Editorial

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Pharmacological chaperone therapies: Can aldehyde dehydrogenase activator make us healthier?

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Alcoholic liver disease (ALD) is characterized by the development of steatosis, inflammation, hepatocyte necrosis, and apoptosis, with eventual development of fibrosis and cirrhosis [1–3]. Despite being one of the major causes of morbidity and mortality in the world, there are actually no current effective drug treatments for severe ALD [1–3]. Accumulating evidence suggests that ethanol metabolite acetaldehyde and its by-products (such as: 4-hydroxy-2-nonenal (4-HNE), and malondialdehyde (MDA)) are highly toxic and even carcinogenic, contributing to the pathogenesis of various alcohol-associated disorders including ALD [1–3]. Over the last twenty years, researchers have been extensively exploring drugs that can activate aldehyde dehydrogenase (ALDH) enzyme and subsequently accelerate acetaldehyde clearance [4], and have demonstrated that these ALDH activators (e.g. ALDH activator-1: Alda-1) can protect against ethanol-induced cardiac injury, ischemic brain injury, radiation dermatitis etc. in animal models [4]. In this issue of the *Journal of Hepatology*, Zhong *et al.* [5] nicely demonstrated that treatment with Alda-1 reversed alcoholic steatosis and apoptosis by accelerating aldehyde clearance in an animal model of ALD.

During lifespan, every organism receives toxic challenge from numerous harmful agents. Some are produced endogenously, while others accumulate after ingestion of food or exposure to environmental pollutants. Organisms have evolved effective protective mechanisms to prevent their propagation, such as: detoxification through enzymatic reactions. Among phase-I oxidizing enzymes, *ALDH* is a gene superfamily responsible for the detoxification of biogenic and xenogenic aldehydes [6], with the most abundant members, being ALDH2, which is involved in the metabolism of ethanol-derived acetaldehyde and other aldehydes [6], and ALDH1, which has been found to be highly expressed in many adult tissue stem cells or progenitor cells, including hematopoietic, neuron, muscle, hepatic, adipose stem cells, and progenitor cells [7–9]. Aldehydes are widespread organic compounds found in the environment or formed from metabolism of various compounds. Importantly, aldehydes are strong electrophilic compounds that can form adducts with cellular components (i.e. proteins and nucleic acids) thereby initiating adverse biological effects (i.e. loss of protein activity and mutation of nucleic acids) [10]. Hence, disposal of aldehyde is a priority for cell protection and survival, even more so for long-living cells such as progenitors. Evidence from human phenotypes directly linked to mutations and polymorphisms in *ALDH* genes, leading to the absence, deficiency or inactivation of ALDH proteins, stress the clinical importance of the ALDH superfamily. Such disorders include type II hyperprolinaemia, Sjögren-Larsson syndrome, alcohol-induced flushing syndrome and others [6]. Diseases caused by mutations in *ALDH* genes involve the building-up of substances in the body that are harmful in large amounts or that impair the function or production of necessary molecules. Therefore, the use of pharmacological activators or inhibitors of ALDH isoenzymes represents a coherent approach for the treatment of these pathological disorders [6].

Among the 19 human ALDH isoenzymes [6,11], ALDH2 (or *ALDH2*1*) is described to be the most efficient for the metabolism of ethanol-derived acetaldehyde, but also to carry the most well-known polymorphism (*ALDH2*2*) with ALDH2 activity deficiency. Eight percent of the world population have this common polymorphism, which renders the enzyme inactive *in vivo* [4]. Accumulation of acetaldehyde after ethanol consumption leads to the development of unpleasant physiological effects comprising facial flushing, nausea, and tachycardia. This condition, termed the alcohol flushing syndrome experienced by persons with the ALDH2*2 polymorphism, renders a large population of East Asians intolerant of what might be considered "normal" levels of alcohol consumption (see Refs. [4,6,12]). However, many people with the dominant inactive form of ALDH2*2 still drink heavily and they have high levels of blood acetaldehyde even after drinking only a moderate amount of alcohol [13]. Several studies have examined the role of ALDH2*2 polymorphism in the pathogenesis of ALD and suggest that ALD patients with inactive ALDH2 had a high risk for the progression of liver disease [14–16]. To increase the activity of this ALDH2*2 mutant allele,

