properties [303]. In the oro-esophageal squamous cell-type carcinoma, alcohol provoked the expansion of the CSC-like population [309].

Conversely, the activation of the p38 MAPK/β-catenin pathways by alcohol promoted stem/progenitor cell expansion [310]. Alcohol prompts the migration/invasion of these cells through the ErbB2/p38γ MAPK axis in breast cancer stem cells [307] and via

the Toll-like receptor 4-Nanog pathway in hepatic cancer stem cells [311]. In the liver of mice treated with alcohol, CSC (Nanog and CD133) upregulate, and proliferation (p53, cyclin D1, BrdU) markers increase [283]. After stimulating CSC expansion, the MAPK isoform p38 γ induces the development/progression/aggressiveness (migration and invasion) of cancer. Its silencing reduces the expression of Sox2, Oct3/4, and Nanog in CSC [312]. In an ErbB2-dependent manner, alcohol activated p38 γ . It appears that the activation of the p38 γ /ErbB2/discs large MAGUK scaffold protein/synapse-associated protein-97 axis mediates, in addition to migration and invasion, the increase in the number of CSC incited by alcohol [308]. RhoC (a protein belonging to the Rho family of GTPase) regulates CSC and increases when alcohol activates p38 γ [313]. This activation/upregulation increases migration and invasion of cancer cells and affects the CSC population [283, 308]. In transgenic mice, long-term alcohol exposure promotes hepatic tumors. Tumor-initiating stem cell-like cells isolated from these mice show tumorigenic activity and self-renewal directed by the Nanog stem cell factor's upregulation, Toll-like receptor 4-dependent. A transforming growth factor β pathway appears defective [279, 314] and mice showing an attenuated path of this factor develop hepatic tumors.

In contrast, alcohol ingestion increased tumor incidence in a Toll-like receptor 4-dependent manner [314, 315]. Thus, Toll-like receptor 4 is involved in the malignant transformation of cells. These findings show new potential therapeutic targets for the treatment of liver tumors. The Toll-like receptor 4/Nanog pathway's activation also promoted the degradation of p53 through the phosphorylation of NUMB (a protective protein) and its p53 dissociation by the TBC1D15 oncoprotein. This oncoprotein probably links cell self-renewal and metabolic reprogramming [316]. Because the Nanog/NUMB/p53 signaling controls CSC and hepatic tumorigenesis's self-renewal, a promising therapeutic method could be the targeting of protein NUMB phosphorylation [317].

Alcohol promotes endotoxemia by decreasing permeability in the gut and inflammatory response after activating the liver Toll-like receptor 4 [317, 318]. The generated endotoxins bind to the Toll-like receptor 4-CD14 complex and induce hepatoblasts/hepatocytes activation and Nanog expression. These mechanisms promote the generation of chemoresistant tumor-initiating stem-like cells, developing hepatocellular carcinoma. It is also important to note that Nanog induces fatty acid oxidation (this mechanism switches stem cell/cancer stem cells fate) and blocks mitochondrial oxidative phosphorylation leading to the inhibition of oxygen consumption rate/ROS production [317]. These metabolic changes facilitate cell self-renewal/oncogenesis. A decrease in fatty acid oxidation and the restoration of oxidative phosphorylation normal levels decreases CSC capacity to induce tumorigenesis and increases chemotherapy sensitivity [315, 317]. Altogether, the data show that Nanog reprograms the metabolism of mitochondria and that the changes observed are responsible for the oncogenicity/chemoresistance of CSC.

Breast cancer stem cells resist radiation action, and this therapy alone fails to induce an antitumor immune response. In this regard, disulfiram/cooper rendered ionizing radiation-resistant breast CSC as sensitive as non-breast CSC to ionizing radiation-induced immunogenic cell death. Inhibition of XBP1s (X-box binding protein 1 spliced) and ROS scavengers partially reverses disulfiram/cooper-induced immunogenic cell death of breast CSC. This study shows the potential of ionizing radiation and disulfiram/cooper to promote immunogenic cell death in differentiated/differentiating breast cancer cells and radiation-resistant breast CSC involved in cancer formation/progression and metastasis [319].

