



Invited critical review

## Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases

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### ABSTRACT

Epidemiological data have identified chronic alcohol consumption as a significant risk factor for cancer in humans. The exact mechanism of ethanol-associated carcinogenesis has remained unknown. The metabolism of ethanol leads to generation of acetaldehyde (AA), which is highly toxic and carcinogenic. The amount of acetaldehyde to which cells or tissues are exposed after alcohol ingestion may be of great importance and may, among others, affects carcinogenesis. Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH). The enzyme responsible for oxidation of acetaldehyde is aldehyde dehydrogenase (ALDH). Both formation and degradation of acetaldehyde depends on the activity of these enzymes. The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in this healthy organs (e.g. liver, stomach, esophagus, colorectum). Moreover the activity of ADH is much higher than the activity of ALDH. This suggests that cancer cells have a greater capability for ethanol oxidation but less ability to remove acetaldehyde than normal tissues. In addition significant differences of ADH isoenzymes activities between cancer tissues and healthy organs may be a factor intensifying carcinogenesis by the increased ability to acetaldehyde formation from ethanol and disorders in metabolism of some biologically important substances (e.g. retinoic acid). The changes in activity of particular ADH isoenzymes in the sera of patients with different cancers, seem to be caused by release of these isoenzymes from cancer cells, and may be useful for diagnostics of this cancer. The particular isoenzymes of ADH present in the serum may indicate the cancer localization.

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### 1. Introduction

Chronic excessive alcohol consumption is a strong risk factor for cancer of the upper gastrointestinal tract (oral cavity, esophagus) as well for cancer of the liver, colorectum, pancreas and some other organs. A great number of epidemiological studies have demonstrated a correlation between alcohol ingestion and the occurrence of cancer

in these organs [1–3]. Although various factors contribute to alcohol-associated cancer development, it has been shown that acetaldehyde (AA) rather than alcohol itself is carcinogenic [4]. Numerous experiments (*in vitro* and *in vivo*) have shown that AA (the first metabolite of ethanol oxidation) has direct mutagenic and carcinogenic effects. Acetaldehyde interferes at many sites with DNA synthesis and repair and consequently can result in tumour development. AA binds rapidly to cellular proteins, what results in morphological and functional impairment of the cells. The formation of stable adducts is one mechanism by which acetaldehyde could trigger the occurrence of replication errors in oncogenes or tumour suppressor genes [5]. In addition to the action of acetaldehyde other mechanisms linked to

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ethanol metabolism may also be involved in the alcohol-associated carcinogenic process:

- induction of cytochrome *P4502E1* leading to the generation of reactive oxygen species and enhanced activation of a variety of procarcinogens, modulation of cellular regeneration and nutritional deficiencies [6];
- alteration of retinal and retinoic acid (RA) metabolism, which leads to a decrease in RA, an important factor for cell differentiation, maturation and regeneration [7].

Acetaldehyde seems to be an important factor in alcohol-associated carcinogenesis. Thus, the amount of AA to which cells or tissues are exposed after alcohol ingestion may be of great importance and may, among others, affects carcinogenesis. The acetaldehyde concentration in tissues depends on its production and degradation which are associated with the activity of two main enzymes. The principal enzymes responsible for ethanol metabolism are alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). The metabolism of ethanol by ADH leads to generation of acetaldehyde. ALDH plays predominant role in the oxidation of acetaldehyde to acetate [8]. Human alcohol dehydrogenase and aldehyde dehydrogenase exists in multiple molecular forms that have been grouped into several classes. The different isoenzymes of ADH and ALDH genetically encoded have different catalytic properties. Therefore, the polymorphism of these enzymes might be a risk factor for cancer of different organs in the case of alcohol consumption [9,10].

## 2. Alcohol dehydrogenase

Mammalian alcohol dehydrogenase is a well-defined system of enzymes in general detoxification of alcohols and, possibly, reactive aldehydes. Human alcohol dehydrogenase is a dimeric protein in the cytosol of cells. The isoenzymes are divided into several classes on the basis of differences in substrate specificity, sensitivity to inhibitors, localization, electrophoretic migration and immunological properties [11]. Amino acid residue identities between classes are at the 60% level (70% in the case of one pair, class I/IV).

Isoenzymes of class I ADH are dimers composed of  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits, encoded by *ADH1A*, *ADH1B* and *ADH1C* loci, which are found in human chromosome 4. Polymorphisms of *ADH1B* and *ADH1C* may also modulate acetaldehyde levels. While the *ADH1B\*2* allele encodes for an enzyme which is approximately 40 times more active than the enzyme encoded by the *ADH1B\*1*, *ADH1C\*1* transcription leads to an ADH isoenzyme 2.5 times more active than that from *ADH1C\*2* [1]. ADH I is mainly expressed in the liver (up to 95% of total activity in this organ) and have been termed “classical” alcohol dehydrogenase. Isoenzymes of class I also exist in the gastrointestinal tract, kidneys and lymes [12].

