Abstract

Aldehyde dehydrogenase 1A1 (ALDH1A1) is a member of the ALDH gene superfamily. Aldehyde dehydrogenases (ALDHs) are responsible for the metabolism of aldehydes (exogenous and endogenous) through NAD(P)+-dependent oxidation to their corresponding carboxylic acids or CoA esters. Different biological functions have been attributed to the different ALDH family members. The cytosolic enzyme ALDH1A1 is involved in the catalysis of retinol (vitamin A) metabolite retinaldehyde to retinoic acid (RA). RA acts as a ligand for the nuclear receptors retinoic receptor (RAR) and the retinoid X receptor (RXR) and therefore regulates the transcriptional activity of genes involved in multiple important processes including proliferation, differentiation, and apoptosis.

Keywords
ALDH1A1, retinaldehyde, retinoic acid, retinol, cancer, stem cell, alcohol

Identity

Other names: ALDC, ALDH-E1, ALDH1, ALDH11, HEL-9, HEL-S-53e, HEL12, PUMB1, RALDH1
HGNC (Hugo): ALDH1A1
Location: 9q21.13
Local order
Starts at 72900662 and ends at 72953317 (according to GRCh38) (Figure 1).

Chromosome 9 - NC_000009.12

Figure 1. Genomic location of human ALDH1A1 (Chromosome 9 - NC_000009.12, GRCh38.p12 Primary Assembly)
The ALDH gene superfamily is found in Archaea, Eubacteria and Eukarya, indicating a vital role for this family throughout evolutionary history (Jackson et al., 2011). A standardized gene nomenclature system based on divergent evolution and amino acid identity was established for the ALDH superfamily in The Ninth International Symposium on Enzymology and Molecular Biology of Carbonyl Metabolism, in 1998 (Figure 2) (Marchitti et al., 2008).

There are 19 known functional aldehyde dehydrogenase (ALDH) genes and many pseudogenes in the human genome (Tomita et al., 2016). ALDH1 family has six members including ALDH1A1, ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1, and ALDH1L2 (C. K. Yang et al., 2017). Since vertebrate ALDH1A1, ALDH1A2 and ALDH1A3 subunit sequences are highly conserved: subsequent gene duplication events are thought to generate ALDH1A1, ALDH1A2 and ALDH1A3 genes in most vertebrate genomes, except some bony fish (Holmes, 2015). ALDH1A1 homologs are present in most vertebrate species, but are absent in Zebra fish and other fishes in the teleost lineage (Table 1) (Jackson et al., 2011).

Description

The ALDH1A1 gene is a protein coding gene. The gene covers 52656 bp, from 72900662 to 72953317 (NC_000009.12). It is located on the plus strand spanning 13 exons (GRCh38, NCBI Homo sapiens Annotation Release 109).

Transcription

This gene has 7 transcripts (splice variants), 161 orthologues and 18 paralogues depending on Ensembl release 95-January 2019 (Table 2). ENST00000297785.7 (ALDH1A1-201) transcript has 13 exons, ENST00000376939.5 (ALDH1A1-202) and ENST00000419959.5 (ALDH1A1-203) transcripts have 8 exons, and ENST00000446946.1 (ALDH1A1-204) transcript has 7 exons (Figure 3).

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Table 1. Pairwise alignment of ALDH1A1 gene (in distance from human) (HomoloGene, NCBI).

| Gene Species | Gene Symbol | Identity (%) DNA |
|--------------|-------------|-----------------|
| Human (H.sapiens) | ALDH1A1 | vs. P.troglodytes ALDH1A1 99.5 |
| Human (H.sapiens) | ALDH1A1 | vs. M.mulatta ALDH1A1 97.9 |
| Human (H.sapiens) | ALDH1A1 | vs. C.lupus ALDH1A1 88.4 |
| Human (H.sapiens) | ALDH1A1 | vs. B.taurus ALDH1A1 90.2 |
| Human (H.sapiens) | ALDH1A1 | vs. M.musculus Aldh1a1 84.6 |
| Human (H.sapiens) | ALDH1A1 | vs. R.norvegicus Aldh1a1 83.9 |
| Human (H.sapiens) | ALDH1A1 | vs. G.gallus ALDH1A1 79.4 |
| Human (H.sapiens) | ALDH1A1 | vs. X.tropicalis aldh1a1 74.4 |
| Human (H.sapiens) | ALDH1A1 | vs. E.gossypii AGOS_ADR417W 54.1 |
| Human (H.sapiens) | ALDH1A1 | vs. A.thaliana ALDH2C4 57.6 |
| Human (H.sapiens) | ALDH1A1 | vs. O.sativa Os01g0591000 56 |
| Human (H.sapiens) | ALDH1A1 | vs. O.sativa Os01g0591300 55.5 |