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researchers have developed Alda-1 (or [N-(1,3-benzodioxol-5-yl-methyl)-2,6-dichlorobenzamide]) that acts as a structural chaperone to activate wild-type ALDH2 and restore the mutant ALDH2*2 to near wild-type activity by aiding in the proper folding of a section of the polypeptide chain that lacks stable structure in its absence, allowing it to break down toxic aldehydes quicker and leaving less time for them to cause damage [17]. Interestingly, Alda-1 also increases productive substrate-enzyme interaction, allowing an increase of ALDH2 activity, and protects the wild-type ALDH2 (i.e. ALDH2*1) from inactivation due to adduct formation between the substrate and the enzyme [17,18]. The manner in which Alda-1 binds to the structure of ALDH2 provides powerful insight into the relationships between chaperones of this detoxifying enzyme leading to the plausible modification of Alda-1 to improve its potency, but also opens up the possibility of designing new analogs that can selectively affect the metabolism of other molecules that are detoxified by ALDHs [17].

The study from Zhong *et al.* [5] demonstrates that enhancing the ALDH2 activity by the use of Alda-1 can ameliorate several deleterious effects related to aldehydes (Fig. 1) and may provide a better protection against both acute and chronic injury pre-established by chronic alcohol exposure [5]. Indeed, in alcohol intoxicated animals, Alda-1 accelerates plasma and hepatic aldehyde clearances, reduces the level of 4-HNE, reverses steatosis, and diminishes alcohol-induced endoplasmic reticulum stress and apoptosis (Fig. 1). These findings are encouraging, and warrant further investigations in other models of ALD. For example, a recent study reported that ALDH2 deficiency exacerbates alcohol and/or hepatotoxin-induced liver inflammation and fibrosis [19]. Thus it is important to test whether Alda-1 treatment also ameliorates alcoholic liver inflammation and fibrosis. Also, alcohol consumption can disrupt the intestinal epithelial barrier resulting in increased gut permeability, recently documented as a major factor in ALD (see reviews [20,21]). Since acetaldehyde-induced intestinal permeability has been demonstrated [22], and also that microbes and intestinal cells can detoxify alcohol into acetaldehyde, it is legitimate to speculate that these microbes and intestinal cells might also uptake Alda-1 once delivered by intraperitoneal injection (see Table 1 in ref [5]). Consequently, Alda-1 may favorably co-influence the course of aldehyde clearance, liver injury (decrease of ALT, AST) and outcome of ALD acting on gut microbiota. In addition, ALDH1 is highly expressed in liver progenitor cells and is believed to play an important role in promoting liver progenitor cell survival [9], thus, activation of ALDH by Alda-1 may have beneficial effects for liver repair via the stimulation of liver progenitor cells. However, cancer stem cells also express high levels of ALDH1 [8], so it is important to examine whether ALDH activator also affects cancer stem cells and has a risk for promoting liver cancer development and progression.

What is the therapeutic potential of ALDH activators such as Alda-1 for the treatment of ALD? Because abstinence is the cornerstone for treatment of ALD, most ALD patients during treatment periods are not active drinkers or are commonly treated with approaches to eliminate alcohol ingestion. Indeed, disulfiram (or Antabuse™), an irreversible inhibitor of ALDH, is commonly prescribed to treat alcoholism to prevent acetaldehyde metabolism, which results in elevation of acetaldehyde and subsequently causes unpleasant effects and aversion to alcohol. Disulfiram is not recommended for patients with advanced ALD due to its potential severe hepatotoxicity. Because ALD patients, who are not active drinkers, most likely have low levels of acetaldehyde, treatment of these patients with Alda-1 may not generate significant beneficial effects. For ALD patients who are active drinkers, treatment with Alda-1 may reduce acetaldehyde

