Review

# Aldehyde dehydrogenase 1: Its key role in cell physiology and oral carcinogenesis

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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## Abstract

Aldehyde dehydrogenase (ALDH), an aldehyde-metabolizing enzyme, is a cytosolic antioxidant. It performs many important physiological catalytic and non-catalytic functions in mammalian cells. Apart from physiological functions, like the biosynthesis of vital molecules, this NAD(P)+ substrate-dependent enzyme superfamily is primarily involved in catalyzing the oxidation of highly reactive exogenous and endogenous aldehydes to their respective carboxylic acids. Among ALDH isoenzymes, ALDH1 has gained much attention as a prominent stem cell marker, as it is associated with the maintenance of stemness and the differentiation of normal stem cells, in addition to involvement in oncogenic functions, like cell proliferation, anti-apoptosis and the reduction of oxidative stress in cancer stem cells (CSCs). In this context, the authors review the physiological functions of ALDH1 in normal cells, normal stem cells and CSCs, along with the discussion of the putative role of ALDH1 in oral carcinogenesis by commenting on its expression in normal oral mucosa cells, oral potentially malignant disorders (OPMDs), like leukoplakia and dysplastic lesions, and oral squamous cell carcinoma (OSCC).

**Keywords:** carcinogenesis, stem cells, oral squamous cell carcinoma, aldehyde dehydrogenase 1

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# Introduction

Aldehyde dehydrogenases (ALDHs) are one of the 3 aldehyde-metabolizing enzyme groups found in virtually all mammalian cellular compartments, the other 2 groups being aldehyde oxidases and aldo-keto reductases.[1] The ALDH NAD(P)$^+$ substrate-dependent enzyme superfamily catalyzes the oxidation reactions of highly reactive exogenous and endogenous aldehydes to their respective carboxylic acids. In addition to their role in aldehyde oxidation, ALDHs also have their share in other, non-catalytic physiological functions, like the biosynthesis of vital molecules, i.e., retinoic acid (RA), folate, gamma-aminobutyric acid, and betaine, binding to endobiotics and xenobiotics, and the absorption of ultraviolet (UV) radiation and its involvement in osmoregulation in humans.[2] In humans, the ALDH superfamily is currently comprised of 11 families (ALDH1, ALDH2, ALDH3, ALDH4, ALDH5, ALDH6, ALDH7, ALDH8, ALDH9, ALDH16, and ALDH18) and 4 subfamilies, which comprise 19 functional genes.[3] Among these, the class 1 ALDH gene in humans is found on chromosome 9, spans about 53 kb and is comprised of 13 exons that are separated by 12 introns. *ALDH1* encodes 501 amino acids, including the chain initiation Met. The 5' upstream region of *ALDH1* contains 2 glucocorticoid response elements, which suggests that *ALDH1* may be influenced by hormones.[4] There are further 6 genes in human ALDH1 family: *ALDH1A1*; *ALDH1A2*; *ALDH1A3*; *ALDH1B1*; *ALDH1L1*; and *ALDH1L2*. Primarily, ALDH1 proteins are localized in cytosol in various tissues, except ALDH1B1, which has a mitochondrial localization.[5] The constitutive expression of ALDH1 in the tissues of mammals and the multifaceted physiological role of ALDH1 highlights its diagnostic, therapeutic and prognostic importance. In this review, we describe the role of ALDH1 in normal cells, normal stem cells and cancer stem cells (CSCs) in detail.

## ALDH1 in cellular physiology

### Retinoic acid metabolism

Retinoic acid and its metabolites are important in embryological development, morphogenesis and the regulation of gene expression. The ALDH1 family includes ALDH1A1, ALDH1A2, ALDH1A3, ALDH1A7, and ALDH1A8, which are primarily involved in the catalysis of retinal to RA. Consequently, RA then enters the nucleus, where it induces c-MYC and cyclin D1 transcription, which promotes resistance to apoptosis and increases cell proliferation, especially in cells with estrogen receptors. However, RA can also cause differentiation and apoptosis through the transcription of the retinoic acid receptor beta (RARβ). When the endogenous concentration of RA is low, exogenous RA can activate the ALDH1A1 promoter to enhance the production of RA.[6]

