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Aldehyde Dehydrogenases in Cellular Responses to Oxidative/ electrophilic Stress

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Abstract

Reactive oxygen species (ROS) are continuously generated within living systems and the inability to manage ROS load leads to elevated oxidative stress and cell damage. Oxidative stress is coupled to the oxidative degradation of lipid membranes, also known as lipid peroxidation. This process generates over 200 types of aldehydes, many of which are highly reactive and toxic. Aldehyde dehydrogenases (ALDHs) metabolize endogenous and exogenous aldehydes and thereby mitigate oxidative/electrophilic stress in prokaryotic and eukaryotic organisms. ALDHs are found throughout the evolutionary gamut, from single celled organisms to complex multicellular species. Not surprisingly, many ALDHs in evolutionarily distant, and seemingly unrelated, species perform similar functions, including protection against a variety of environmental stressors like dehydration and ultraviolet radiation. The ability to act as an ‘aldehyde scavenger’ during lipid peroxidation is another ostensibly universal ALDH function found across species. Up-regulation of ALDHs is a stress response in bacteria (environmental and chemical stress), plants (dehydration, salinity and oxidative stress), yeast (ethanol exposure and oxidative stress), *Caenorhabditis elegans* (lipid peroxidation) and mammals (oxidative stress and lipid peroxidation). Recent studies have also identified ALDH activity as an important feature of cancer stem cells. In these cells, ALDH expression helps abrogate oxidative stress and imparts resistance against chemotherapeutic agents such as oxazaphosphorine, taxane and platinum drugs. The ALDH superfamily represents a fundamentally important class of enzymes that significantly contributes to the management of electrophilic/oxidative stress within living systems. Mutations in various ALDHs are associated with a variety of pathological conditions in humans, underscoring the fundamental importance of these enzymes in physiological and pathological processes.

Keywords

Aldehyde dehydrogenase; Cancer stem cells; Chemical stress; Dehydration; Electrophilic stress; Oxidative stress

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Introduction

Aldehyde dehydrogenases (ALDHs) are involved in a variety of biological processes in prokaryotic and eukaryotic organisms. Their expression is up-regulated in response to abiotic and biotic stress generated by perturbed endobiotic and/or xenobiotic metabolism. Such stress-responsive expression of ALDHs manifests in a broad range of plant and animal species, underscoring the evolutionary conservation of biological adaptations to oxidative and electrophilic stresses (Table 1). Living organisms are constantly confronted by oxidative stress and the reactive oxygen species (ROS) derived therefrom. In animals, inflammation, mitochondrial respiration, xenobiotic metabolism and other processes generate oxidants that contribute to ROS formation. ALDHs are known to decrease oxidative stress, particularly that caused by aldehydes [1, 2]. ALDH induction has been observed in a variety of plants species exposed to heat, dehydration, salinity, oxidants, ultraviolet (UV) radiation, pesticides or metals. Mechanical trauma and fungal infection can also elicit ALDH up-regulation in plants [3]. Pathogenic bacteria encounter oxidative stress emanating from the host immune response that must be overcome during invasion and sustained infection [4, 5]. Organisms, including yeast and *Caenorhabditis elegans*, also express a variety of ALDHs in response to oxidative stress [6, 7]. The representation of the *ALDH* gene superfamily in all three taxonomic domains (*Archaea*, *Eubacteria* and *Eukarya*) is suggestive of a crucial role for these enzymes throughout evolutionary history [8]. Aldehydes are strongly electrophilic, highly reactive and relatively long-lived compounds. Reactive aldehydes readily form adducts with DNA, RNA and proteins, leading to impaired cellular homeostasis, enzyme inactivation, DNA damage and cell death [9-11]. They have been implicated in oxidative stress-associated diseases, such as atherosclerosis, cancer, diabetes, chronic alcohol exposure, acute lung injury, and in neurodegenerative diseases like Alzheimer's and Parkinson's disease [9, 12, 13]. The ALDH superfamily contains NAD(P)⁺-dependent enzymes that oxidize a wide range of endogenous and exogenous aldehydes to their corresponding carboxylic acids [1]. The ability of ALDHs to act as 'aldehyde scavengers' is grounded in the observation that many have broad substrate specificities and can metabolize a wide range of chemically- and structurally-diverse aldehydes. Many of the ALDH isozymes overlap in relation to substrate specificities, tissue distribution and subcellular localization but vary in their efficiency in metabolizing specific aldehydes [14-17]. The human genome contains 19 protein-coding *ALDH* genes. ALDH proteins are found in one or more subcellular compartments including the cytosol, mitochondria, endoplasmic reticulum and nucleus, as well as plastids in plants [14]. Mutations and polymorphisms in *ALDH* genes are associated with various pathophysiological conditions in humans and rodents [1, 18] including Sjögren-Larsson syndrome [19], type II hyperprolinemia [20], γ -hydroxybutyric aciduria [21], pyridoxine-dependent epilepsy [22], hyperammonemia [23], alcohol-related diseases [24], cancer [25] and late-onset Alzheimer's disease [14, 26] (Table 2). ALDH enzymes may also play important antioxidant roles by producing NAD(P)H [27, 28], directly absorbing UV radiation [29, 30] and scavenging hydroxyl radicals *via* cysteine and methionine sulphydryl groups [31].

Aldehyde generation and metabolism

Aldehydes are generated during metabolism of various endobiotic and xenobiotic compounds. For example, aldehydes are associated with the metabolism of alcohols, amino acids (e.g., lysine, valine, proline and arginine), anticancer drugs (e.g., cyclophosphamide) and neurotransmitters (e.g., -aminobutyric acid (GABA), serotonin, noradrenaline, adrenaline, dopamine) [1, 32, 33]. Lipid peroxidation (LPO) of cellular phospholipids induces the formation of more than 200 highly-reactive aldehyde species, including 4-hydroxy 2-nonenal (4-HNE), malondialdehyde (MDA), 4-oxononenal (4-ONE), acrolein,

crotonaldehyde and methylglyoxal [14, 34, 35]. Environmental pollutants, such as smog, cigarette smoke, motor vehicle exhaust, pesticides and various food additives, either contain or contribute to the formation of aldehydes, including formaldehyde, acetaldehyde and acrolein [14, 34, 35]. While some aldehydes play vital roles in normal physiological processes, including vision, embryonic development and neurotransmission, many aldehydes are cytotoxic and carcinogenic [14, 25]. ALDHs play critical roles in metabolizing these endogenous and exogenous molecules.