Table 1. Pairwise alignment of ALDH1A1 gene (in distance from human) (HomoloGene, NCBI).

Figure 3. Display of human ALDH1A1 gene transcript exons (Ensembl release 95 - January 2019)
ALDH1A1 (Aldehyde Dehydrogenase 1 family member A1)

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Table 2. Transcripts of human ALDH1A1 gene (Ensembl release 95-January 2019)

| Name                  | Transcript ID       | bp  | CCDS       | RefSeq          |
|-----------------------|---------------------|-----|------------|-----------------|
| ALDH1A1-201           | ENST0000029777-85.7 | 2107| 7          | CCDS6644 NM_000689 |
| ALDH1A1-202           | ENST0000037693-39.5 | 822 | -          | -               |
| ALDH1A1-203           | ENST0000041999-59.5 | 806 | -          | -               |
| ALDH1A1-204           | ENST0000044699-46.1 | 805 | -          | -               |
| ALDH1A1-205           | ENST000004822-10.5  | 879 | -          | -               |
| ALDH1A1-206           | ENST000004931-13.1  | 604 | -          | -               |
| ALDH1A1-207           | ENST000004933-11.1  | 209 | -          | -               |

Table 3. Protein products of human ALDH1A1 gene (Ensembl release 95-January 2019)

| Name     | Transcript ID       | bp   | Protein | Charge | Isoelectric Point | Molecular Weight | CCDS       | UniProt   | RefSeq          |
|----------|---------------------|------|---------|--------|-------------------|------------------|------------|-----------|-----------------|
| ALDH1A1-201 | ENST00000297785.7   | 2107 | 501aa   | 1.0    | 6.6811            | 54,861.84 g/mol  | CCDS6644   | P00352   | V9HW83         |
| ALDH1A1-202 | ENST00000376939.5   | 822  | 230aa   | -0.5   | 6.2427            | 25,314.22 g/mol  | -          | Q5SYQ9   | -               |
| ALDH1A1-203 | ENST00000419959.5   | 806  | 238aa   | -1.0   | 6.1061            | 26,097.05 g/mol  | -          | Q5SYQ8   | -               |
| ALDH1A1-204 | ENST00000446946.1   | 805  | 203aa   | -1.0   | 5,8174            | 22,654.11 g/mol  | -          | Q5SYQ7   | -               |

Table 4. Pairwise alignment of ALDH1A1 protein sequences (in distance from human) (HomoloGene, NCBI)

| Gene Species | Gene Symbol | Identity (%) | Protein |
|--------------|-------------|--------------|---------|
| H.sapiens    | ALDH1A1     |              | 100     |
| vs. P.troglodytes | ALDH1A1    |              | 98.8    |
| vs. M.mulatta | ALDH1A1     |              | 91.2    |
| vs. C.lupus  | ALDH1A1     |              | 87      |
| vs. B.taurus | ALDH1A1     |              | 86.4    |
| vs. M.musculus | Aldh1a1    |              | 84.2    |
| vs. X.tropicalis | Aldh1a1    |              | 78.2    |
| vs. E.gossypii | AGOS_ADR417W |              | 50.7    |
| vs. A.thaliana | ALDH2C4    |              | 52      |
| vs. O.sativa | Os01g0591000 |              | 53.8    |
| vs. O.sativa | Os01g0591300 |              | 51.8    |

Protein

Aldehyde dehydrogenase 1 family, member A1, also known as ALDH1A1 or retinaldehyde dehydrogenase 1 (RALDH1), is an heterotetramer enzyme that is encoded by the human ALDH1A1 gene.

Human ALDH1A1 is 501 amino acids in length (Table 3). ALDH1A1 protein similarity across species are given in Table 4.