### Acetaldehyde metabolism

Ethanol, a common by-product of carbohydrate metabolism, is metabolized to acetaldehyde by several enzymes, such as catalase, alcohol dehydrogenase (ADH) and cytochrome P4502E1. The reactive oxygen species (ROS) generated by acetaldehyde contribute to oxidative stress, which promotes the formation of DNA and protein adducts. The ALDH1A1 enzyme is involved in acetaldehyde metabolism – acetaldehyde is subsequently metabolized to acetate by ALDH2 – and hence ALDH1A1 acts as part of the cellular anti-oxidative defense system.[7]

### Oxidative stress

Reactive aldehydes are detrimental to humans. They may be generated when endobiotic and xenobiotic compounds such as alcohols, amino acids, neurotransmitters, and environmental pollutants (e.g., food additives, motor vehicle exhaust, cigarette smoking, pesticides) are metabolized. Reactive aldehydes are strongly electrophilic, long-lasting compounds that readily form macromolecule adducts on proteins, RNA and DNA. Such modifications lead to DNA damage, enzyme inactivation, cell death, and carcinogenesis. The expression of ALDHs is generally upregulated in response to the oxidative stress induced by aldehydes. ALDH1, specifically ALDH1A1, along with ALDH2 catalyze the reactive aldehydes generated as a result of alcohol toxicity. These reactive aldehydes comprise, among others, 4-hydroxy-2 nonenal (4-HNE) as well as malondialdehyde (MDA), which are ALDH1B1 substrates. In addition to alcohol-induced oxidative stress, ALDHs, specifically ALDH1A1 along with ALDH3A1, are involved in detoxifying the reactive aldehydes produced by UV radiation by inhibiting the formation of 4-HNE and MDA.

## ALDH1 in stem cells

### Normal stem cells

Increased ALDH activity has been associated with stemness, owing to the consistent expression of ALDHs in the stem cells of several tissues. Aldehyde dehydrogenases have also been implicated in the functioning of stem cells, including expansion, self-protection and differentiation. Retinoic acid metabolism also contributes to the retinoid signaling pathway, and thereby plays an important role in maintaining stemness in stem cells.[7] The protection conferred by ALDHs in stem cells can be attributed to the detoxifying capabilities of the enzymes, mainly against various exogenous and endogenous aldehydes. In addition to aldehydes, ALDH1 also confers protection against various cytotoxic drugs, like cyclophosphamide and 4-hydroperoxycyclophosphamide (4-HC). In vitro experiments in both murine and human experimental models show that ALDH1 inhibition through inhibitors such as N,N-diethyl-

aminobenzaldehyde (DEAB) results in the expansion and differentiation of hematopoietic stem cells (HSCs) by delaying the G0/G1 transition, which results in a large number of HSCs remaining in the G0 phase.[8,9] Almost all tissues have a stem cell population. In bone marrow, among the population of stem cells, there are cells of high ALDH activity. Hematopoietic progenitors and neural stem cells usually express high levels of ALDH activity ($ALDH^{hi}$ cells). Besides, stem cells from adipose tissue, being multipotent mesodermal cells, also embrace a $ALDH^{hi}$ cell population.[10] Amongst all ALDH isoenzymes, ALDH1A1 seems to be expressed predominantly in the aforementioned stem cell populations. Reportedly, ALDH1A1 significantly contributes to the maintenance of stem cell populations by restricting cell proliferation through the irreversible conversion of 10-formyltetrahydrofolate (10-FTHF) into tetrahydrofolate (THF).[10] As ALDH1 activity in normal stem cells differs from tissue to tissue, Deng et al. classified tissues into 3 types according to the level of ALDH1 expression: 1. tissues with no expression or limited expression, such as lung and breast; 2. tissues with a weaker expression as compared to others, such as gastric epithelium and colon; and 3. tissues that have a greater expression level, such as liver and pancreas.[11]

### Cancer stem cells

Analogous to normal stem cells, the functional contribution of ALDH1 in CSCs mainly revolves around RA metabolism. In the classical pathway, ALDH metabolizes RA to products like 13-cis-retinoic acid (13-cis-RA), all-trans-retinoic acid (ATRA) and 9-cis-retinoic acid (9-cis-RA), which bind to retinoic acid receptor alpha (RARα) prior to entering the nucleus. In order to induce the expression of downstream target RARβ, RA binds to RARα and X retinoid receptor (RXR) dimers. This eventually results in cell differentiation as well as growth inhibition. In contrast to this, and through non-classical pathways, RA can induce anti-apoptosis, anti-differentiation and proliferative activity by activating the phosphoinositide 3-kinase (PI3K) signaling pathway and reducing the activity of protein kinase C. In addition, in cells with estrogen receptor alpha (ERα) and peroxisome proliferator-activated receptors beta/delta (PPARβ/δ), RA can form heterodimers with these receptors to upregulate pro-survival genes.[6,9]