In addition to acting as general aldehyde scavengers, many ALDHs play important roles in homeostatic pathways. Five members of the ALDH family, *viz.* ALDH1A1, ALDH1A2, ALDH1A3, ALDH1A7 and ALDH8A1, catalyze the irreversible conversion of retinaldehyde to retinoic acid (RA), which plays critical role in developmental process by modulating retinoid signaling [1, 36]. ALDH1L1, also known as 10-formyltetrahydrofolate dehydrogenase (FDH), is involved in the conversion of 10-formyltetrahydrofolate to tetrahydrofolate, a critical reaction for replenishing the cellular folate pool [1, 37]. Several ALDHs are also involved in the detoxification of LPO-derived reactive aldehydes, which are implicated in promoting covalent modification of proteins and DNA and in diseases resulting from such modifications [38, 39]. ALDH3A2 catalyzes the oxidation of fatty aldehydes; loss of this enzyme results in Sjögren-Larsson syndrome [19]. ALDH4A1 and ALDH6A1 have been implicated in the metabolism of the amino acids arginine, proline and L-valine [1]. The ALDHs have important functions in the synthesis and metabolism of GABA, a major inhibitory neurotransmitter in central nervous system. Specifically, ALDH5A1 converts succinic semialdehyde, a product of GABA metabolism, to succinic acid [40]. In contrast, ALDH9A1 is involved in the alternative biosynthetic pathway for GABA from γ -aminobutyraldehyde [41]. ALDH2, ALDH1B1 and ALDH1A1 metabolize acetaldehyde, the ethanol metabolite implicated in ethanol intolerance and in various cancers [1]. Elevated expression of ALDH isozymes (ALDH1A1, ALDH3A1 and ALDH5A1) has also been proposed as a major mechanism by which cancer cells develop resistance against cyclophosphamide (CP) [42, 43].

ALDHs and organismal response to oxidative stress

Bacteria

Bacteria are constantly confronted by oxidative stress. ROS are generated from a number of sources including leakage of single electrons from respiratory enzymes, environmental stresses (e.g., UV radiation), redox cycling agents (e.g., menadione and paraquat), as well as metal-catalyzed oxidation *via* exposure to free copper (Cu^+) or iron (Fe^{2+}) [4]. Pathogenic bacteria also encounter oxidative stress related to a host immune response. Owing to their longer half-lives relative to reactive oxygen and nitrogen species, aldehydes formed during oxidative stress can be significant contributors to an organism's defense against bacteria. The full complement of bacterial ALDHs has not been systematically examined. Nevertheless, any putative ALDHs would presumably metabolize and thereby mitigate the toxicity of aldehydic intermediates.

Investigation of global changes in bacterial protein expression has revealed the up-regulation of ALDH as occurring after exposure to environmental and chemical stressors. There is evidence that such up-regulation is a critical component of general stress response pathways in bacteria and of oxidative stress responses in particular. For example, exposure of *Escherichia coli* to low levels of the oxidant hydrogen peroxide (H_2O_2) renders bacteria less vulnerable to the toxic effects of what would normally be lethal H_2O_2 concentrations. This presumably occurs as a result of induction of cytoprotective mechanisms. The H_2O_2 -exposed *E. coli* were also protected from normally toxic doses of several reactive aldehydes including formaldehyde, glutaraldehyde, glyoxal, methyl glyoxal and chloroacetaldehyde

[44]. These observations support the notion that aldehyde metabolism is an important component of the bacterial cytoprotective response to oxidative stress. Mechanistically, the response of bacteria to oxidative stress requires expression of RecA, a gene normally associated with the “SOS response” triggered by DNA damage. However, RecA activation by oxidative stress appears to function independently of SOS response pathways [44]. In another study, *E. coli* exposed to oxidative stress *via* H₂O₂ treatment exhibited higher levels of known aldehyde metabolites, specifically glycolate, 4-aminobutyrate and succinic acid. These compounds are generated by the bacterial ALDHs aldA (ALDH50A1), ydcW (ALDH51A1) and yneI (ALDH52A1)/gabD (ALDH5H1), respectively [45]. Arsenite (As³⁺) exposure induces oxidative stress by disrupting the citric acid cycle and releasing unbound Fe²⁺ which then elicits ROS generation *via* the Fenton reaction. Exposure of *Pseudomonas aeruginosa* to arsenite causes an up-regulation of several proteins, including the predicted ALDH KauB (ALDH1P1) [46]. The potential bioremediation bacterium *Acidothiobacillus ferrooxidans* up-regulates an unknown ALDH (ALD1Q1) (NCBI Entrez gene ID: 198283897) when exposed to bornite (Cu₅ FeS₄), an agent that induces oxidative stress through the release of copper ions into media during solubilization [47]. In addition, two ALDH genes are up-regulated in *Phanerochaete chrysosporium* exposed to lead (Pb²⁺). While Pb²⁺ is not redox-reactive *per se*, it has been shown to cause oxidative stress leading to ROS formation and LPO [48].

A key molecule in the mitigation of oxidative stress is the cytosolic reductive molecule, NADPH. Many antioxidant enzymes, including catalase, superoxide dismutase and glutathione peroxidase, utilize NADPH as a co-factor and, consequently, are dependent upon the cellular NADPH pools for activity [49]. Another ALDH, PaBADH (ALDH9D1) protects bacteria from osmotic stress (which can cause oxidative stress *per se*), and additionally allows a bacterium to use choline as a backup carbon source while restoring pools of NADPH [50]. As such, ALDHs can also contribute to the management of oxidative stress by generating NADPH.

Plants

The ALDH superfamily in plants is equally as diverse as is the one within mammalian genomes. However, there appears to be a greater degree of variation in the gene number than is typically observed between mammalian species. The *Arabidopsis thaliana* (Thale Cress), *Zea mays* (Maize) and *Populus trichocarpa* (Black Cottonwood) genomes have been fully sequenced and contain 14, 24 and 27 *ALDH* genes, respectively. Expansion of a specific *ALDH* family is often responsible for the increased gene number seen in some plant species. For example, most plants have a single *ALDH6* gene; however, a species-specific expansion has taken place within the *Populus trichocarpa* genome which contains four predicted protein-coding *ALDH6* homologues. Mammalian *ALDH6A1* is known to encode a methylmalonate semialdehyde dehydrogenase involved in valine catabolism and *ALDH6* family expansion in *Populus tricarpha* may be the result of a specific environmental or metabolic challenge faced by this particular species [51]. There is a high degree of amino acid homology between plant and mammalian ALDH orthologues suggesting functional conservation throughout evolution. ALDH families found within both plants and animals include *ALDH1/2*, *ALDH3*, *ALDH5*, *ALDH6*, *ALDH7* and *ALDH18*. Plants also contain *ALDH10* and *ALDH12* family members, as well as *ALDH11*, *ALDH19*, *ALDH21*, *ALDH22*, *ALDH23* and *ALDH24*, which appear to be plant-specific ALDH families [52, 53]. Similar to their mammalian homologues, plant ALDHs appear to have multifaceted roles within the cell. Plant ALDHs are localized throughout the cell, including the cytosol, mitochondria, peroxisomes, endoplasmic reticulum, leucoplasts and chloroplasts, and exhibit tissue-specific expression patterns [54-56]. Under physiological conditions, most ALDHs have a well-defined function in metabolizing intermediates in the biosynthetic or