Description

The human ALDH1 family shares over 60% protein sequence identity and has six subfamily members (C. K. Yang et al., 2017).

Crystal structures of mammalian ALDH enzymes have shown that each subunit contains three domains: (1) an NAD(P)⁺ cofactorbinding domain, (2) a catalytic domain, and (3) a bridging domain. A funnel passage leading to the catalytic pocket is found at the interface of these domains.

In mouse hepatoma cells, RARA transactivates the Aldh1a1 promoter by binding to the RARE region, located between -91 and -75 bp. Moreover, CEBPB has been demonstrated to transactivate the ALDH1A1 promoter by interacting with the CCAAT box that resides at -75 to -71 bp adjacent to the RARE (Alam et al., 2013).

Pseudogene

Not identified.
**Expression**

ALDH1A1 is a highly conserved homotetramer somatic cell plasma protein, expressed in numerous tissues, including liver, kidney, red blood cells, skeletal muscle, lung, breast, lens, stomach, brain, pancreas, testis, prostate, ovary (Jackson et al., 2011; Mamat et al., 2011). The detailed RNA and protein expression information can be found in: Human Protein Atlas (https://www.proteinatlas.org/ENSG00000165092-ALDH1A1/tissue).

**Localisation**

ALDH1A1 is present in the cytosol. Interestingly, Kahlert et al. observed nuclear expression of ALDH1A1 in a small subgroup of patients with colon cancer and rectal cancer, and found that in colon cancer patients, nuclear expression of ALDH1A1 was significantly associated with shortened overall survival (Kahlert et al., 2012).

**Function**

In retinol metabolism (Figure 4), retinol is oxidized by retinol dehydrogenases (RD) to retinal. Later on, retinal is oxidized to retinoic acid (RA) in a reaction catalyzed by the human ALDH isoenzymes ALDH1A1, ALDH1A2, ALDH1A3, and ALDH8A1. The metabolized product RA includes all-trans RA (ATRA), 9-cis RA, and 13-cis RA. The ALDH isoforms, especially ALDH1A1, have an affinity for ATRA and 9-cis RA. RA diffuses into the nucleus and acts as a ligand for the retinoic acid receptors (RARA, RARB, RARG) and retinoic X receptors (RXRA, RXRB, RXRG). Then, the ligand-receptor complex binds to the retinoic acid response element (RARE) in the promoter of target genes and therefore regulates differentiation, apoptosis and/or cell cycle arrest in a context-dependent manner (Marcato et al., 2011b; Tomita et al., 2016). RXRA/c mice were shown to have decreased liver ALDH1A1 levels, suggesting that RA binding is an activating factor in ALDH1A1 gene expression (Gyamfi, 2006). RA is required for testicular development and ALDH1A1 is absent in genital tissues of humans with androgen receptor-negative testicular feminization. Being an androgen binding protein, ALDH1A1 expression is thought to be regulated also by the androgen receptor (Li et al., 2010; Marchitti et al., 2008).

Aldehyde dehydrogenase (ALDH) enzyme family plays an important role in cellular signal transmission and protection by catalyzing the oxidation of aldehydes (Alam et al., 2013). ALDH1A1 mainly contributes to the biosynthesis of retinoic acid (RA) from vitamin A (Van Der Waals et al., 2018). Inside the cell, Retinol (vitamin A) is oxidized to retinal by retinal dehydrogenases. The retinal is then oxidized to RA in a reaction catalyzed with ALDH1A1, ALDH1A2, ALDH1A3, and ALDH8A1 (Tomita et al., 2016). The RA enters the cell nucleus and binds and activates RA receptors (RARs) or retinoid X receptors (RXRs) to regulate gene expression (Zhao et al., 2014).

ALDH1A1 also plays a role in acetaldehyde metabolism. Acetaldehyde is the first product of ethanol metabolism. Alcohol, taken with alcohol consumption, is converted to acetaldehyde by alcohol dehydrogenase (ADH), catalase and cytochrome P450 2E1. Then, acetaldehyde is metabolized to acetates by ALDH2 and ALDH1A1. Indeed, low ALDH1A1 activity is suggested to be related to alcohol sensitivity in some Caucasian populations ("Identification And Characterisation Of Alcohol-Induced Flushing In Caucasian Subjects", 2017). Moreover, decreased levels of ALDH1A1 were shown in RXRA/c mice, which were more susceptible to alcoholic liver injury (Gyamfi, 2006), while increased ALDH1A1 expression found in brains of alcohol-avoiding DBA/2 mice (Bhave et al., 2006).