Class II alcohol dehydrogenase is made up of homodimeric isoenzyme  $\pi\pi$ , encoded by the *ADH2* locus and is found only in the liver [13].

Isoenzyme of class III ADH is identical to the glutathione-dependent formaldehyde dehydrogenase. It contains the  $\chi\chi$  subunits encoded by the *ADH3* locus. ADH III exists in all tested tissues [14].

Class IV is expressed preferably in the stomach and esophagus, although it can be found in lesser quantities in the other tissues such as liver, skin, and cornea. ADH IV is composed of  $\sigma\sigma$  (or  $\mu\mu$ ) subunits, encoded by the *ADH4* locus [15].

The higher classes of mammalian alcohol dehydrogenase, ADH V and ADH VI, have been poorly characterized. So far none of these ADHs have been isolated at the protein level. ADH V and ADH VI have been defined in man and rodents respectively. Isoenzyme of class V has been found in gastric epithelium, and is made up of a homodimer encoded by the *ADH5* locus. Class VI is expressed principally in liver and in minimum quantities in kidneys of rats. It presents its main similarity (67%) with ADH V. There is no knowledge about their

activities, role in ethanol metabolism and participation in metabolic pathways [16,17].

Alcohol dehydrogenase plays a significant role in the metabolism of many biologically important substances, catalyses the oxidation or reduction of a wide spectrum of substrates specificity. The best characterized functions of ADH are protection against excess of endogenous alcohols, products of lipid peroxidation and some exogenous xenobiotics [18]. Among all classes of ADH isoenzymes, class I is the main ethanol-metabolizing isoenzyme in human body. It was also found that this class of isoenzymes participates in bioamine and prostaglandin metabolism and steroid dehydrogenation and  $\omega$ -oxidation of fatty acids. Moreover ADH I catalyses the oxidation of retinol to retinal, the first step in the biosynthesis of retinoic acid [19]. Isoenzyme of class II possesses a high affinity for ethanol and participates actively in the degradation of circulating epinephrine and norepinephrine [20]. The substrates of class III ADH isoenzyme include the endogenous long-chain alcohols and aldehydes e.g. intermediates of lipid metabolism. ADH III catalyses also oxidation of *S*-hydroxymethylglutathione much more effectively than ethanol. The kinetic properties of human class III ADH isoenzyme indicate that this isoenzyme cannot be saturated by ethanol even at high concentrations [21]. Class IV ADH represents a metabolic barrier against ethanol produced from carbohydrates through bacterial fermentation and against orally administered ethanol. Isoenzyme of this class, owing to the kinetic properties and their localization in the superficial part of the gastric mucosa, plays predominant role in the first-pass metabolism of ethanol (FPM) in stomach [22]. Other substrates for ADH IV include retinol, 4-hydroxynonenal (lipid peroxidation product) and nitrobenzaldehyde. The metabolic role of classes V and VI isoenzyme of alcohol dehydrogenase is still enigma. The Table 1 shows the different classes of ADH described above as well as the subunits that they comprise and their tissue localization.

## 3. Aldehyde dehydrogenase

Aldehyde dehydrogenases are a group of enzymes catalyzing the oxidation more than 90% of all acetaldehyde produced from ethanol, transforming it into acetate in a reaction coupled to  $\text{NAD}^+$  reduction. Mammalian ALDH activity was first observed in the liver nearly 60 years ago and thereafter several types of aldehyde dehydrogenase were distinguished based on their physicochemical characteristics, enzymatic properties, subcellular localization, and tissue distribution [23]. Ten known human ALDH genes and corresponding enzymes are listed in Table 2. Tissue distribution and subcellular localization of individual ALDHs are also shown in this table. Comparison of the aldehyde dehydrogenase isoenzymes indicates a wide range of divergence among them. However, several protein regions, some of which are implicated in functional activities, are conserved in the family members [24]. Aldehyde dehydrogenase can be divided into groups according to their Michaelis constant values for acetaldehyde. ALDH I and ALDH II isoenzymes belong to the low  $K_m$  (3–50  $\mu\text{mol/l}$ ) forms, whereas e.g. ALDH3 and ALDH4 are the high  $K_m$  (5–83  $\text{mmol/l}$ )