catabolic pathways of vitamins, carbohydrates, amino acids and lipids. ALDH families present in both plants and animals tend to participate in metabolic pathways common to both kingdoms. The different metabolic and physiological requirements of plants and animal species would be anticipated to underlie the need for unique ALDH families. Moreover, newly identified plant subfamilies may have emerged *via* divergent evolution as a result of organism-specific challenges. For example, studies characterizing a recently identified plant ALDH, ALDH2C4, suggested this isozyme plays a role in the biosynthesis of ferulic acid and sinapic acid, important compounds contributing to cell wall strength [57, 58]. Characterization of the ALDH isozymes is considerably more advanced in mammalian cells than in plant cells, particularly in regards to kinetic characterization and substrate specificity. Nevertheless, a large number of studies have examined ALDH expression in plants. Some plant ALDHs appear to be constitutively expressed while others are induced by a wide variety of abiotic and biotic stressors. The response of plant *ALDH* gene expression to stress is highly species-specific. Further, it appears that certain plants may up-regulate a different panel of genes in response to the same stressor. Studies in experimental plant models have examined the protective actions of ectopic ALDH expression against stress, as well as enhanced susceptibility to stress as a consequence of ALDH deficiency [53, 56, 59, 60]. Together, these studies have revealed that ALDH gene expression appears to be a key feature of plant stress response pathways, especially for those insults known to induce oxidative stress [53, 60].

Expression of plant ALDHs is highly responsive to dehydration and salinity. These conditions bring about a water imbalance within cells and tissues, triggering osmotic stress throughout the plant. As water leaves the cells, there is a concomitant increase in ROS generation and oxidative stress. Plant ALDHs contribute to the synthesis of a number of osmolytes, the intracellular accumulation of which helps counter the damaging effects of osmotic imbalance. ALDH up-regulation has the potential to perform multiple functions within the cell. *ALDH7* and *ALDH10* family members participate in generating important osmolytes including betaine and dimethylsulfoniopropionate (DMSP) [61, 62]. Betaine is a quaternary ammonium compound and predominant osmolyte. It also functions as a chemical chaperone and stabilizes protein structure. In plants, betaine is synthesized within the chloroplasts from choline which is oxidized to betaine aldehyde and then to betaine. Interestingly, many cellular osmolytes (including sorbitol, mannitol, myo-inositol and proline) have hydroxyl radical scavenging activity [63]. In addition to osmolyte synthesis, plant ALDHs metabolize a wide range of LPO-derived aldehydes. ALDH activity can therefore both prevent oxidative stress (through osmolyte synthesis) and protect against oxidative stress (*via* detoxification of reactive aldehydes). In angiosperms (or flowering plants), the expression of *ALDH3*, *ALDH7*, *ALDH10*, *ALDH11* and *ALDH21* families are increased during osmotic challenge [54, 64, 65].

Plants are often confronted by metal-catalyzed oxidative stress due to high levels of metals in the soil. An *ALDH2* homologue was significantly up-regulated in a resistant strain of *Vaccinium corymbosum* (Highbush Blueberry) [66] by aluminum stress. Aluminum is a major environmental pollutant and aluminum stress is a well characterized inducer of oxidative stress [67]. A number of ALDH1/2 isozymes have also been shown to have very important reproductive functions in plants. In tobacco plants, TobAldh2A is expressed at very high levels within the male and female reproductive organs. This protein is expressed at low levels within vegetative tissues and expression levels do not respond to anaerobic incubation [68]. Furthermore, ALDH inhibitors cause defects in pollen tube growth. In this context, ALDH activity is believed to play a crucial role in biosynthetic pathways and during energy production within reproductive tissues. Rf2a was the first *ALDH* identified within the maize genome. The gene encodes an ALDH2 homologue that localizes to the mitochondria [69, 70]. Studies have shown that Rf2a is required for male fertility and anther

development in maize [71]. Biochemical characterization of Rf2A indicates that the enzyme may play an important role in ethanolic fermentation during anaerobic conditions by metabolizing acetaldehyde [70].

ALDH3 in *Arabidopsis thaliana* is up-regulated in response to sodium chloride (NaCl) and metals, including Cu^{2+} and Cd^{2+} [64]. In addition, chemicals that induce oxidative stress, such as H_2O_2 and the herbicide paraquat, also elicit ALDH3 up-regulation [64]. Transgenic plants overexpressing ALDH3 show reduced lipid peroxidation and increased resistance to dehydration, osmotic stress (*via* NaCl), metal toxicity (Cu^{2+} and Cd^{2+}), H_2O_2 and paraquat treatment [64]. *ALDH5F1* in *Arabidopsis thaliana* encodes a succinic semialdehyde dehydrogenase which is thought to play an important role in the γ -aminobutyric acid shunt in plants [72]. Plants lacking *ALDH5F1* exhibit stunted growth and suffer from necrotic lesions. Elevated ROS as well as enhanced susceptibility to both UV-B radiation and heat stress have also been documented in the *ALDH5F1*-deficient plants [73].

Ectopic expression of ALDH7 in both *Arabidopsis* and tobacco confers protection against various forms of osmotic stress, including dehydration and high salinity [61]. ALDH7 isozymes are also associated with higher seed germination and maintaining shoot pressure under stress conditions [61]. Leafy tissues in ALDH7-expressing plants exhibit fewer necrotic lesions than their control counterparts after paraquat treatment. LPO is also lower in the ALDH7 transgenic *Arabidopsis* and tobacco plants after paraquat treatment, suggesting decreased oxidative stress in the transgenic plants. Purified ALDH7 from the common garden pea metabolizes malondialdehyde, acetaldehyde and glyceraldehyde, all of which are produced during LPO. Such an action may explain the decrease in total LPO noted above [74].

ALDH10 family members, also commonly referred to as betaine aldehyde dehydrogenases (BADHs), were initially described as participating in the generation of the osmolyte and quaternary ammonium compound glycine betaine. This is formed from betaine aldehyde which is considered to be a toxic aldehydic intermediate [75, 76]. Interestingly, *Arabidopsis* does not accumulate betaine. Nevertheless, ALDH10 transcript levels are still up-regulated in this species in response to drought, salinity, cold and oxidative stress, suggesting some other important function for this enzyme. ALDH10 isozymes are also capable of metabolizing several aminoaldehydes to their corresponding amino acids, as well as utilizing other quaternary ammonium and tertiary sulfonium compounds as substrates [77]. The plant osmolyte DMSP is synthesized by ALDH10 from dimethylsulfoniopropionaldehyde [62]. Moreover, *ALDH10A8* and *ALDH10A9* are up-regulated in response to abscisic acid (ABA), salinity, cold and oxidative stress in *Arabidopsis* [56]. By contrast, exposure of *Amaranthus tricolor* to a variety of insults, including heat, dehydration, salinity, Cu^{2+} , Hg^{2+} and H_2O_2 , has no effect on *ALDH10* expression [78]. Both plant species are responsive to oxidative stress provoked by paraquat. *Arabidopsis* lacking *ALDH10A8* are more sensitive to both salinity and drought [56]. *ALDH10* family members also play a role in polyamine metabolism through the oxidation of aminoaldehydes [56]. Many aminoaldehyde intermediates are highly toxic [79-81]. During oxidative stress, ALDHs provide cytoprotection by metabolizing aminoaldehydes to their corresponding amino acids [56]. ALDH10 isoforms also metabolize γ -aminobutyraldehyde to GABA [56]. *In vitro* studies have shown that GABA can directly act as a hydroxyl radical scavenger [63].