ALDH1A1 is predominantly expressed by a subgroup of dopaminergic (DA) neurons in the midbrain (Maring et al., 1985). In DA neurons, ALDH1A1 mediates the oxidation of the cytotoxic dopamine intermediate, 3,4-dihydroxyphenylacetaldehyde (DOPAL), to the less reactive 3,4-dihydroxyphenylacetic acid (DOPAC), and thereby protects the DA neurons from toxicity (Pan et al., 2019). Very recently, ALDH1A1 was reported to mediate the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Kim et al., 2015) in DA neurons, where co-release of dopamine and GABA regulates alcohol consumption and preference (Pan et al., 2019). In addition, as a metabolic product of ALDH1A1, RA is known to play a crucial role in neuronal patterning, differentiation, and survival (Pan et al., 2019).

In addition to its role in aldehyde metabolism, ALDH1A1 possesses esterase activity. Collard et al. proposed ALDH1A1 being the major if not the only enzyme responsible for the oxidation of 3-deoxyglucosone to 2-keto-3-deoxygluconate (Collard et al., 2007).

ALDHs are generally categorized as detoxification enzymes. ALDH1A1 was found to offer cellular protection against cytotoxic dopamine intermediate, 3,4-dihydroxyphenylacetaldehyde (DOPAL), to the less reactive 3,4-dihydroxyphenylacetic acid (DOPAC), and thereby protects the DA neurons from toxicity (Pan et al., 2019). In addition, as a metabolic product of ALDH1A1, RA is known to play a crucial role in neuronal patterning, differentiation, and survival (Pan et al., 2019).

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ALDH1 activity and ALDH1A1 overexpression are associated with poor cancer prognosis, high ALDH1 and ALDH1A1 levels are not always correlated with highly malignant phenotypes and poor clinical outcome in a range of cancers (Tomita et al., 2016). It is suggested that ALDH1A1 can be a useful marker for cancer stem cells derived from tumors that normally do not express high levels of ALDH1A1, including breast, lung, esophagus, colon, and stomach (Tomita et al., 2016; Xing et al., 2014).

ALDH1A1 also plays a key role in the cellular defense against oxidative stress: ALDH activity is required to maintain sufficiently low Reactive Oxygen Species (ROS) level. Human ALDH1A1 was shown to efficiently oxidize lipid peroxidation-derived aldehydes, like 4-Hydroxynonenal (4-HNE), hexanal, and Malondialdehyde (MDA) (MANZER et al., 2003), and Aldh1a1 knock-out mouse models demonstrated that ALDH1A1 plays a crucial role in protecting the mouse eye lens and cornea by detoxifying lipid peroxidation-derived aldehydes and preventing cataract formation induced by oxidative stresses (Mice et al., 2008).

In addition to its catalytic functions, ALDH1A1 has also non-catalytic roles. Similar with other ALDHs, ALDH1A1 acts as corneal and lens crystallins in mammalian eye tissue and contributes to the transparent and refractive properties of the eye (Vasiiliou et al., 2013), as well as protects the eye from tissue damage as mentioned earlier.

Finally, since ALDH1A1 can bind thyroid hormone and its expression is induced by estrogens, it is suggested that the enzyme may be regulated by or involved in hormone signaling (Marchitti et al., 2008).

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**Figure 4. Retinoic acid signaling pathway:** Retinoic acid (RA), generated by ALDHs, can function in the paracrine or endocrine manner by diffusing into neighboring cells or the nucleus. In the nucleus, RA binds to heterodimers of the retinoic acid receptor (RAR) and retinoid X receptor (RXR). Activated receptor complexes induce transcription of target genes by binding to retinoic acid response elements (RAREs).