In patients suffering from malignant hepatocellular carcinoma, ethanol augments both tumors' aggressiveness and progression [320]. Alcohol consumption positively correlates with vessel invasion and TNM stage, and non-drinker patients with hepatocellular carcinoma show a slow progression rate and a better prognosis than chronic drinkers [320]. Ethanol increases the CSC population and enhances the invasion/metastasis and hepatocellular carcinoma cells' stemness. Moreover, it promotes an epithelial to mesenchymal transition by activating the Wnt/ β -catenin signaling pathway. Application of salinomycin (an inhibitor of the previous pathway) or β -catenin siRNA partially rescues

ethanol-induced epithelial to mesenchymal transition. This study demonstrates that ethanol promotes metastasis and stemness of hepatocellular carcinoma cancer cells by inducing an epithelial to mesenchymal transition. Moreover, the Wnt/β-catenin/glycogen synthase kinase 3 β signaling pathway regulates CSC [320]. The activation of this pathway by alcohol promotes tumorigenesis and increases the migration and invasion of cancer cells [283].

High alcohol exposure develops cancer in tissues in direct contact with alcohol (e.g., esophagus, upper larynx, pharynx, oral cavity). Its carcinogenic action mechanism is unknown, but its metabolite, acetaldehyde, exerts a mutagenic activity [321]. A direct effect of long-term use of alcohol-containing mouthwashes suggests a possible link between oral cancer and ethanol cytotoxicity [321, 322]. In keratinocytes, alcohol-induced cell death promotes the mitosis of stem cells (cell division can induce cancer-promoting errors as mutations during DNA replication) [322, 323]. In a concentration-dependent manner, ethanol stimulates stem cells' division to regenerate the damaged epithelium, increasing cancer development risk in those tissues in direct contact with alcohol [322, 324]. Augmented stem cell divisions favor more DNA alterations and a higher risk of malignant transformation [323]. Noteworthy, tissues' self-renewal capacity relates to the risk of developing cancer. A tissue showing a high self-renewal capacity develops cancer more frequently than tissue with a lower capacity [325]. Besides, alcohol intake by favoring stem cell divisions also increases the risk of cancer development in both the esophagus and pharynx and these stem cells become very vulnerable to acetaldehyde and other carcinogenic tobacco components. Therefore, a non-cytotoxic concentration of ethanol could reduce the risk for esophagus, oral cavity, larynx, and pharynx cancer development and decrease tobacco smoking's synergistic effect on these cancers [323]. Altered transcriptional regulation mechanisms are crucial in cellular transformation. Ethanol and nicotine abrogate DNA methylation/histone modifications in normal human oral keratinocytes [326]. Quiescent cells are less vulnerable to DNA damaging agents than dividing cells. In the former, the nuclear membrane protects the DNA highly packaged into chromatin. Due to the lack of protective events in the dividing cells, DNA interacts more efficiently with DNA-damaging agents [323].

Chronic alcohol administration promotes pancreatic cancer development by transforming human pancreatic normal ductal epithelial cells into cancer stem-like cells [327]. During the transformation process, cells showed the phenotype of CSC and expressed stem cell markers (CD133, CD44, CD24) and pluripotency maintaining factors (KLF4, c-myc, Sox2) [327] (Figure 8). Oct4, Sox2, and Nanog are transcription factors that negatively regulate genes favoring differentiation mechanisms [328]. SATB2 (a transcription factor that regulates the expression of pluripotency factors) can bind to the promoters of c-myc, Oct4, Bcl-2, Sox2, and KLF4 genes. Interestingly, inhibition of the SATB2 expression blocked colony formation, CSC markers, pluripotency, and cell proliferation [327]. SATB2 overexpression was associated with cell stemness phenotype acquisition [292, 329]. All data taken together point that chronic ethanol exposure to human pancreatic normal ductal epithelial cells promoted a CSC phenotype via the SATB2.

Witte et al. [330] report high global transcriptional similarities between CSC from different cancers (prostate, uterus, lung, brain). These cancers share upregulated gene expression related to ribosomal and mitochondrial activities. Therefore, CSC from the tumors exhibits many similarities, which are independent of their tumor of origin. This finding is relevant and offers promising research lines for the targeting of CSC.