The *ALDH11* gene family is unique to plants and encodes a class of non-phosphorylating glyceraldehyde 3-phosphate dehydrogenases (GAPDHs) which catalyze the conversion of glyceraldehyde-3-phosphate to 3-phosphoglycerate [52]. This reaction is essential for the glycolytic 'bypass' pathway unique to plants and is major source of NADPH required for biosynthesis of the osmolyte mannitol [82]. These enzymes also appear to play a role during

the stress response to desiccation in *Arabidopsis thaliana* and *Craterostigma plantagineum*, suggesting up-regulation of ALDH11 may be an evolutionarily-conserved biological adaption to dehydration [83, 84].

ALDH12A1 family members, commonly referred to as delta-1-pyrroline-5-carboxylate (P5C) dehydrogenases, play an important role in proline (Pro) degradation. Proline is synthesized from glutamate in the cytosol and then oxidized to P5C in the mitochondria by proline dehydrogenase (ProDH), an enzyme that utilizes FAD^+ as a cofactor and directly transfers electrons to the mitochondrial electron transport chain. Glutamate, the product of P5C metabolism by ALDH12A1, is transported to the cytosol where it can be converted back to Pro by P5C-reductase [85]. In solution, P5C is in a non-enzymatic, pH-dependent equilibrium with γ -glutamic semialdehyde. Pro-P5C cycling, commonly referred to as the 'proline cycle', is a mechanism by which redox equivalents can be shuffled between the mitochondria and the cytoplasm. Disturbances in P5C-Pro cycling, such as those occurring under low ALDH12A1 activity, can influence the mitochondrial ascorbate-glutathione cycle by decreasing mitochondrial NAD(P)H generation and thereby limiting the activity of glutathione reductase and the subsequent regeneration of reduced glutathione. In mammals, ALDH4A1 is thought to be primarily responsible for oxidation of P5C to glutamate. Not surprisingly, deleterious mutations in ALDH4A1 are associated with type II hyperprolinemia in humans [86]. In plants, osmotic stress causes down-regulation of ALDH12A1. This hinders Pro degradation, leading to intracellular accumulation and enhancement of its actions as an osmolyte [85]. Proline accumulation is thought to be protective during dehydration, cold and salt stress [87]. Additional studies have shown that Pro also has hydroxyl radical scavenging activity [63].

ALDH21 isozymes are only found within mosses and other, more primitive plants [65]. Like other angiosperm ALDH enzymes, ALDH21A1 is up-regulated in response to both desiccation and high salt [88]. It has been hypothesized that these isoenzymes participate in the removal of stress-induced aldehydes, some of which may be toxic [88]. The *ALDH22* gene family is also unique to plants. Dehydration, high salinity and ABA induce *ALDH22A1* expression in maize. Overexpression of ALDH22A1 in transgenic tobacco plants increases stress tolerance and decreases levels of MDA [89]. A conflicting study in *Arabidopsis* indicated that mRNA levels were unaffected by osmotic stress [54]. These studies underscore how regulation of plant ALDHs during stress may be species-specific.

The plant ALDH superfamily plays a very important role in many fundamental metabolic pathways under physiological, unstressed conditions. They facilitate the synthesis and catabolism of a broad range of biomolecules including vitamins, carbohydrates, amino acids and lipids. Furthermore, ALDH up-regulation appears to be a vital component of general stress-response pathways in plants. The multifaceted role of ALDHs within the cell underscores the importance of these enzymes. The ability of ALDH expression to promote stress tolerance in plants has made it the focus of studies developing stress-resistant crops for cultivation in areas that experience severe draught, cold, heat, poor soil and other unfavorable conditions.

Saccharomyces cerevisiae

A number of studies have characterized stress responses in yeast, *Saccharomyces cerevisiae*. The most extensively characterized stressors inducing such responses are those eliciting severe osmotic or oxidative changes, heat, glucose deprivation and heavy metal or high ethanol exposures [90-93]. One of the primary responses of yeast to stress is a dramatic change in gene transcription, characterized by tight regulation of proteins associated with redox metabolism, cellular structure preservation and also of the transcription factors regulating these proteins.

In yeast, cell wall integrity is especially challenged by ethanol exposure or hyperosmolarity, as reflected in increased membrane fluidity and the up-regulation of unsaturated fatty acids (UFAs) and ergosterol [94]. Amino acids, such as isoleucine, methionine, phenylalanine and L-proline, and the carbohydrate inositol are thought to confer ethanol tolerance to stressed cells by reinforcing the cell membrane structure [95].

Glycerol, an important osmolyte, is tightly controlled under conditions of osmotic stress. The glycerol channel Fps1p closes to maintain the intracellular levels of glycerol and its biosynthesis is regulated by the activation of the high osmolarity glycerol (HOG) pathway. Also involved in the protection are chaperone proteins that stabilize and repair denatured proteins [96]. Heat shock proteins (HSPs), trehalose and ALDHs (a recent addition) represent this group of stress-protective elements in the yeast cell [97, 98]. The genes encoding these proteins, along with several other stress response genes in yeast, have the stress response element (STRE) in their promoter region to which transcription factors bind when stress-regulated specific pathways are activated [97]. Cyclic AMP-dependent protein kinase, target of rapamycin (TOR) and HOG pathways are among those that regulate the Msn2p and Msn4p transcription factors that bind to the STRE [6, 97, 99]. Several other proteins (Tdh3, Eno2, Adh1, Tpi1, Ald6 and Fba1) and transcription factors (Tef2, Tef5, Nip1 and Rps5) undergo protein-S-thiolation under oxidative stress to escape the irreversible modification of critical cysteine residues [100].

ALDHs have a distinct role in maintaining redox balance in yeast by supplying reducing equivalents in the form of NADH and NADPH. So far, there are six ALDHs identified and annotated in the *Saccharomyces* Genome Database, viz. ALD2 (*ALDH1G2*), ALD3 (*ALDH1G1*), ALD4 (*ALDH1D2*), ALD5 (*ALDH1D1*), ALD6 (*ALDH1F1*) and HFD1 (*ALDH14*) [101]. They are distinct in their (i) sub-cellular expression, (ii) induction under different stress conditions, (iii) strain dependency, (iv) preferred co-factors and (v) regulation. ALDH1G1 and ALDH1G2 are NAD⁺-dependent, cytosolic enzymes that are stress-induced, while ALDH1F1 is a constitutively-expressed, NADP⁺-dependent, cytosolic enzyme that uses Mg²⁺ for activation [6]. Stress-induced ALDH1D2 and constitutively-expressed ALDH1D1 are mitochondrial enzymes activated by K⁺; ALDH1D2 prefers both NAD⁺ and NADP⁺ while ALDH1D1 prefers NADP⁺ alone [6].