**Figure 5. ALDH1A1 regulation and function:** Once inside the cytoplasm, retinol is oxidized to retinal, then retinal is oxidized to RA by several isoforms of ALDH. RA binds to dimers of RARA and RXRs to induce the expression of its downstream target genes. RA can bind to dimers of RXRs and ESR1 (ERα) as well as induce the expression of MYC and CCND1 (cyclin D1) in ERα-expressing cells. In addition to RA binding to the RAR, CEBPB and OCT1 binding to the ALDH1A1 promoter enhances the ALDH1A1 transcription. NFYA was also shown to activate ALDH1A1 transcription while DDB2 was shown to suppress ALDH1A1 expression by preventing CEBPB binding to the promoter. The details can be found in the text. The figure is modified from Tomita et al. (Tomita et al., 2016).
ALDH1A1 (Aldehyde Dehydrogenase 1 family member A1)  Tunçer S et al.

Figure 6. Structure of human ALDH1A1: Structure of human ALDH1A1 determined using X-ray diffraction (PDB ID: 4WJ9) (Morgan and Hurley, 2015; Rose et al., 2018).

Mutations

A list of ALDH1A1 mutations in cancer can be found in: COSMIC, the Catalogue of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=ALDH1A1.

Implicated in

ALDH1A1 encodes the enzyme ALDH1A1 (also known as retinaldehyde dehydrogenase 1-RALDH1) which is involved in several metabolic processes and therefore implicated in various diseases and conditions.

Parkinson’s disease

Deficiency in ALDH activity, specifically in ALDH1A1 activity in the substantia nigra, is suggested to lead accumulation of neurotoxic aldehydes and subsequent cell death seen in Parkinson’s disease, and possibly in other neurodegenerative disorders. ALDH1 mRNA expression was reported to be decreased in surviving neurons of Parkinson’s disease patients (Basso et al., 2004). Wey et al. showed that deletion of two isoforms of aldehyde dehydrogenase, Aldh1a1 and Aldh2, which are known to be involved in dopamine metabolism in the brain, resulted in elevated levels of the neurotoxic aldehydes DOPAL and 4-HNE and loss of dopaminergic neurons in the substantia nigra, and caused a Parkinsonian phenotype characterized by age-dependent deficits in motor performance (Wey et al., 2012).

Obesity

Adipogenesis is a process regulated by retinoids. Being an ALDH1A1 substrate, retinaldehyde was shown to down-regulate the expression of adipogenesis genes in vitro. In vivo, retinaldehyde decreased fat levels and increased insulin sensitivity in an obese mouse model. Therefore, both in vivo and in vitro results suggest that retinaldehyde may act as an adipogenesis inhibiting signaling metabolite (Ziouzenkova et al., 2007).

As an ALDH1A1 metabolite, RA has also an effect on adipogenesis. RA treatment of obese mice resulted in weight loss and increased insulin sensitivity in addition to increased expression of RAR and other genes (Berry and Noy, 2009). In comparison with other vitamin A metabolizing enzymes responsible in the production of RA, the major enzyme expressed during adipogenesis is ALDH1A1, and ALDH1A1 deficiency was shown to result in impaired adipogenesis (Harrison et al., 2011). Retinal, the substrate of ALDH1A1, is suggested to inhibit PPARG (peroxisome proliferator-activated receptor-gamma) a transcription factor known as the master regulator of adipogenesis. Ziouzenkova et al. showed that retinal is present in rodent fat, binds retinol-binding proteins (CRBP1, RBP4), inhibits adipogenesis and suppresses PPARG and RXR responses. In vivo, mice lacking the Aldh1a1 resisted diet-induced obesity and insulin resistance and showed increased energy dissipation. In ob/ob mice, administrating retinal or an Aldh1a1 inhibitor reduced fat and increased insulin sensitivity (Ziouzenkova et al., 2007).

Alcohol-related phenotypes

Because of its involvement in ethanol metabolism, ALDH1A1 is a candidate for alcohol research. ALDH1A1 has been implicated in several alcohol-related phenotypes, including alcoholism, alcohol-induced flushing, and alcohol sensitivity. Studies suggest that low ALDH1A1 activity may contribute to alcohol sensitivity and alcohol-induced flushing reaction in Caucasians and some Asians. Polymorphisms located on both coding and promoter regions of ALDH1A1 were found to influence alcoholic predisposition (Spence et al., 2003). Kim et al. showed that an evolutionarily conserved GABA synthesis pathway involves Aldh1a1. They found that repeated ethanol exposure reduces GABA co-release from the ventral tegmental area (VTA) dopamine neurons and downregulation of Aldh1a through gene targeting or RNA interference increases alcohol consumption in mice. These findings highlight the importance of Aldh1a1 and VTA GABA co-release in moderating alcohol consumption (Kim et al., 2015).