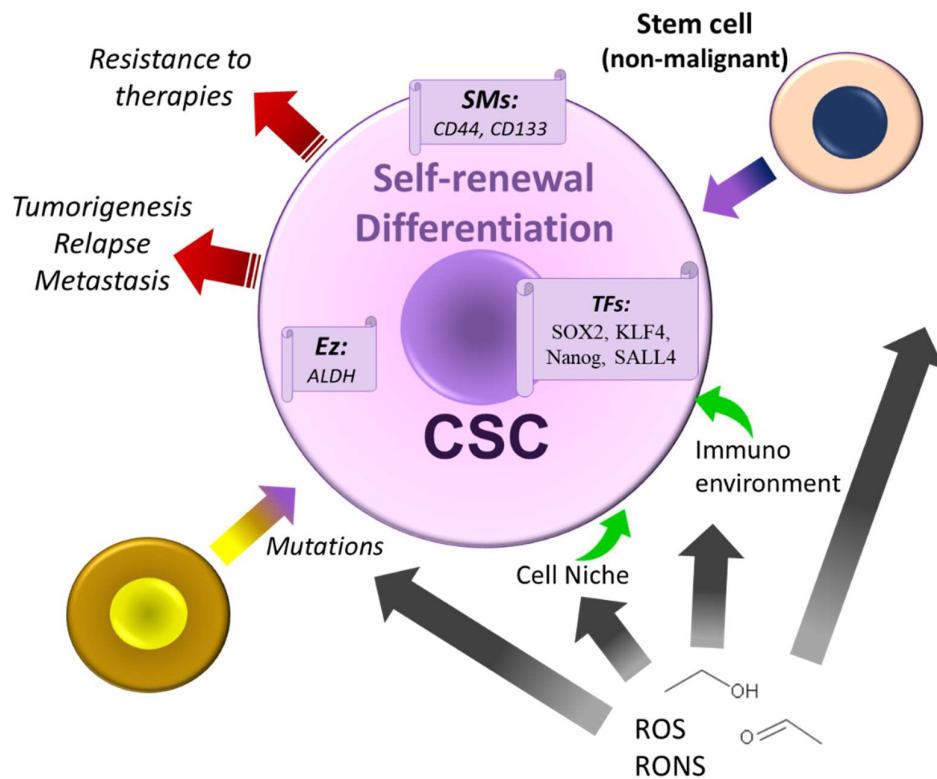


Figure 8. Schematic representation of a cancer stem cell (CSC) generated from non-malignant progenitor stem cells or somatic and differentiated cells by altering essential signaling pathways, epigenetic mechanisms, and mutations. Ethanol and its metabolites may interfere with critical molecular events related to signaling pathways, gene expression regulators, and environmental factors and consolidate CSC phenotypes and clonal heterogeneity within a tumor in different tissues (see text for details). Labels (Ez, SMs, and TFs) include markers that characterize CSC. ALDH, aldehyde dehydrogenase; Ez; enzymes; SMs, cell surface markers; TFs, transcription factors [266, 269, 270, 275, 283, 293, 299-303, 311, 313, 328, 331-335].

CSC (Figure 8) can arise from normal stem cells suffering an oncogenic transformation or progenitor/differentiated somatic or tumor cells suffering a de-differentiation process (de-differentiated cells acquire stemness features). Mechanisms increasing the number of CSC also raise cancer/recurrence [292]. As mentioned above, the accumulation of stem cell divisions is a significant cause of cancer. It seems that cancer originates in these cells [323], which means that the mutagenic agents are not the only cause to produce cancer. By increasing the CSC population or inducing stemness traits in cancer cells, alcohol can prompt cancer therapy resistance, recurrence, and aggressiveness [283]. CSC are refractory to surgical resection, radiation therapy, and chemotherapy, and a report shows that 40% of hepatocellular carcinoma derive from CSC [317]. This example shows the importance of CSC in cancer development/recurrence. The targeting of these cells is crucial to inhibit both processes since CSC are chemoresistant and promote cancer recurrence. CSC express pluripotency (stemness)-associated transcription factor networks (e.g., Notch, Wnt/β-catenin) (Figure 8). Also, they exhibit dysregulation in gene expression. Besides, some signaling pathways surface altered (e.g., phosphatidylinositol 3-kinase/Akt, STAT3, and Sonic hedgehog, transforming growth factor β) [317]. In CSC, alcohol induces ROS (which activates Toll-like receptor 4-Nanog, Wnt/β-catenin/glycogen synthase kinase three β, p38 MAPK signaling pathways), activates epidermal growth factor receptors, and alters the CSC microenvironment. Additional signaling pathways (e.g., transforming growth factor β, JAK-STAT) are also involved in CSC proliferation.