Apart from RA metabolism, ALDH plays a significant protective role by reducing the level of ROS production and oxidative stress in CSCs, which thus prevents their apoptosis. Oncogenic pathways, like Notch-DLL4, MUC1-C, ERK, and Wnt/β-catenin, either upregulate ALDH1 transcription or increase its activity in CSCs (Fig. 1).[6,12] Regardless of whether oxidative stress is of endogenous (aerobic metabolism) or exogenous (due to chemotherapeutic or radiotherapeutic agents) origin, ALDH can reduce the ROS level in CSCs. Cancer stem cells are an important contributor to drug resistance in cancer treatment. Cumulative evidence of the strong association of chemotherapeutic drug resistance with ALDH1 expression in CSCs indicates the potential role of ALDH1 in molecular targeted therapies for several cancers. Various mechanisms have been suggested for describing the protective role of ALDH1 against these cytotoxic drugs, such as the oxidation of the aldehyde group to carboxylic acid and ultimately the transformation of the drugs into non-toxic forms, and the induction of RA-mediated signaling pathway.[6]

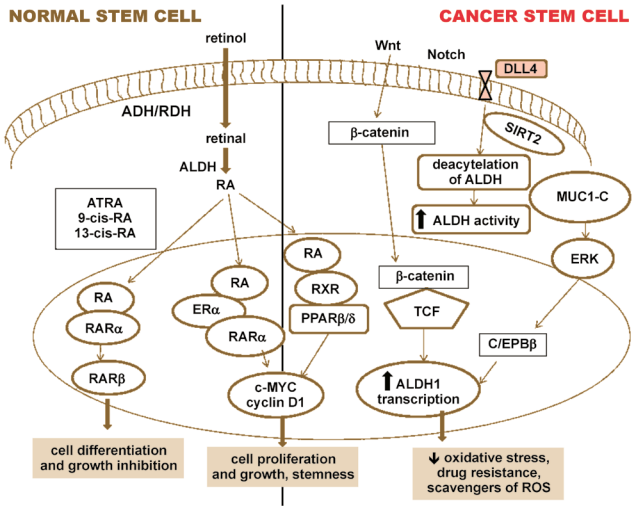


Fig. 1. Potential role of aldehyde dehydrogenase 1 (ALDH1) in normal and cancer stem cells

ALD – alcohol dehydrogenase; ALDH – aldehyde dehydrogenase; ATRA – all-trans-retinoic acid; ERα – estrogen receptor alpha; PPARβ/δ – peroxisome proliferator-activated receptors beta/delta; RA – retinoic acid; RARα – retinoic acid receptor alpha; RARβ – retinoic acid receptor beta; RDH – retinol dehydrogenase; ROS – reactive oxygen species; RXR – X retinoid receptor; TCF – T-cell factor.

With this knowledge regarding the physiological and pathological role of ALDH1 at the cellular level, we attempted to revisit its putative role in oral carcinogenesis by observing its expression in various premalignant and malignant lesions of oral cavity.

## Methodology

### Eligibility criteria

In the present study, we considered P (Population) as human samples of oral potentially malignant disorders (OPMDs) and oral cancer; I (Intervention) – immunohistochemical staining for ALDH1; C (Comparison) – normal oral mucosa; and O (Outcome) – the expression of ALDH1 in OPMDs and oral cancer.

### Research question

Is there a difference in the expression of ALDH1 in the samples of OPMDs and oral cancer as compared to normal oral mucosa based on immunohistochemical staining?

## Search strategy

An electronic search of the PubMed, Google Scholar and Scopus databases was performed up to October 2021, using a combination of keywords: "aldehyde dehydrogenase 1", "ALDH1" with "oral premalignant/precancerous lesion", "oral premalignant/precancerous condition", "oral potentially malignant disorders", "oral leukoplakia", "oral erythroplakia", "oral lichen planus", "oral epithelial dysplasia", "oral submucous fibrosis", "actinic cheilitis", "dyskeratosis congenita", "keratoacanthoma", "verrucous hyperplasia", "verrucous carcinoma", "proliferative verrucous leukoplakia", "smokeless tobacco keratosis", "discoid lupus erythematosus", "cheilitis glandularis", "xeroderma pigmentosum", "oral cancer", "oral squamous cell carcinoma", and AND/OR boolean operators. Only full texts of original research articles published in the English language, pertaining to the expression of ALDH1 in OPMDs and oral cancer were included for the review. Review articles and abstracts were excluded.

