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Review

Post-translational modifications of mitochondrial aldehyde dehydrogenase and biomedical implications

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ABSTRACT

Aldehyde dehydrogenases (ALDHs) represent large family members of NAD(P)$^+$-dependent dehydrogenases responsible for the irreversible metabolism of many endogenous and exogenous aldehydes to the corresponding acids. Among 19 ALDH isozymes, mitochondrial ALDH2 is a low K_m enzyme responsible for the metabolism of acetaldehyde and lipid peroxides such as malondialdehyde and 4-hydroxynonenal, both of which are highly reactive and toxic. Consequently, inhibition of ALDH2 would lead to elevated levels of acetaldehyde and other reactive lipid peroxides following ethanol intake and/or exposure to toxic chemicals. In addition, many East Asian people with a dominant negative mutation in *ALDH2* gene possess a decreased ALDH2 activity with increased risks for various types of cancer, myocardial infarct, alcoholic liver disease, and other pathological conditions. The aim of this review is to briefly describe the multiple post-translational modifications of mitochondrial ALDH2, as an example, after exposure to toxic chemicals or under different disease states and their pathophysiological roles in promoting alcohol/drug-mediated tissue damage. We also briefly mention exciting preclinical translational research opportunities to identify small molecule activators of ALDH2 and its isozymes as potentially therapeutic/preventive agents against various disease states where the expression or activity of ALDH enzymes is altered or inactivated.

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Abbreviations: AEN, aminoethyl nitrate; ALDH, aldehyde dehydrogenase; ALDH1A1, cytosolic aldehyde dehydrogenase; ALDH2, mitochondrial low-Km aldehyde dehydrogenase 2; CYP2E1, ethanol-inducible cytochrome P450 2E1 isozyme; DIGE, fluorescence 2-D difference in gel electrophoresis; DTT, dithiothreitol; GSK-3, glycogen synthase kinase-3; GSNO, nitrosoglutathione; GTN, glyceryl trinitrate; 4-HNE, 4-hydroxynonenal; I/R, ischemia–reperfusion; JNK, c-Jun N-terminal protein kinase; MDA, malondialdehyde; MDMA, 3,4-methylenedioxymethamphetamine; PI3K, phosphatidyl-inositol-3-kinase; PKCε, protein kinase Cε isozyme; PTM, post-translational modification; RNS, reactive nitrogen species; ROS, reactive oxygen species; S-NO-Cys, S-nitrosylated Cys; SNP, single nucleotide polymorphism.

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Contents

1. Introduction

Various reactive aldehydes can be produced from endogenous and exogenous precursors under many different pathophysiological states as well as following exposure to potentially toxic agents including abused substances such as alcohol (ethanol) and cocaine. For instance, in mammals, toxic acetaldehyde can be produced as an intermediate during alcohol metabolism catalyzed by alcohol dehydrogenase (ADH)[1] before it is further oxidized to acetic acid by mitochondrial aldehyde dehydrogenase 2 isozyme (ALDH2). Both ADH and ALDH2-mediated reactions require NAD^+ as a cofactor. Upon exposure to exogenous toxic chemicals [e.g., carbon tetrachloride (CCl_4)] or under physiological conditions [e.g., UV exposure], lipid peroxidation takes place due to increased oxidative stress. As a result, the cellular levels of toxic lipid peroxides such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) are elevated. These aldehydes are highly reactive and thus interact with cellular macromolecules including DNA and proteins [1,2]. Consequently, normal functions of DNA and protein targets are negatively affected, resulting in DNA damage/deletion/mutation and inactivation of proteins, respectively. In severe cases, these toxic aldehydes can directly promote cell/tissue damage (via apoptosis and necrosis) through promoting a loss of mitochondrial potential and activating the mitochondria-dependent cell death pathways [2–5]. However, under normal conditions, these reactive aldehydes can be effectively managed by various antioxidants (e.g., glutathione and ascorbic acid) as well as different metabolic enzymes such as alcohol dehydrogenase, aldehyde dehydrogenase (ALDH), aldo-keto reductase, aldehyde oxidase, glutathione transferase, etc. [6–8].

Among the cellular protective enzymes listed above, ALDH isozymes (EC 1.2.1.3) represent $NAD(P)^+$-dependent enzymes involved in the metabolism (oxidation) of various toxic aldehydes of endogenous and exogenous origins into their corresponding acids. In general, the ALDH-mediated reactions are considered irreversible. The *ALDH* superfamily consists of at least 19 *ALDH* genes in the human genome and that mutations in some ALDH isozymes are associated with inborn errors with altered aldehyde metabolisms and thus increased susceptibility to certain disease states [9–11]. Although many ALDH isozymes share overlapping substrate specificities and tissue/subcellular distribution, they may have different kinetic parameters such as distinct K_m values and catalytic activities toward each substrate compound [9–11]. In addition, the biochemical properties of each homologous ALDH isozyme depend on the species examined. For instance, human cytosolic ALDH1A1 isozyme exhibits a high K_m value (a range of 170–190 μM) for acetaldehyde [12]. However, the K_m value for acetaldehyde in rodent ALDH1A1 is relatively low (a range of 12–17 μM measured at pH 7.5), and comparable to that of rodent ALDH2 (0.2 μM) [12]. Therefore, it is reasonable to consider that ALDH2 in humans and ALDH2/1A1 isozymes in rodents likely represent the major enzyme(s) responsible for the metabolism of acetaldehyde produced from ethanol metabolism [12–14].

Because of the important roles of ALDH isozymes in efficiently removing potentially toxic aldehyde compounds, their tissue/subcellular distribution, substrate specificity, regulation of gene expression, and biochemical properties of each ALDH isozyme have been extensively studied [see reviews 9–11]. In general, most ALDH isozymes are expressed in large amounts in the liver while extra-hepatic tissues usually contain lower amounts of ALDH isozymes. However, certain tissues may contain a relatively large amount of a specific ALDH isozyme depending on the unique function of each tissue. For instance, ALDH5A1, NAD^+-dependent succinic semialdehyde dehydrogenase involved in the metabolism of a neurotransmitter GABA, is highly expressed in the brain compared to other non-neuronal tissues including the liver [15]. In contrast, ALDH7A1, responsible for cellular protection against salinity, dehydration, and hyper-osmotic stress and betaine aldehyde metabolism, is highly expressed in the kidney, heart, ovary, cochlea, and eye [9,16].

It is now known that the catalytic activities of ALDH2 and ALDH isozymes are usually suppressed under pathophysiological conditions through synergistic interaction between genetic factors (e.g., gender, allelic variation/mutation/single nucleotide polymorphism (SNP)/copy number variation in *ALDH* genes) [14,17–23] and environmental factors (e.g., alcohol, drugs, smoking, high-fat diet, viral/bacterial infections, toxic chemicals, etc.) [24–29] (Fig. 1). However, the causal roles of ALDH isozymes in the disease states are incompletely