**Table 1**  
Human alcohol dehydrogenase (ADH) polymorphism

Class	Gene	Subunit	Tissue distribution
I	<i>ADH1A</i>	$\alpha$	Liver
	<i>ADH1B*1</i>	$\beta_1$	Liver, lungs, kidneys
	<i>ADH1B*2</i>	$\beta_2$	
	<i>ADH1B*3</i>	$\beta_3$	
	<i>ADH1C*1</i>	$\gamma_1$	Liver, stomach,
	<i>ADH1C*2</i>	$\gamma_2$	
II	<i>ADH2</i>	$\pi$	Liver
III	<i>ADH3</i>	$\chi$	All tissues
IV	<i>ADH4</i>	$\sigma$ ( $\mu$ )	Stomach, esophagus, liver, skin, cornea
V	<i>ADH5</i>	?	Stomach

**Table 2**  
Aldehyde dehydrogenase (ALDH) polymorphism

Class	Locus genu	Allele	Structure	Tissue distribution (subcellular localization)
I	<i>ALDH-1</i>	ALDH1	Tetramer	Liver, stomach, brain (cytosol)
II	<i>ALDH-2</i>	ALDH2*1	Tetramer	Liver (mitochondrium)
		ALDH2*2	Tetramer	Liver, stomach (mitochondrium)
III	<i>ALDH-3</i>	ALDH3	Dimer	Stomach, lung, liver (cytosol)
IV	<i>ALDH-4</i>	ALDH4	Dimer	Liver, kidney (mitochondrium)
V	<i>ALDH-5</i> ( <i>ALDH-χ</i> )	?	?	Testis, liver, brain, stomach (mitochondrium)
VI	<i>ALDH-6</i>	?	?	Salivary gland, stomach (cytosol)
VII	<i>ALDH-7</i>	?	?	Kidney, lung (microsomes)
VIII	<i>ALDH-8</i>	?	?	Parotid (microsomes)
IX	<i>ALDH-9</i>	?	?	Liver, kidney, muscle (cytosol)
X	<i>ALDH-10</i>	?	?	Liver, heart (mitochondrium)

forms [25]. Isoenzymes of classes I and II play predominant role in the acetaldehyde metabolism.

ALDH I is a cytosolic enzyme ubiquitously distributed in various tissues including liver, stomach and brain. This class has tetrameric structure with 54 kDa subunits, encoded by the *ALDH-1* gene, which is found in chromosome 9. ALDH I possesses a high affinity for retinal and plays a vital role in the oxidation of both *all-trans*- and *9-cis*-retinal [26]. Class I exhibits a high affinity for metabolism of aldophosphamide and participate in the detoxification of widely used anticancer drugs [27].

ALDH II exists in the mitochondrial matrix of various tissues with the highest level in the liver. It is composed of tetrameric enzymes with 5 kDa subunits, encoded by the *ALDH-2* genes located in chromosome 12, which possesses two alleles, *ALDH2\*1* and *ALDH2\*2*. Investigations of alcohol consumption and the frequency of ALDH II deficiency showed a high correlation. It was found that individuals possessing the *ALDH2\*2* gene (deficient ALDH II) may refrain from excessive drinking and thus alcoholism, due to adverse reactions such as increased heart rate, flushing and headache [28]. ALDH II exhibits a high activity for oxidation of acetaldehyde. Liver mitochondrial aldehyde dehydrogenase (ALDH II) is responsible for the metabolism of more than 65% of acetaldehyde, whereas cytosolic form (ALDH1) catalyses 20% of acetaldehyde generated during ethanol oxidation [29].

Other classes of ALDH isoenzymes play minor role in AA oxidation but have been considered as general enzymes which eliminate toxic biogenic and xenobiotic aldehydes, such as those present in monoamines, diamines and polyamines. They also participate in the metabolism of aldehydes generated during membrane lipoperoxidation processes [30].

#### 4. ADH and ALDH in the cancer

The transformation of healthy cells to cancer cells is based on the loss of control mechanisms, cell differentiation disorders and uninhibited growth. Cancer cells have the ability to indemnify substances necessary

to growth and development, leading to a change in intracellular metabolism in neoplastic tissue. The metabolism of cancer is in many ways different than in healthy cells. Some metabolic pathways are intensified, and others are inhibited. Differences of ADH and ALDH activity between cancer cells and healthy tissue may be one of the factors intensifying carcinogenesis. The differences of the activities of total ADH, ALDH and ADH isoenzymes between cancer and healthy tissue are demonstrated in Table 3. Table 3 shows also the changes of these enzymes activity in the serum of patients with cancer.

