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Ocular aldehyde dehydrogenases: Protection against ultraviolet damage and maintenance of transparency for vision

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ABSTRACT

Aldehyde dehydrogenase (ALDH) enzymes catalyze the NAD(P)$^+$-dependent oxidation of a wide variety of endogenous and exogenous aldehydes to their corresponding acids. Some members of the ALDH superfamily of enzymes are abundantly expressed in the mammalian cornea and lens in a taxon-specific manner. Considered to be corneal and lens crystallins, they confer protective and transparent properties upon these ocular tissues. ALDH3A1 is highly expressed in the cornea of most mammals, with the exception of rabbit that expresses exclusively ALDH1A1 in the cornea. ALDH1A1 is present in both the cornea and lens of several animal species. As a result of their catalytic and non-catalytic functions, ALDH3A1 and ALDH1A1 proteins protect inner ocular tissues from ultraviolet radiation and reactive oxygen-induced damage. In addition, these corneal crystallins contribute to cellular transparency in corneal stromal keratocytes, supporting a structural role of these ALDH proteins. A putative regulatory function of ALDH3A1 on corneal cell proliferation has also been proposed. Finally, the three retinaldehyde dehydrogenases cooperatively mediate retinoic acid signaling during the eye development.

Contents

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1. Introduction

The human eye is routinely exposed to sunlight and artificial light. While transmission of incident light through the eye is fundamental for vision, this radiation can pose a hazard to ocular tissues, potentially leading to impaired vision. A plethora of studies have established an association between ultraviolet radiation (**UVR**) exposure and numerous ocular disease states, such as cataracts and macular degeneration (Roberts, 2011).

The aldehyde dehydrogenase (**ALDH**) superfamily of enzymes plays an important role in the metabolism of endogenous and exogenous aldehydes (Marchitti et al., 2008). Through their catalytic functions, ALDH enzymes detoxify reactive aldehydes and modulate some important cellular processes, such as embryogenesis and neurotransmission. Through involvement in retinoic acid (**RA**) biosynthesis, members of the ALDH family are also implicated in vertebrate eye development (Duester, 2009). Additionally, ALDHs can exhibit biological functions unrelated to catalytic activity, an example of which is physicochemical binding to hormones and small molecules. Specific ALDH isozymes have been found to be abundantly expressed in the cornea and lens in a taxon-specific manner (Cooper et al., 1993). Studies using cell cultures and transgenic animal models have identified these ALDHs to be corneal and lens crystallins (Estey et al., 2007a, 2007b; Lassen et al., 2007). Like other crystallin proteins, the ALDH molecules have a structural role and contribute to cellular transparency (Jester, 2008). They also function as important components of cellular defense mechanisms against UVR and reactive oxygen species-induced ocular damage (Lassen et al., 2008). This review summarizes the current state of knowledge about the properties and functions of ocular ALDHs, with a focus on the unique roles of ALDH1A1 and ALDH3A1 as corneal and lens crystallins. The discussion covers the following topics: (i) an overview of the ALDH superfamily of enzymes, (ii) taxon-specific expression of ALDHs in the cornea and lens, (iii) protective properties of ALDH1A1/3A1 against UV exposure, (iv) structural and regulatory roles of ALDH1A1/3A1 in the cornea, and (v) ALDH enzymes in the developing eye.

2. ALDH superfamily of enzymes

2.1. Structure and catalytic sites of ALDH enzymes

The ALDH superfamily comprises nicotinamide-adenine dinucleotide phosphate (**NAD(P)**$^+$)-dependent enzymes that irreversibly catalyze the oxidation of aldehyde substrates to their respective carboxylic acids (Jackson et al., 2011). Isozymes are given the name based on their peptide sequence identity such that families within the superfamily share >40% identity and members of the same subfamily share >60% identity. ALDH proteins are widely expressed in mammalian tissues, albeit different isozymes exhibit distinct tissue distributions. Although these enzymes share some common physiological functions and substrates, each of the isozymes