Given the multiple signaling pathways implicated, a combined therapeutic approach to eliminate or block CSC is imperative. The targeting of these cells within the context of alcohol consumption pertains to niches/microenvironment, surface markers, differentiation, and stemness-concerned pathways. The direct effects of ethanol and its metabolites on specific molecular targets responsible for the homeostasis of stem/progenitor cells and the molecular changes related to those effects are summarized in Table 3.

Alcohol may also act by modifying epigenetic mechanisms in stem-like and differentiated cells. In the context of alcohol exposure, the analysis of the implication of oncogenic miRNAs and other epigenetic events in cell transformation may lead to possible pharmacological targets. The altered function of some miRNAs induced by alcohol intoxication and other concomitant factors relates to the formation of head and neck squamous cell carcinoma[336] or hepatic inflammation and fibrosis [337]. Besides, alcohol may change lncRNAs actions and trigger cell transformation of liver stem cells leading to hepatocellular cancer [317].

Table 3. Summary of observations that link alcohol exposure with changes in stem/progenitor cells leading to cancer development, cancer progression, and resistance to current and conventional treatments (see text for details)

ACTORS	MECHANISMS	EFFECTS	REFERENCES
Alcohol long-term treatment.	Upregulated expression of malignant genes (e.g., TP63, KRT15, SAMD9, STEAP4, ITGB6)	Oncogenic transformation and appearance of breast cancer	[269]
ROS imbalance.	Biomembranes, DNA, and protein damage	Affects differentiation/self-renewal of different types of stem cells	[268, 271, 272]
Ethanol and acetaldehyde	Alteration of epigenetic mechanisms (DNA methylation, histone modifications, and noncoding RNAs)	Dysregulation of self-renewal and differentiation pathways in embryonic and adult stem cells	[275-277, 285, 286]
Ethanol and its metabolites.	Changes in stem cell niche's microenvironment, modification of membrane fluidity, and derangement of the extracellular matrix composition and organization.	Block of cell differentiation, DNA damage, and promotion of apoptosis	[268]
Acute and chronic treatments.	Activation of intestinal stem cell divisions and dysregulation of β -catenin signaling	More frequent divisions cause mutations and malignant cell transformation	[284]
ROS and acetaldehyde (mitochondrial oxidative overload)	Alteration of hepatic progenitor cells formation and differentiation	Development of steatosis and hepatocarcinoma	[287-289]
ROS imbalance	Modification of CSC microenvironment and control of ErbB2 expression	Increased number of CSC, augmented cell survival and potentiated malignity, and tumor propagation	[268, 306, 307, 338]
ROS imbalance	Activation of the p38 MAPK/ β -catenin pathways	Promotion of stem/progenitor cell expansion.	[309]
High alcohol exposure	Direct cytotoxic effect or through acetaldehyde-induced mutations	Development of tumors of the oropharynx and gastrointestinal tract (mechanisms not well understood)	[320]

Chronic alcohol drinking	Promotes transformation (alteration of stemness markers)	Human pancreatic ductal epithelial cells transform into cancer stem-like cells	[339]
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6. Concluding remarks and future perspectives

To date, the molecular/cellular mechanisms responsible for carcinogenesis and induced by alcohol are not well understood [269, 340]. Cancers encompass heterogeneous diseases with multifactorial etiology, common characteristics, and specific features depending on the cell type and tissue affected. The relationship between alcohol and cancer appearance rests on an intricate net of molecular events hard to isolate. To decipher whether alcohol is the principal causal effect for a given type of cancer requires further study. Moreover, alcohol shares etiological impact with other environmental factors and individual genetic backgrounds contributing to tumor development and progression.