There is clear evidence of increased expression of ALDH1G1, 1G2 and 1D2 under conditions of high ethanol exposure and with depleted glucose reserves. ALDH1G1 is also induced by several other stress conditions regulated by the Msn2,4 transcription factors in a general stress response [6, 90]. ALDH1G2 is induced by ethanol and osmotic stress but not by heat shock, DNA damage or oxidative stress conditions [6]. However, both ALDH1G1 and ALDH1G2 genes are expressed independently of the HOG pathway [6]. It has been suggested that ALDH1G1 may play a partial role in cytoplasmic redox balance during glycerol biosynthesis by providing NADH to the dihydroxyacetone phosphate reduction [102, 103]. Contrary to *ALDH1F1* mutants no increased sensitivity is observed towards heat shock, DNA damage or oxidative stress in the *ALDH1G1/ALDH1G2* double knockouts, [6]. The majority of the NADH for this reduction may still be supplied by the mitochondrial ALDH1D2. The *ALDH1G1/ALDH1G2* double knockout mutant exhibits no growth on glucose media but the single mutants show a 50% reduction in growth on ethanol media. No growth occurs on either glucose or ethanol in the *ALDH1F1* knockout mutant [6]. These results corroborate the role of these ALDH genes in ethanol stress tolerance. Acetyl-CoA, required for growth, is normally produced by mitochondrial pyruvate decarboxylase. The 50% growth observed in *ALDH1G1/ALDH1G2* mutants that are devoid of pyruvate decarboxylase indicates the potential of these enzymes to contribute to the acetyl-CoA synthesis, required for growth [6].

ALDH1F1 is a crucial source of NADPH in yeast cells lacking glucose-6-phosphate dehydrogenase (G6PD) activity (from the pentose phosphate pathway) displaying methionine auxotrophy [104] and over-expression of ALDH1F1 rescues this phenotype.

It is evident that ALDHs have a crucial function in yeast cells by providing tolerance against a variety of stresses, such as high ethanol, osmotic stress, oxidative stress and depleted glucose reserve.

Caenorhabditis elegans

To date, thirteen *ALDH* genes have been identified and annotated in the nematode *Caenorhabditis elegans*. This organism has been used as a model system to study environmental and physiological stress signaling in non-mammalian systems, some of which are well conserved in mammalian systems as well. Exposure of *C. elegans* to a variety of environmental stress conditions, including elevated temperatures, water scarcity (osmotic stress), overcrowding, metal ion toxicity and low levels of oxygen, elicits, in most cases, a decrease in metabolism. Under these conditions, the organisms enter a stage of arrested development termed 'dauer' larvae [105]. Anaerobic respiration is the norm during this stage and, consequently, oxidative stress management is critical. Signalling pathways, comprising insulin growth factor signaling and the Akt response, that modulate anti-oxidant capacities (including expression of alcohol dehydrogenases (ADHs) and ALDHs confer increased survival and longevity to the dauer larvae [106]. mRNA expression of these ALDH genes, which are also a part of fermentation pathways, are found elevated in the dauer stage, although protein levels still need to be investigated [107]. ALH-12 (ALDH9B1) is up-regulated in newly hatched larvae [108], an observation consistent with the role of ALDHs in inducing differentiation during developmental stages in vertebrates

An important aspect of abrogating oxidative stress is control of LPO. 4-HNE, an important product of oxidative stress, promotes protein adduct formation *via* LPO. In *C. elegans*, ALH-1 (ALDH1J1) and ALH-10 (ALDH8B1) contribute to NAD⁺-dependent 4-HNE oxidation. *ALDH1J1*, when silenced, leads to increased fat accumulation which is thought to be the product of impaired 4-HNE metabolism and a subsequent malonyl-CoA increase [7]. Under ethanol stress, *ALDH1J1* is down-regulated 6 hrs after exposure, leading to it being classified as a late repression gene, as opposed to the early induction genes which are comprised primarily of heat shock proteins (among others) [109]. *ALDH1J1* is orthologous to the human mitochondrial ALDH2.

In *C. elegans*, ALDHs promote survival during the 'dauer' larval stage and also support the mitigation of oxidative stress by metabolizing LPO-derived aldehydes.

Mammals

Alcohol toxicity

Ethanol is predominantly oxidized to acetaldehyde by ADH and then is further oxidized to acetic acid, mainly by ALDH2. Alcohol-induced oxidative stress plays a critical role in development of alcohol-related diseases, such as alcoholic liver disease, cardiomyopathy and gastritis [110-112].

After absorption, ethanol is subject to rapid metabolism. Nicotinamide adenine dinucleotide (NAD⁺), a co-factor required by both ADH and ALDH, is converted to the reduced form, NADH; this process can lead to a NAD⁺/NADH imbalance (Fig. 1). As both NAD⁺ and NADH are important for mitochondrial function, it is easy to envisage how alcohol abuse can promote mitochondrial dysfunction. The documented inhibition of liver adenosine triphosphate (ATP) production by ethanol supports such a proposal [113]. Given the

capacity of mitochondria to generate ROS, it is reasonable to assume that impaired mitochondrial function promotes ROS formation and increased oxidative stress that contributes to a wide variety of cell and tissue injury [114].

Mitochondrial glutathione (mGSH) protects the mitochondrion from the ROS it continuously generates [115]. Alcohol abuse causes down-regulation of mitochondrial glutathione levels, although the mechanism by which this occurs remains to be elucidated [116-118]. Such down-regulation would promote ROS accumulation and, subsequently, increased oxidative stress. Another important source of ROS derived from alcohol is a result of the enzymatic activity of cytochrome P450 2E1 (CYP2E1), which is induced by ethanol intake [119] (Fig. 1). ROS, such as superoxide anion radical ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), are produced as a by-product of CYP2E1-induced oxidation of ethanol [119]. Iron can also enhance oxidative stress by generating the most highly reactive ROS, hydroxyl radical ($\bullet OH$), *via* the non-enzymatic Fenton reaction ($Fe(II) + H_2O_2 \rightarrow Fe(III) + \bullet OH + ^-OH$). Alcohol abuse causes uptake of iron into the liver [120, 121]. As such, alcohol consumption can also promote oxidative stress through the Fenton reaction [110, 119].