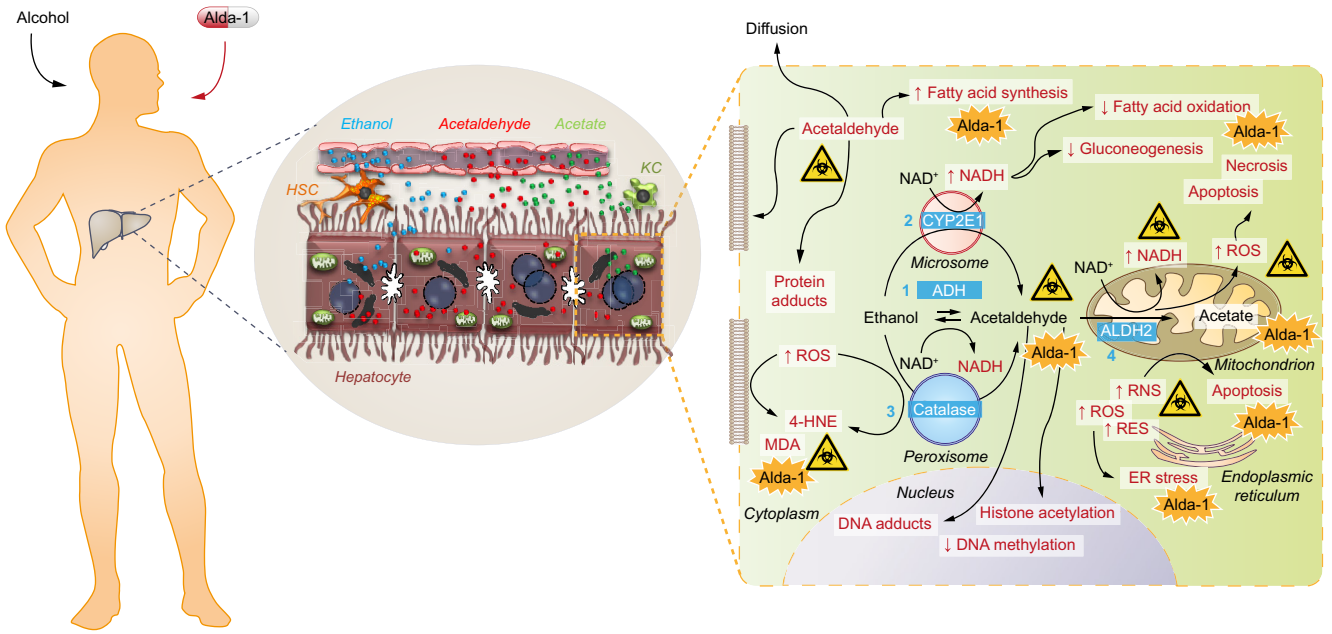

Fig. 1. The pharmacological chaperone Alda-1 exerts multiple beneficial effects against acetaldehyde toxicity. The liver is the main site of alcohol metabolism and 3 main pathways exist: alcohol dehydrogenase (ADH), cytochrome P-450 (CYP) 2E1, and catalase. ALDH2 enzyme breaks down a by-product of alcohol called acetaldehyde, forming free radicals that can damage cells. Toxic effects of alcohol on organs and tissues in human are largely a consequence of its metabolism to acetaldehyde, and associated formation of ROS, RNS and RES, depletion of co-factors, and impairments in energy homeostasis. Enhancing the ALDH2 activity by the use of Alda-1 can ameliorate several deleterious effects related to aldehydes represented by red balloons in the scheme.

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levels and consequently ameliorate liver toxicity, but may also have a risk to promote alcohol drinking in these patients. Therefore, the therapeutic potential of ALDH activators for ALD remains to be carefully determined. Alda-1 treatment may have some therapeutic potential to reduce alcohol toxicity in patients with excessive acute alcohol consumption especially in those with inactive ALDH2. Finally, whether treatment with ALDH activators has beneficial effects for other aldehyde accumulation-related diseases deserves further studies.

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Conflict of interest

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