## Study selection process

The retrieved records were reviewed systematically by 2 independent reviewers and any disagreement was resolved by mutual consensus. Initially, the titles were reviewed and irrelevant records were excluded. The abstracts of the selected records were evaluated based on the inclusion and exclusion criteria. In cases of insufficient abstracts, the full-text articles were analyzed for relevance to the topic. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were consulted while conducting the review. The flowchart for article selection is shown in Fig. 2.

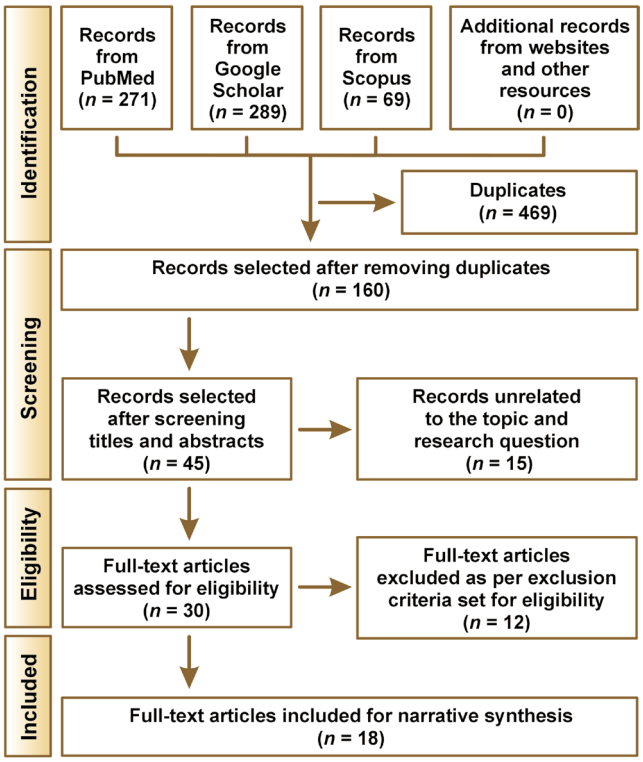


Fig. 2. Flowchart for the selection of articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Table 1. Details of the conducted clinical studies on the aldehyde dehydrogenase 1 (ALDH1) immunoexpression in oral potentially malignant disorders (OPMDs)

| Authors, year | Details of the sample | Expression pattern of ALDH1 |
|---|---|---|
| Habiba et al. 2017[14] | oral leukoplakia ($n$ = 79) | positive expression in 48% of cases<br>50% and 73% of UT and MT cases exhibit expression, respectively (a 3.02-fold increase in risk) |
| Feng et al. 2013[17] | oral erythroplakia ($n$ = 34) | positive expression in 55.9% of cases<br>29.4% and 82.4% of UT and MT cases exhibit expression, respectively (an 11.20-fold increase in risk) |
| Feng et al. 2020[18] | | ALDH1 immunoreactivity increased in the multiple transformed group as compared to UT cases, supporting the field cancerization theory |
| Custódio et al. 2018[19] | actinic cheilitis ($n$ = 43) | positive expression in 51.1% of cases |
| Liu et al. 2013[20] | oral leukoplakia ($n$ = 141) | positive expression in 38.3% of cases<br>26.9% and 70.3% of UT and MT cases exhibit expression, respectively (a 4.17-fold increase in risk) |
| Xu et al. 2013[21] | oral lichen planus ($n$ = 101) | positive expression in 34.6% of cases<br>30.3% and 66.7% of UT and MT cases exhibit expression, respectively (a 6.71-fold increase in risk) |
| Mansourian et al. 2017[22] | oral lichen planus ($n$ = 30) (immunoabsorbent assay of unstimulated saliva) | the mean level of ALDH1 was higher in non-reticular oral lichen planus than in the reticular types |
| Rao et al. 2020[23] | oral epithelial dysplasia ($n$ = 40) | positive expression in 35% of cases<br>25% and 10% cases showed low and high expression, respectively |
| Abdulmajeed et al. 2013[24] | oral epithelial dysplasia ($n$ = 61) | increased expression in severe dysplasia as compared to those with minimal dysplasia |
| Marangon et al. 2019[31] | verrucous carcinoma ($n$ = 7) | negative expression in all cases, suggestive of the indolent behavior of the lesion |

UT – untransformed; MT – malignant transformed.