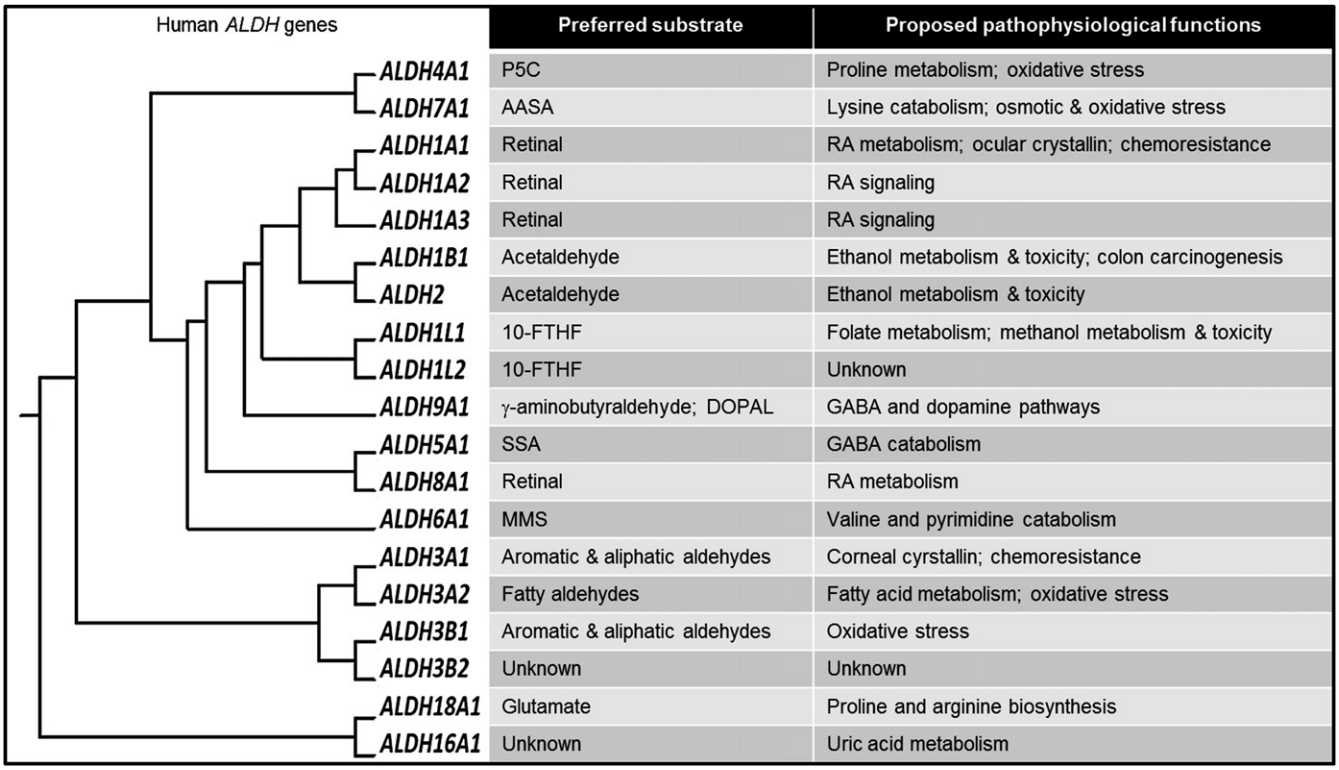

Fig. 1. Human ALDH superfamily. Clustering dendrogram of the nineteen human *ALDH* genes shows the evolution of human ALDH superfamily from a single gene. For each isozyme, the preferred substrates and proposed pathophysiological function are provided (Marchitti et al., 2008). 10-FTHF, 10-formyltetrahydrofolate; AASA, α-aminoadipic semialdehyde; DOPAL, 3,4-dihydroxyphenylacetaldehyde; GABA, γ-aminobutyric acid; MMS, methylmalonate semialdehyde; P5C, pyrroline-5-carboxylate; RA, retinoic acid; SSA, succinic semialdehyde.