Oxidative stress initiates LPO and yields reactive aldehydes, such as 4-HNE, which induce covalent modification of proteins and DNA [38]. ALDH2 and ALDH1A1 catalyzes the detoxification of 4-HNE by converting it to 4-hydroxynon-2-enoic acid [122-125]. Another LPO product, MDA, also appears to play an important role in several diseases, including diabetes and alcoholic liver injury [110, 126]. Early studies showed that ALDHs oxidize MDA [127] and that higher MDA levels manifest in the patients with inactive ALDH2, suggesting this enzyme contributes significantly to MDA removal [128]. MDA is also a substrate for ALDH1A1 and ALDH1B1 (K_m 's of 0.1 mM and 0.5 mM, respectively) [125, 129].

UV Radiation

The cells of the eye are constantly subjected to oxidative stress due to their intense exposure to sunlight and high oxygen tension. Solar ultraviolet (UV) radiation is the major environmental inducer of free radical formation in the eye. It consists of UVA (315-400 nm), UVB (280-315 nm) and UVC (100-280 nm). Exposure to UVC is minimized due to the protection afforded by the upper atmosphere of the Earth. Most UVB is absorbed by the cornea and UVA by the lens. No UVC or UVB and very little UVA reach the posterior portion of the eye, most importantly the retina. UV radiation absorption by these ocular tissues, particularly that associated with UVB, lead to photochemically-generated ROS, including singlet oxygen, superoxide anion, hydroxyl and peroxy radicals [130]. Generation of peroxy radicals can lead to the downstream production of over 200 cytotoxic reactive aldehyde species, such as 4-HNE and MDA [131]. UV radiation exposure has been shown to cause strand breakage, pyrimidine and thymine dimer formation in DNA strands and protein cross-linking [132, 133]. These UV radiation-induced molecular modifications have been implicated in several eye pathologies, including cataract formation and corneal and retinal degeneration [134]. In order to cope with such an intense oxidant burden, the cornea and lens have developed robust antioxidant defense systems in the form of metabolic enzymes and small molecules, which serve to maintain the redox homeostasis and protect against oxidative damage.

Members of the ALDH superfamily have been identified as crystallins in the cornea and lens of both vertebrates and invertebrates [135]. Indeed, ALDH3A1 is considered to be the first enzyme to be categorized as a corneal crystallin, a molecule that provides the necessary transparency, refractive and protective properties of the cornea [136]. It is highly expressed in the cornea of most mammalian species, representing 5–50% of total soluble proteins (depending on the species). In contrast to other mammals, rabbits primarily express

ALDH1A1 in the cornea, with no detectable amounts of ALDH3A1 [8, 137]. Other vertebrates, including chicken, frog and fish, also express ALDH1A1 and, in some cases, ALDH2 rather than ALDH3A1 in the cornea [138]. It is speculated that the absence of ALDH3A1 from the corneal epithelium of some species is compensated for by the expression of ALDH1A1 or other ALDH isozymes in order to provide the necessary properties to the cornea. ALDH1A1 is a lens crystallin in humans, where it constitutes 2% of the soluble proteins in lens epithelium. Other ALDH1 family proteins contribute as crystallins in a species-specific manner. ALDH1A8 (η -crystallin) is a lens crystallin in the elephant shrew [139]. ALDH1A9 and ALDH1C1/2 (Ω -crystallins) are lens crystallins in scallops and cephalopods, respectively [135]. Although expressed in a taxon-specific fashion, ALDH1 isozymes and ALDH3A1 are well conserved in mammals, sharing 90% identity in amino acid sequence between human, rabbit, cow, sheep, mouse and rat [125].

The important protective function of ALDH3A1 and ALDH1A1 in the eye is well illustrated in studies using transgenic animals. Spontaneous cataracts develop in *Aldh3a1*^{-/-} knockout and *Aldh1a1*^{-/-}/*Aldh3a1*^{-/-} double knockout mice by one month of age, and in *Aldh1a1*^{-/-} knockout mice by 6–9 months [30]. In addition, these *Aldh*-null mice are much more sensitive to UV radiation-induced cataract formation [30]. ALDH3A1 and ALDH1A1 are believed to protect the eye from UV radiation-induced damage by multifaceted mechanisms. First, ALDH3A1 can serve as a major UV radiation filter. UV radiation-induced modifications may lead to enzyme inactivation, partial unfolding and non-native protein aggregation [140], all of which may contribute to the observed accumulation of aggregated proteins in the lens during cataract formation [141]. ALDH3A1 may function to protect other corneal proteins (at the expense of their own molecular inactivation) by functioning to directly absorb UV radiation. For example, recombinant ALDH3A1 is inactivated and covalently cross-linked by direct UV radiation exposure, while diminishing UV radiation-induced inactivation of G6PD [142]. Similarly, UV irradiation of mice leads to an 85% decrease in the activity of corneal ALDH3A1 and ALDH1A1, whereas the activities of other corneal enzymes remain unaltered [142]. Second, ALDH3A1 and ALDH1A1 metabolize toxic aldehydes produced by UV radiation-induced lipid peroxidation. Human ALDH3A1 has high affinity for 4-HNE [143] whereas ALDH1A1 metabolizes both 4-HNE and MDA [125]. Given that increased levels of 4-HNE and/or MDA have been associated with various forms of ocular pathologies (including cataracts) [144–146], the enzymatic detoxification of these reactive aldehydes represents yet another mechanism by which ALDH3A1 and ALDH1A1 protect ocular tissues against UV radiation-induced damage. Furthermore, the presence of ALDH1A1 in the cornea may compensate ALDH3A1 by oxidizing MDA, a poor substrate of ALDH3A1 [143]. Indeed, numerous studies using human cell lines [147] and experimental animal models [30] have shown a negative correlation between cellular levels of these proteins and formation of 4-HNE- and MDA-protein adducts and 4-HNE-induced cytotoxicity. Third, ALDH3A1 and ALDH1A1 act as antioxidants by directly scavenging UV radiation-induced free radicals or by producing the antioxidant NAD(P)H. In corneal fibroblasts treated with oxidants, the level of ALDH3A1 carbonylation increases 2–3 fold, suggesting that high concentrations of corneal ALDH3A1 may serve as a direct target for ROS and reactive aldehydes and thereby provide a passive protective effect for other proteins [29, 31]. NAD(P)H produced during ALDH-mediated metabolism contributes to the antioxidant environment of the cornea. Aside from serving as a reducing agent in the regeneration of GSH from the oxidized form, GSSG [148], NADPH can directly absorb UV radiation [149]. In addition, it helps to maintain a reducing potential for various redox-active enzymes involved in protecting eye tissues, such as isocitrate dehydrogenase, malic dehydrogenase and 6-phosphate dehydrogenase [27]. Taken together, through their enzymatic and non-enzymatic functions, ALDH3A1 and ALDH1A1 play key roles in the cellular response to oxidative/electrophilic stress in ocular tissues.