# Results

All the selected studies ($n$ = 18) were systematically analyzed. Table 1 presents the list of clinical studies focused on the expression of ALDH1 in OPMDs. Out of all the evaluated studies ($n$ = 10), only 4 recorded the follow-up of patients and observed the association between the expression of ALDH1 and the risk of malignant transformation in OPMDs (a 3–11-fold increase in risk). The overall ALDH1 positivity was reported in 35–56% of all cases of OPMDs, while no expression was observed for verrucous carcinoma. The clinical studies depicted in Table 2 show a wide range (13.5–70%) in the positive expression of ALDH1 in the tumor cells of (oral squamous cell carcinoma) OSCC patients. A positive association between the ALDH1 expression and the prognostic parameters (the lymph node status and angiolymphatic invasion) and the overall survival outcome in OSCC patients was identified in 1 study.

# Discussion

## Expression in normal mucosa

A few researchers have attempted to examine the ALDH1 expression in normal or normal-like oral mucosa, only to observe negative immunoreactivity.[8,13–15] An in-depth study conducted by Kato et al. revealed a differential expression pattern of ALDH isoenzymes in human palatal mucosa.[16] According to their study, the expression of ALDH1A1 was absent throughout the epithelium; the expression of ALDH1A1 and ALDH1A3 cytoplasmic protein and mRNA was confined to the upper suprabasal layer. However, the signals of *ALDH1A3* mRNA in the basal and parabasal cell layers were observed without any protein expression. This discrepancy could be a result of inadequate translation into protein, the inhibition of translation initiation or post-transcriptional dysregulation.[16]

**Table 2.** Details of the conducted clinical studies on the aldehyde dehydrogenase 1 (ALDH1) immunoexpression in oral squamous cell carcinoma (OSCC)

| Authors, year | Details of the sample | Expression pattern of ALDH1 | Inference |
|---|---|---|---|
| Michifuri et al. 2012[15] | OSCC ($n$ = 80) | positive expression in 50% of cases | ALDH1 expression was positively correlated with lymph node metastasis |
| Custódio et al. 2018[19] | LSCC ($n$ = 20) | positive expression in 55% of cases | ALDH1 expression was positively correlated with carcinogenesis in the lip |
| Rao et al. 2020[23] | OSCC ($n$ = 40) | positive expression in 70% of cases 5% and 65% cases showed low and high expression, respectively | ALDH1 reactivity was correlated with higher chances of lymph node metastasis and lower survival rates of patients |
| Abdulmajeed et al. 2013[24] | OSCC ($n$ = 127) | overexpression of ALDH1 in OSCC as compared to the dysplastic or normal counterpart | disorganized distribution of ALDH1 expression in cancerous tissue as compared to dysplastic tissue |
| Juvencio de Freitas Filho et al. 2021[25] | oral cancer ($n$ = 56) | positive expression in 25.4% of cases | increased ALDH1 immunoreactivity was correlated with a higher grade of oral malignancy the basaloid variant showed the highest ALDH1 expression (56.3%) |
| Huang et al. 2014[26] | TSCC ($n$ = 66) | positive expression in 63.6% of total cases weak and strong positive expression in 36.4% and 27.2% of cases, respectively | the cancer sphere-formation ability of ALDH1 observed when co-expressed with other stem cell markers, like SOX2 |
| Tamatani et al. 2018[27] | OSCC ($n$ = 70) | positive expression in 25.7% of cases | ALDH1 was significantly associated with histological differentiation, invasion mode and lymph node metastasis, and hence observed as a prognostic factor for disease-free survival |
| Wu et al. 2017[28] | OSCC ($n$ = 78) | higher expression observed | higher expression of ALDH1 was not significantly associated with the clinicopathogologic status of patients |
| Ortiz et al. 2018[29] | OSCC ($n$ = 50) | positive expression in 46% of cases | ALDH1 high immunoexpression was positively associated with angiolymphatic invasion by tumor cells |
| Qian et al. 2014[30] | OSCC ($n$ = 2) OPSCC ($n$ = 65) | negative expression in OSCC positive expression in 49% of OPSCC cases | ALDH1A1 was an independent prognostic factor for survival |
| Marangon et al. 2019[31] | OSCC ($n$ = 163) | positive expression in 47.24% of cases | ALDH1 expression was higher in the tumor budding area than in the area outside budding, especially in tumors with high-intensity tumor budding |
| Prudente de Moraes et al. 2017[32] | OSCC ($n$ = 52) | positive expression in 13.5% of cases | the 5-year survival outcome was found to be lower in ALDH1-positive cases |

LSCC – lip squamous cell carcinoma; TSCC – tongue squamous cell carcinoma; OPSCC – oropharyngeal squamous cell carcinoma.