This review provides a detailed analysis based on *in vivo* and *in vitro* experiments of metabolic pathways that suffer modifications and detours after ethanol exposure. The reactivity of oxidation products such as acetaldehyde and free radicals generates DNA adducts that induce genetic instability and may accentuate oncogenic machinery. Consequently, somatic and stem cells accumulate mutations eventually responsible for tumorigenesis. Besides, nonoxidative metabolites that influence membrane dynamics may compromise membrane function. On the other hand, the imbalance of microbiome communities in the oral and gastrointestinal tract observed after ethanol presence reinforces direct damage through bacterial metabolites affecting the system's normal function and generating a leaky gut that paves the way for inflammation events. Human population studies offer valuable data concerning the influence of polymorphisms on the impact of alcohol. The analysis of human tumor samples offers the possibility of ascertaining molecular changes linked to alcohol consumption.

We propose further studies on the influence of ethanol metabolism using different cell culture and experimental animal approaches (chronic, acute, and binge exposure, both *in vitro* and *in vivo*). In addition, studies on the role of critical enzymes involved in ethanol oxidation and other metabolic routes, including antioxidant pathways or reactions within the one-carbon metabolism hub, might provide a clearer picture. Moreover, the study of signaling pathways, such as TLR4/Nanog, the EGFR/ErbB2, TP53, APC, or KRAS, will give new light to visualize how and to what extent ethanol leads to cell proliferation and malignancy.

The evidence relating direct alcohol biochemical damage with the onset of cell transformation is not conclusive. However, the strong indication provided by basic and clinical research sets ethanol and its metabolic realm as a crucial etiological element. It prompts to analyze in detail some targets with increased sensitivity to ethanol or its metabolites that may have a predominant role in the etiopathogenesis of some cancers in a specific patient. Clinical and molecular views must collaborate to define profiles of cancers to designing tailored therapeutic strategies. Table 4 presents some targets and lines of research to design new and more effective therapies to tackle different cancers.

Alcohol is an avoidable external agent. Therefore, the design of prevention programs should prioritize contributing to better health standards and saving healthcare expenses. The latter assertion may sound naïve since alcohol drinking tendency and behavior lie in deep domains of interconnected human genetic backgrounds, human cultural traditions, and social behavior.

Table 4. Representative examples of candidate targets for developing new treatments to reverse ethanol's damaging effects on cell development, proliferation, and metabolism homeostasis associated with cancers.

TARGET	TUMOR/S	THERAPEUTICS DESIGN	REFERENCES
Acetaldehyde and ROS formation. Mouth and gut microbiomes.	The gastrointestinal tract, oropharynx, lung, liver, and other tissues.	Reduction of acetaldehyde and acetaldehyde reactivity and regulation of glutathione concentrations. Antioxidant strategies to quench free radicals and modulation of antioxidant enzymes: catalase, glutathione S-transferase, glutathione peroxidase, and glutathione reductase. Control of microbiome	[13, 341-345]
The hub of one-carbon metabolism	Colorectal and other tissues.	Increased plasma concentrations of betaine and methionine	[346]
Regulation of NAD synthesis.	Stomach, skin, and other tissues.	Diet supplement of nicotinamide riboside and nicotinic acid riboside and enzymatic regulation of NAMPT (nicotinamide phosphoribosyltransferase) and NMNAT (nicotinamide mononucleotide adenyllyltransferase)	[347-349]
PARP /Sirtuins	Liver, breast	Development of specific PARP inhibitors	[106, 350, 351]
NUMB protein	Breast, liver	Targeting phosphorylation at specific amino acid residues	[316]
Wnt/β-catenin/glycogen synthase kinase 3-β signaling pathway.	Liver	Inhibition of β-catenin with siRNA	[319]
EGFR and ErbB2	Breast	Targeting phosphorylation	[338]
TLR4/Nanog signaling	Liver	Control of oxidative phosphorylation and fatty acid oxidation.	[316]
Long-noncoding RNAs	Liver, esophagus, ovary	Control of expression of long noncoding RNAs	[316]
microRNAs	Liver	Drugs aimed at blocking microRNAs involved in liver fibrosis (For example, microRNA-378, miR-34c)	[337, 352]
Critical proteins in CSC: Notch, Wnt, Hippo, Hedgehog, PIK3/Akt/mTOR.	Several tissues	Immuno control and regulation of activity through reversible and irreversible covalent changes of signaling routes and transcription factors responsible for uncontrolled stem role.	[265, 268, 274, 283, 291, 298-302, 310, 312, 327, 329, 331-334, 338]

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