Cancer stem cells

It is becoming increasingly apparent that ALDHs may play an important role in normal and cancer stem cells. In this respect, high ALDH activity (as measured by Aldefluor® assay, for example) has been proposed as a general marker for both normal and cancer stem cells. This high stem cell ALDH activity has been attributed to the ALDH1A1 isozyme. Recently, however, the activity of other ALDH isozymes, including ALDH1A2, ALDH1A3, ALDH1A7, ALDH2, ALDH3A1, ALDH4A1, ALDH5A1, ALDH6, and ALDH9A1, have shown to contribute to the elevated ALDH activity observed in cancer stem cells [150, 151]. For example, ALDH1B1 is expressed in the stem cell compartment of normal colon and is highly up-regulated in colonic adenocarcinoma [152]. ALDHs are also highly expressed in cancer stem cells and can function to protect these cells against alkylating agents of the oxazaphosphorine (OP) family, such as CP and its derivatives [153]. CP is one of the most efficacious anticancer agents available today and was one of the initial agents designed to selectively target cancer cells [154]. Metabolism of its intermediate product, aldophosphamide, into carboxyphosphamide by ALDH isozymes (i.e., ALDH1A1, ALDH3A1 and ALDH5A1) prevents the formation of its cytotoxic metabolites, phosphoramidate mustard and acrolein (Fig. 2). Elevated expression of these isozymes is a means by which cancer cells can develop resistance against CP [42, 43].

ALDHs decrease the sensitivity of the cell to the toxic effects of CP by enzyme-catalyzed bioinactivation. As such, mutations that elevate levels of one or more ALDHs in a malignant cell render the cells resistant to the therapeutic effects of CP. Such acquired resistance to CP (and other OPs) is a problem commonly encountered in chemotherapy regimens involving these drugs [42]. Various cell lines showing acquired (resistance acquired by CP treatment), intrinsic (without any stimulation) or transfection/transduction induced resistance to OPs are presented in the Tables 3-5, along with the up-regulated ALDHs.

In addition to being OP-resistant, ALDH1A1-positive ovarian cancer cells have also been found to be resistant to the chemotherapeutic drugs taxane and platinum. These cells can become re-sensitized to chemotherapy by inducing down-regulation of ALDH1A1 expression [155]. It appears that a subpopulation of cells over-expressing ALDH1A1 is associated with chemoresistance and poor prognosis in ovarian cancer patients [155]. Most chemotherapeutic drugs, including taxane and platinum, are known to generate oxidative stress and elevate levels of LPO-derived aldehydes. Clearly, high ALDH levels could protect these cells against the toxic effects of such drugs [59].

ALDH activity has been used to identify and separate cancer stem cells [103, 156]. ALDH family members appear to play important roles in a variety of biological activities in cancer stem cells including oxidative stress response, differentiation and drug resistance. ALDHs, specifically ALDH1A1, ALDH1A2, ALDH1A3, ALDH1A7 and ALDH1B1, metabolize retinol to retinoic acid and thereby modulate stem cell proliferation and differentiation. They can also confer resistance to chemotherapeutic alkylating agents by oxidizing intracellular aldehydes. The detoxification capacity of the ALDHs has the potential to protect stem cells against oxidative insults and could be one of the important factors governing their longevity [156].

Conclusion

The ALDH gene superfamily comprises NAD(P)H-dependent enzymes catalyzing the irreversible oxidation of endogenously and exogenously generated aromatic and aliphatic aldehydes. ALDHs play important roles in fundamental pathways involved in synthesis of various biomolecules including vitamins, carbohydrates, amino acids and lipids. In plants, they metabolize the toxic aldehyde intermediate betaine aldehyde into glycine betaine, an

osmolyte that also protect plants from the dehydration, salinity, cold and oxidative stress and other unfavorable conditions. In bacteria, ALDHs facilitate the evasion of oxidative, osmotic and host immune response generated stress. Up-regulation of ALDHs in yeast and *C. elegans* in response to stressors underscores the significance of ALDHs in protecting these organisms against adverse conditions. ALDHs also protect animals and humans against oxidative stress induced by alcohol, UV radiation and some chemotherapeutic agents. In summary, ALDHs are found throughout the *Archaea*, *Eubacteria* and *Eukarya* domains including microorganisms, plants and animals and appear to play important roles in normal physiological processes as well as in various stress conditions.

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Abbreviations

ABA	abscisic acid
ADHs	alcohol dehydrogenases
ALDH	aldehyde dehydrogenase
As³⁺	arsenite
ATP	adenosine triphosphate
BADHs	betaine aldehyde dehydrogenases
CP	cyclophosphamide
Cu⁺	copper
CYP2E1	cytochrome P450 2E1
DMSP	dimethylsulfoniopropionate
FDH	10-formyltetrahydrofolate dehydrogenase
Fe²⁺	iron
G6PD	glucose-6-phosphate dehydrogenase
GABA	γ -aminobutyric acid
GAPDHs	glyceraldehyde 3-phosphate dehydrogenases
H₂O₂	hydrogen peroxide
4-HNE	4-hydroxy 2-nonenal
HOG	high osmolarity glycerol
HSPs	heat shock proteins
LPO	lipid peroxidation
MDA	malondialdehyde
mGSH	mitochondrial glutathione
MMSADH	methylmalonate semi-aldehyde dehydrogenase
NAD	nicotinamide adenine dinucleotide

4-ONE	4-oxononenal
OP	oxazaphosphorine
P5C	delta-1-pyrroline-5-carboxylate
Pb²⁺	lead
ProDH	proline dehydrogenase
RA	retinoic acid
ROS	reactive oxygen species
SSADH	succinic semialdehyde dehydrogenase
STRE	stress response element
TOR	target of rapamycin
UFAs	unsaturated fatty acids
UV	ultraviolet

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Highlights

- Aldehyde dehydrogenases (ALDHs) metabolize electrophilic aldehydes.
- ALDHs are expressed in all forms of life from simple to complex multicellular organisms.
- ALDHs are elevated by stress in these organisms to protect against oxidative damage.
- Mutations in *ALDH* genes are associated with a variety of diseases in humans.

Fig. 1. Mechanisms by which ALDHs mitigate alcohol-induced oxidative stress

ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; mGSH, mitochondrial glutathione; 4-HNE, 4-hydroxy-2-nonenal; MDA, malondialdehyde; NAD, nicotinamide adenine dinucleotide

Fig. 2. Metabolism of cyclophosphamide

ALDH, aldehyde dehydrogenase; NAD, nicotinamide adenine dinucleotide

Table 1
Catalytic properties of ALDH families and their proposed roles against stress responses