## Expression in OPMDs

Due to being a potent antioxidant enzyme and having a consistent association with the pathophysiology and clinical outcomes of various human carcinomas, the role of ALDH1 in OPMDs has fascinated many researchers. The details of the studies are described in Table 1.[14,17–24] All the studies performed an immunohistochemical analysis of ALDH1 in the biopsied tissue samples; only 1 study used an immunoabsorbent assay of unstimulated saliva. Increased ALDH1 expression and the severity of dysplasia were found to be positively correlated. Irrespective of the nature of the study and the sample, the observations of all studies implicate ALDH1 in oral carcinogenesis as well as its prognostic significance in the risk assessment for malignant transformation in OPMDs.

## Expression in oral cancer

The studies not only targeted the ALDH1 expression in OSCCs, but also focused on the correlation of the ALDH1 expression with the co-expression of other stem cell markers, like Bmi-1, CD44, OCT4, ABCG2, and SOX2 (Table 2).[15,19,23–32] The overexpression of ALDH1, with or without the co-expression of other stem cell markers, was observed to be negatively associated with clinical outcomes and prognosis in OSCC patients. These observations could be explained by the contribution of ALDH1 as a potent antioxidant enzyme in protecting CSCs from oxidative damage from endogenous aldehydes, and chemotherapeutic and radiotherapeutic agents. In addition, ALDH1 also helps to maintain the stemness of CSCs through RA metabolism, which explains the mechanism of drug resistance in ALDH1$^{hi}$ stem cell population-containing cancers. With the co-expression of other stem cell markers, ALDH1 was found to significantly contribute to the formation of foci and spheres as well as invasion and migration, which thus resulted in more aggressive tumor cells responsible for a poor clinical outcome in cancer patients.

# Conclusions

Apart from its vital role in cell physiology, cumulative evidence shows that high levels of ALDH1 expression is associated with a greater degree of stemness in CSCs, and suggests that molecular therapies that target ALDH1 may be promising anticancer therapies. Aldehyde dehydrogenase 1 was found to be a prognostic indicator for aggressiveness, survival and drug resistance in oral cancer. Furthermore, in OPMDs, the co-expression of ALDH1 with other stem cell markers could be used to assess the risk of malignant transformation, thus adding benefit to the prevention of oral cancer.

## Ethics approval and consent to participate

Not applicable.

## Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Consent for publication

Not applicable.