Cancer

ALDH1A1 has been shown to be related to the stemness of both cancer stem cells and normal tissue stem cells. Recent reports reveal that ALDH1 and specifically ALDH1A1 is a useful cancer stem cell marker that can be used to enrich tumor-initiating
subpopulations from various cell lines and primary tumors (Tomita et al., 2016).

**Breast cancer**

ALDH1A1 is a breast cancer biomarker for prediction of tumor progression and its expression is correlated with poor survival (Liu et al., 2014). High ALDH activity and CD44 expression (ALDHiCD44+) were found to contribute to metastatic behavior and therapy resistance to breast cancer (Croker et al., 2017).

**Colorectal cancer**

ALDH1A1 protein expression was found to be increased significantly in colorectal cancer (CRC) tissues compared with matched non-tumor adjacent tissues using immunohistochemistry (IHC). Therefore, the protein is suggested to be a potential prognostic marker in patients with CRC. Moreover, in patients with CRC, increased expression of the ALDH1A1 protein was shown to be associated with the lymph node metastasis (W. et al., 2018). ALDH1A1 expression was found to be associated also with features of poor prognosis, including a poorly differentiated histology and “right-sidedness” of the primary tumor, and with shorter overall survival (Van Der Waals et al., 2018).

**Esophageal cancer (squamous cell carcinoma)**

Depending on Yang et al., ALDH1A1 (high) cancer stem-like cells contribute to the invasion, metastasis and poor outcome of human esophageal squamous cell carcinoma. ALDH1A1 high esophageal squamous cell carcinoma cells were found to have increased levels of mRNA for VIM (vimentin), matrix metalloproteinase 2, 7, and 9 (MMP2, MMP7 and MMP9), but decreased the level of CDH1 (E-cadherin) mRNA, suggesting that epithelial-mesenchymal transition and MMPs may be associated with the high invasive and metastatic capabilities of ALDH1A1 high cells (L. Yang et al., 2014).

**Gastric cancer**

The positive rate of ALDH1A1 expression was shown to be 60% in gastric cancer patients (L. Yang et al., 2017), but there was no significant difference between survival rates of ALDH1A1-positive and ALDH1A1-negative patients (Li et al., 2016; L. Yang et al., 2017).

**Liver cancer**

Tanaka et al. found there was no significant difference in the ALDH1A1-mRNA level between tumorous and non-tumorous tissues of hepatocellular carcinoma patients. In addition, there was no correlation between tumorous ALDH1A1-mRNA level and the clinic-pathological features. They found that in human hepatocellular carcinoma, ALDH1A1-overexpressing cells are differentiated cells rather than cancer stem or progenitor cells (Tanaka et al., 2015).

**Lung cancer**

The expression of LGR5 and ALDH1A1 were found to be closely associated with the tumorigenicity, metastasis and poor prognosis of non-small cell lung cancer, and LGR5 + cells in non-small cell lung cancer are proposed to be the cancer cells with stem cell-like properties due to the significant correlation between LGR5 and ALDH1A1 (Gao et al., 2015).

**Multiple myeloma**

Yang et al. reported that increased expression of ALDH1 in multiple myeloma (MM) is a marker of tumor-initiating cells (TICs) that is further associated with chromosomal instability (CIN). They found, between the ALDH1 members, ALDH1A1 is most abundantly expressed member in myeloma and enforced expression of ALDH1A1 in myeloma cells results in increased clonogenicity, tumor formation in mice, and resistance to myeloma drugs in vitro and in vivo (Y. Yang et al., 2014).

**Ovarian cancer**

Lenden Jr et al. showed that in ovarian cancer, ALDH1A1-positive population has properties of cancer stem cells, and this population is associated with taxane and platinum resistance. Additionally, this population was found to be resensitized to chemotherapy both in vitro and in vivo by down-regulation of ALDH1A1 expression (Laden et al., 2010). More recently, Cui et al. showed that in ovarian cancer, DNA damage-binding protein 2 (DDB2) suppresses non-cancer stem cell to cancer stem cell conversion by repressing ALDH1A1 transcription. Mechanistically, DDB2 binds to the ALDH1A1 gene promoter, enhances the enrichment of histone H3K27me3, and thereby competes with the transcription factor CEBPB for binding to this region, and eventually inhibits the promoter activity of the ALDH1A1 gene (Cui et al., 2018) (Figure 5).