<i>ALDH Family</i>	<i>Catalytic function (s)</i>	<i>Stress Response</i>
Plants		
ALDH2	Ferulic and sinapic acid biosynthesis	Aluminum stress, cell wall strength biosynthesis
ALDH3	LPO-derived aldehyde oxidation	Osmotic, salt, oxidative and desiccation stress; paraquat (herbicide) tolerance
ALDH5	SSADH	ROS, UV radiation, Heat stress
ALDH6	MMSADH	Valine catabolism
ALDH7	BADH, DMSP generation, malondialdehyde, acetaldehyde oxidation	Oxidative, desiccation and salt stress; glyceraldehyde metabolism
ALDH10	BADH, DMSP generation	Osmotic, salt, cold and oxidative stress
ALDH11	GAPDH	Desiccation stress
ALDH12	P5CDH	Proline toxicity, oxidative stress
ALDH21	N/A	Desiccation and salt stress
ALDH22	N/A	Desiccation and salt stress
Bacteria		
ALDH1	N/A	Arsenite, bornite exposure
ALDH5	SSADH	GABA shunt (stress response)
ALDH9	BADH	Osmotic stress
ALDH50	Glutamate synthesis	GABA shunt (stress response)
ALDH51	GABA synthesis	GABA shunt (stress response)
ALDH52	SSADH	GABA shunt (stress response)
<i>Saccharomyces cerevisiae</i>		
ALDH1	Through STRE binding Msn2/4	Ethanol, heat, oxidative and osmotic stress transcription factors
<i>C. Elegans</i>		
ALDH1	4-HNE oxidation	Oxidative stress
ALDH8	4-HNE oxidation	Oxidative stress

BADH, betaine- aldehyde dehydrogenase; DMSP, dimethylsulfoniopropionate; GABA, γ -aminobutyric acid; GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; 4-HNE, 4-hydroxy 2-nonenal; LPO, lipid peroxidation; MMSADH, methylmalonate semi-aldehyde dehydrogenase; N/A, not available; P5CDH, delta-1-pyrroline-5-carboxylate dehydrogenase; ROS, reactive oxygen species; SSADH, succinic semialdehyde dehydrogenase; STRE, stress response element; UV, ultraviolet

Table 2
Conditions associated with dysfunctions in mammalian ALDH isozymes

	<i>ALDH isozyme</i>	<i>Associated condition</i>	<i>Possible substrate involved</i>	<i>Reference</i>
1	ALDH1A1	Drug resistance Alcohol sensitivity, alcohol-induced flushing Parkinson's disease and schizophrenia	Aldophosphamide Acetaldehyde 3,4-dihydroxyphenylacetaldehyde LPO-derived aldehydes Retinal	[43] [157-159] [32, 160]
2	ALDH1A2	Tumors Early embryonic death	Retinal Retinal	[161, 162] [163]
3	ALDH1A3	Perinatal lethality	Retinal	[164]
4	ALDH1A7	Development Hemorrhagic shock	Retinal Involved in other metabolic pathways	[165] [166]
5	ALDH1B1	Ethanol sensitivity and hypersensitivity Colon cancer	Acetaldehyde Retinal, Acetaldehyde	[129, 167, 168] [152], unpublished
6	ALDH1L1	Tumors Methanol toxicity Neural tube defect	10-Formyltetrahydrofolate 10-Formyltetrahydrofolate	[37, 169, 170] [171] [172]
7	ALDH1L2	Tumors	10-Formyltetrahydrofolate	[173, 174]
8	ALDH2	Alcohol sensitivity Cancer Cardiovascular disorders	Acetaldehyde Acetaldehyde Nitroglycerin	[175-177] [25, 178] [179-181]
9	ALDH3A1	Tumors Sensitivity to UV light, lens opacification and cataract Drug resistance	Medium chain aldehydes LPO-derived aldehydes, UVR absorption, ROS scavenging Aldophosphamide	[14] [14, 30] [182-184]
10	ALDH3A2	Sjögren-Larsson syndrome	Medium and long chain aliphatic aldehydes, fatty aldehydes	[14, 19]
11	ALDH3B1	Paranoid schizophrenia	LPO-derived aldehydes	[14, 185, 186]
12	ALDH3B2	Unknown		
13	ALDH4A1	Type II hyperprolinemia	Pyrroline-5-carboxylate	[20, 187, 188]
14	ALDH5A1	Neurological disorder 4-Hydroxybutyric aciduria	Succinic semialdehyde	[21, 189]
15	ALDH6A1	Developmental delay	Methylmalonate semialdehyde	[151, 190]

	<i>ALDH isozyme</i>	<i>Associated condition</i>	<i>Possible substrate involved</i>	<i>Reference</i>
16	ALDH7A1	Hyperosmotic stress Pyridoxine dependent epilepsy	Betaine aldehyde, LPO-derived aldehydes Alpha-amino adipic semialdehyde	[191] [22, 192, 193]
17	ALDH8A1	Unknown	9-cis retinal	[194]
18	ALDH9A1	Role in GABA and dopamine pathways Non-alcoholic steatohepatitis	3,4-dihydroxyphenylacetaldehyde, γ -aminobutyraldehyde Candidate gene	[14, 195] [196]
19	ALDH16A1	Gout Mast Syndrome	Variant associated with gout Interaction with maspardin	[197, 198] [198]
20	ALDH18A1	Hypoprolinemia, hypornithinemia, hypocitrulinemia, hypoargininemia, hyperammonemia and cataract formation, neurodegeneration, connective tissue anomalies	Glutamate	[14, 199, 200]

Table 3
Cell lines exhibiting intrinsic oxazaphosphorine resistance

	<i>Cell line</i>	<i>Type</i>	<i>Elevated isozyme</i>	<i>References</i>
1	Colon C	Human colon carcinoma cell line	ALDH3A1	[201]
2	CFU-S	Murine pluripotent hematopoietic stem cells	ALDH	[202]

Table 4
Cell lines exhibiting acquired oxazaphosphorine resistance

	<i>Cell line</i>	<i>Type</i>	<i>Elevated isozyme(s)</i>	<i>References</i>
1	L1210/ CPA	Mouse lymphocytic leukemia	ALDH1A1	[203, 204]
2	P388/CPA	Mice lymphocytic leukemia	Cytosolic ALDH	[203, 204]
3	MCF7/ OAP	Human breast adenocarcinoma cell line	ALDH3A1	[182]
4	D283 MED (4-HCR)	Human medulloblastoma	ALDH, ALDH1B1	[205, 206]
5	Daoy (4-HCR)	Human medulloblastoma	ALDH	[205]
6	LBN AML Cell line	Rat acute myeloid leukemia	ALDH	[207]

Table 5
Cell lines exhibiting transfection/transduction-induced oxazaphosphorine resistance

	<i>Cell line</i>	<i>Type</i>	<i>Elevated isozyme(s)</i>	<i>References</i>
1	L1210/ OAP	Mouse lymphocytic leukemia	ALDH1A1	[208]
2	K562	Human leukemia	ALDH1A1	[209-211]
3	U937	Human hematopoietic cell line	ALDH1A1	[208]
4	MCF7/ OAP	Human breast adenocarcinoma cell line	ALDH3A1	[212]
5	A549	Human lung cancer cell line	ALDH1A1	[213]
6	V79	Chinese hamster lung fibroblast cells	ALDH1A1, ALDH3A1	[214-216]
7	CD34+ cells	Human cord blood CD34+ cells	ALDH1A1	[217]
8	PBPC	Human peripheral blood hematopoietic progenitor cells	ALDH3A1, ALDH1A1,	[184, 218]