The direct correlation between chronic ethanol abuse and the development of hepatocellular cancer remains still unknown. After ethanol ingestion, the liver represents the major site of its metabolism by alcohol dehydrogenase, which leads to the acetaldehyde generation. The activity of ADH I, the main ethanol-metabolizing isoenzymes in the liver is about 26% higher in the hepatocellular cancer than in healthy hepatocytes. Moreover the total activity of alcohol dehydrogenase and aldehyde dehydrogenase is significantly higher in cancer liver tissue. This would suggest that cancer cells have a greater capability of exogenous ethanol oxidation and higher ability to remove acetaldehyde than healthy hepatocytes. However the ALDH activity is much lower than ADH in the cancer tissue. The increased activity of class I ADH in hepatocarcinoma cells might be a factor which can intensify carcinogenesis in the liver by the increased ability to acetaldehyde formation from ethanol [31]. In addition the changed activities of ADH or ALDH in cancer cells could be reflected by enzyme activity in the serum of patients with cancer. In the case of liver cancer the activity of class I alcohol dehydrogenase isoenzymes is elevated only in the serum of patients with metastatic liver tumour. This increase of activity seems to be caused by the enzyme released from liver cancer cells and maybe from primary tumors originating in other organs or it depends on the size of cancer tissue [32].

Colorectal cancer cells exhibited ADH and ALDH activities. The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in healthy ones (about 27–29%). In contrast, the total activity of ALDH is lower in cancer tissues than in healthy mucosa (about 25%). The ALDH activity seems to be disproportionately low to the activity of ADH. The activity of ADH and ALDH is in the ratio of 20.5:1 in cancer cells and only 10:1 in normal mucosa. Among all classes of ADH isoenzymes, only activity of class I is significantly higher in cancer tissue than in healthy cells of colorectum. The increased activity of ADH (especially class I) and decreased ALDH activity in the colorectal cancer tissue suggest that the cancer cells have a greater capability for ethanol oxidation and less ability to remove acetaldehyde than healthy mucosa. This may lead to the accumulation of acetaldehyde in the colonic mucosa and contribute to the development of alcohol-related colorectal cancer [33]. The activity of ADH in cancer tissues of drinkers did not differ from that in nondrinker specimens. This would suggest that the increase of ADH activity in colorectal cancer tissues is carcinogenesis. In the course of colorectal cancer, class I alcohol dehydrogenase isoenzymes is elevated in the serum of patients. The changes in activity appear to be caused by isoenzyme being released from colorectal cancer cells [34].

**Table 3**  
ADH and ALDH in the cancer tissue and serum of tested patients

Activity	ADH I		ADH II		ADH III		ADH IV		ADH total		ALDH	
	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum	Tissue	Serum
Cancer												
Liver	↑	↑	↔	↔	↔	↔	↔	↔	↑	↑	↑	↔
Esophagus	↔	↔	↔	↔	↔	↔	↑	↑	↑	↑	↔	↔
Stomach	↔	↔	↔	↔	↔	↔	↑	↑	↑	↑	↔	↔
Colorectum	↑	↑	↔	↔	↔	↔	↔	↔	↑	↑	↓	↔
Pancreas	↔	↔	↔	↔	↑	↑	↔	↔	↔	↑	↔	↔
Breast	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

↑ Higher activity in the cancer.

↔ No differences of activity between cancer and healthy.

↓ Lower activity in the cancer.

ADH and ALDH activities are present in the gastric cancer cells. The activity of ADH is significantly higher in cancer tissues than that in healthy and the activity of ALDH is not different between both tissues. It is important also that activity of ADH is much higher than the activity of ALDH. The comparison of ADH isoenzymes activities showed that the highest activity is exhibited by class IV ADH. Moreover the activity of class IV ADH is significantly higher in gastric cancer than in healthy stomach. The situation is the same in the esophageal cancer which contains relatively higher ADH and lower ALDH activity, compared to the healthy mucosa. This suggests that there is a very high ethanol-oxidizing activity and considerably low acetaldehyde-oxidizing activity in the esophageal and gastric cancer cells. Isoenzyme of class IV ADH, owing to the kinetic properties and their localization in the superficial part of the stomach or esophageal mucosa, plays a predominant role in the acetaldehyde production. The increased activity of this class in cancer cells leads to an increased ability of acetaldehyde formation from exogenous ethanol. ADH IV participates also in retinoid acid, 4-hydroxynonenal (a lipid peroxidation product), and nitrobenzaldehyde (a dietary carcinogen) metabolism [35]. Their interaction with metabolism of ethanol might be a factor for disturbances in low mature cancer cells and can intensify the carcinogenesis in the stomach or esophagus [36,37]. The increased total activity of alcohol dehydrogenase and class IV isoenzyme in the sera of patients with gastric or esophageal cancer can be caused by the release of this isoenzyme from cancer cells [38,39].