**Pancreatic cancer**

ALDH1A1 is a pancreatic stem cell marker and is highly enriched in a subpopulation of cells which are extremely resistant to chemotherapy. Furthermore, ALDH1 is highly enriched in surgical specimens from patients with pancreatic cancer who had undergone preoperative chemo-radiation therapy compared to untreated patients (Mizukami et al., 2014).
**Papillary thyroid carcinoma**

ALDH1A1 levels were significantly higher in papillary thyroid carcinoma samples than normal thyroid samples and ALDH1A1 overexpression was significantly associated with extrathyroid extension, pT status, pN status and TNM stage. The Kaplan-Meier survival analysis shows that high ALDH1A1 expression reflects a poorer lymph node recurrence-free survival (LN-RFS) and distant recurrence-free survival (DRFS) in papillary thyroid carcinoma patients, as compared with patients who have low ALDH1A1 expression. Multivariate analysis confirmed ALDH1A1 expression as an independent prognostic factor for LN-RFS and DRFS in papillary thyroid carcinoma patients (Xing et al., 2014).

**Prostate cancer**

ALDH1A1 is a cancer stem cell marker in prostate cancer (Kalantari et al., 2017). Cojoc et al. found that the expression of ALDH1A1 is regulated by the WNT signaling pathway. Inhibition of the WNT pathway led to a decrease in ALDH (+) tumor progenitor population and to radiosensitization of cancer cells (Cojoc et al., 2015).

**To be noted**

Aldefluor assay is widely used to detect ALDH activity by flow cytometry. This assay is based on the conversion of the ALDH substrate BODIPY-aminoacetaldehyde (BAAA) to the fluorescence product BODIPY-aminoacetate. Therefore, the level of fluorescence corresponds to the amount of ALDH activity present in the cell. N,N-diethylamino-benzaldehyde (DEAB), an inhibitor of ALDH activity, is supplied as a negative control for the assay. When the assay has been developed, DEAB was found to be a potent inhibitor of cytosolic ALDH (ALDH1) but not mitochondrial ALDH (ALDH2). Because of this, the Aldefluor Assay was thought to measure cellular ALDH1A1 activity. However, recent studies have shown that DEAB inhibits other ALDH isoenzymes and as a result, the Aldefluor assay will detect stem cells with high levels of other ALDH isoenzyme activity, including ALDH1A2, ALDH1A3, and ALDH2 (Marcato et al., 2011a; Moreb et al., 2012). Morgan et al. analyzed the mechanism underlying DEAB dependent inhibition and found that DEAB is a substrate for ALDH3A1, ALDH1A1, ALDH1A3, ALDH1B1, ALDH5A1, but the turnover rates are so slow that it acts as an inhibitor for more rapidly metabolized aldehyde substrates. Additionally, they did not find appreciable turnover of DEAB with either ALDH1A2 or ALDH2, where DEAB behaves as a covalent inhibitor for both isoenzymes (Morgan et al., 2015).

In IHC analyses, ALDH1A1 can be specifically identified with isotype-specific antibodies. However, when it is the stem cell population, Aldefluor assay has to be used to identify ALDH1A1 activity (Tomita et al., 2016). Because of the broad and varied nature of the interaction between DEAB and ALDH isoenzymes, the results of Aldefluor assay should be interpreted with caution with regard to which particular ALDH isoenzymes contribute to the observed fluorescence in the flow cytometry assay. Together with Aldefluor assay, other specific measurement methods are needed to determine ALDH1A1 expression and activity in the biological samples. In this sense, the generation of selective inhibitor(s) for ALDH1A1 appears to be particularly important.

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This article should be referenced as such:

Tunçer S, Çamlca R, Yilmaz I. ALDH1A1 (Aldehyde Dehydrogenase 1 family member A1). Atlas Genet Cytogenet Oncol Haematol. 2020; 24(3):102-111.