The total activity of ADH is higher in the cancer cells of liver, colorectum, stomach and esophagus than in healthy tissue of these organs. However this is not a general finding. For example, in the pancreatic cancer the analysis of ADH activity does not indicate differences between cancer and healthy cells. There are, in addition, no significant differences in ALDH activity between both tissues [40]. Estival et al. reported that the pancreas have a limited capacity for oxidation of ethanol, while Guynn et al. concluded that ethanol is not oxidized by the pancreas [41,42]. In contrast Haber et al. reported that ADH III is responsible for the oxidized significant amount of ethanol in pancreatic acinar cells [43]. The metabolism of ethanol in the pancreas remains undefined. There is also nonoxidative pathway of ethanol metabolism which occurs predominant. In nonoxidative pathway the fatty acid ethyl esters are generated in the reaction catalysed by fatty acid ethyl esters synthase (FAEE) [44]. Thus it is not possible to say that metabolism of ethanol by alcohol dehydrogenase might be responsible for carcinogenesis in the pancreas. Moreover the activity of class III ADH in the pancreas cancer is about 30% higher than that in normal pancreatic tissue. However, the kinetic properties of this class (high Michaelis constant) indicate that ADH III cannot be saturated by ethanol in pancreas cancer cells or pancreatic acinar cells. This isoenzyme participates in the metabolism of *S*-hydroxymethylglutathione, which is responsible for maintenance of redox state in the cells [14]. Probably it leads to depletion of glutathione and production of superoxide radical. An enhanced generation of superoxide radical may lead to oxidative stress. Oxidative stress has been implicated in the development of pancreatic cancer. The high activity of ADH III in cancer cells may explain the marked increase of this isoenzyme in the sera of patients with pancreatic cancer. Probably it is released from cancer cells [45].

Another situation is in breast cancer. The total activity of alcohol dehydrogenase and aldehyde dehydrogenase in cancer tissues does not differ from normal parenchyma but the activity of the class I ADH isoenzyme is about 2 times lower in breast cancer cells than that in healthy mammary tissues. ADH I participate in retinoid acid metabolism. It is a principal mediator in action of retinoids required for maintaining epithelia in a differentiated state [46,47]. Decrease of class I ADH activity in breast cancer cells might be a factor of some disorders in metabolism of biologically important substances which are indispensable to correct differentiation and maturation of the breast parenchyma cells [48]. It is commonly accepted that alcohol

may influence the levels of reproductive steroid hormones that play a critical role in breast carcinogenesis by either decreasing metabolic clearance or increasing the production of estrogens [49]. On the other hand breast cancer may involve sex hormones, which affect ADH activity and intensify carcinogenesis. The analysis of total ADH and ALDH activity in the serum does not indicate significant difference between the patients with cancer and healthy women. Among all tested classes of ADH isoenzymes, only class I has higher activity in the serum of patients with breast cancer in stage IV. The changes in activity of class I ADH, appear to be caused rather by isoenzymes being released from the organ damaged by metastatic disease, than from breast tumour [50].

## 5. Summary

Chronic alcohol consumption is a major risk factor for cancer of some human organs (upper digestive tract, colorectum, liver, pancreas, breast). The mechanisms of alcohol influence on the processes of carcinogenesis are not yet completely understood. Increased metabolism of several carcinogenic substances may take place in cancer cells. Evidences have accumulated that acetaldehyde, first product of ethanol metabolism, is predominantly responsible for carcinogenesis. Acetaldehyde is produced in different organs by various isoenzymes of alcohol dehydrogenase and is degraded by aldehyde dehydrogenase to acetate. Both formation and degradation of acetaldehyde is modified by the activity of ADH and ALDH. The total alcohol dehydrogenase activity is significantly higher in cancer tissues than in these healthy organs. Moreover the ADH activity seems to be disproportionally higher to the activity of ALDH in cancer tissue. This would suggest that cancer cells have a greater capability for ethanol oxidation and considerably less ability to remove acetaldehyde than healthy tissues. It may increase its concentration in cancer tissue and intensify the carcinogenesis. Differences of activity of various ADH isoenzymes between cancer cells and healthy tissue might be a factor of some disorders in metabolic pathways with participation of these isoenzymes what can lead to carcinogenesis. The changes in activity of ADH isoenzymes in the sera of patients with cancer, appear to be caused by isoenzymes being released from cancer cells, and may be useful for diagnostics of this cancer.

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