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### References


1. Lindahl R. Aldehyde dehydrogenases and their role in carcinogenesis. *Crit Rev Biochem Biol*. 1992;27(4–5):283–335. doi:10.3109/10409239209082565
2. Rodríguez-Zavala JS, Calleja LF, Moreno-Sánchez R, Yoval-Sánchez B. Role of aldehyde dehydrogenases in physiopathological processes. *Chem Res Toxicol*. 2019;32(3):405–420. doi:10.1021/acs.chemrestox.8b00256
3. Muzio G, Maggiora M, Paiuzzi E, Oraldi M, Canuto RA. Aldehyde dehydrogenases and cell proliferation. *Free Radic Biol Med*. 2012;52(4):735–746. doi:10.1016/j.freeradbiomed.2011.11.033
4. Yoshida A. Molecular genetics of human aldehyde dehydrogenase. *Pharmacogenetics*. 1992;2(4):139–147. doi:10.1097/00008571-199208000-00001
5. Black WJ, Stagos D, Marchitti SA, et al. Human aldehyde dehydrogenase genes: Alternatively spliced transcriptional variants and their suggested nomenclature. *Pharmacogenet Genomics*. 2009;19(11):893–902. doi:10.1097/FPC.0b013e3283329023
6. Xu X, Chai S, Wang P, et al. Aldehyde dehydrogenases and cancer stem cells. *Cancer Lett*. 2015;369(1):50–57. doi:10.1016/j.canlet.2015.08.018
7. Tomita H, Tanaka K, Tanaka T, Hara A. Aldehyde dehydrogenase 1A1 in stem cells and cancer. *Oncotarget*. 2016;7(10):11018–11032. doi:10.18632/oncotarget.6920
8. Singh S, Brocker C, Koppaka V, et al. Aldehyde dehydrogenases in cellular responses to oxidative/electrophilic stress. *Free Radic Biol Med*. 2013;56:89–101. doi:10.1016/j.freeradbiomed.2012.11.010
9. Ma I, Allan AL. The role of human aldehyde dehydrogenase in normal and cancer stem cells. *Stem Cell Rev Rep*. 2011;7(2):292–306. doi:10.1007/s12015-010-9208-4
10. Moreb JS. Aldehyde dehydrogenase as a marker for stem cells. *Curr Stem Cell Res Ther*. 2008;3(4):237–246. doi:10.2174/157488808786734006
11. Deng S, Yang X, Lassus H, et al. Distinct expression levels and patterns of stem cell marker, aldehyde dehydrogenase isoform 1 (ALDH1), in human epithelial cancers. *PLoS One*. 2010;5(4):e10277. doi:10.1371/journal.pone.0010277
12. Clark DW, Palle K. Aldehyde dehydrogenases in cancer stem cells: Potential as therapeutic targets. *Ann Transl Med*. 2016;4(24):518. doi:10.21037/atm.2016.11.82
13. Ota N, Ohno J, Seno K, Taniguchi K, Ozeki S. In vitro and in vivo expression of aldehyde dehydrogenase 1 in oral squamous cell carcinoma. *Int J Oncol*. 2014;44(2):435–442. doi:10.3892/ijo.2013.2188
14. Habiba U, Hida K, Kitamura T, et al. ALDH1 and podoplanin expression patterns predict the risk of malignant transformation in oral leukoplakia. 2017;13(1):321–328. doi:10.3892/ol.2016.5379
15. Michifuri Y, Hirohashi Y, Torigoe T, et al. High expression of ALDH1 and SOX2 diffuse staining pattern of oral squamous cell carcinomas correlates to lymph node metastasis. *Pathol Int*. 2012;62(10):684–689. doi:10.1111/j.1440-1827.2012.02851.x
16. Kato H, Izumi K, Saito T, et al. Distinct expression patterns and roles of aldehyde dehydrogenases in normal oral mucosa keratinocytes: Differential inhibitory effects of a pharmacological inhibitor and RNAi-mediated knockdown on cellular phenotype and epithelial morphology. *Histochem Cell Biol*. 2013;139(6):847–862. doi:10.1007/s00418-012-1064-7

17. Feng JQ, Xu ZY, Shi LJ, Wu L, Liu W, Zhou ZT. Expression of cancer stem cell markers ALDH1 and Bmi1 in oral erythroplakia and the risk of oral cancer. *J Oral Pathol Med*. 2013;42(2):148–153. doi:10.1111/j.1600-0714.2012.01191.x
18. Feng J, Zhou Z, Shi L, Yang X, Liu W. Cancer stem cell markers ALDH1 and Bmi1 expression in oral erythroplakia revisited: Implication for driving the process of field cancerization. *J Oral Pathol Med*. 2020;49(1):96–99. doi:10.1111/jop.12955
19. Custódio M, Pellisari C, Santana T, Trierveiler M. Expression of cancer stem cell markers CD44, ALDH1 and p75NTR in actinic cheilitis and lip cancer. *Eur Arch Otorhinolaryngol*. 2018;275(7):1877–1883. doi:10.1007/s00405-018-5002-8
20. Liu W, Wu L, Shen XM, et al. Expression patterns of cancer stem cell markers ALDH1 and CD133 correlate with a high risk of malignant transformation of oral leukoplakia. *Int J Cancer*. 2013;132(4):868–874. doi:10.1002/ijc.27720
21. Xu Z, Shen Z, Shi L, Sun H, Liu W, Zhou Z. Aldehyde dehydrogenase 1 expression correlated with malignant potential of oral lichen planus. *Ann Diagn Pathol*. 2013;17(5):408–411. doi:10.1016/j.anndiagpath.2013.04.008
22. Mansourian A, Shanbehzadeh N, Kia SJ, Moosavi MS. Increased salivary aldehyde dehydrogenase 1 in non-reticular oral lichen planus. *An Bras Dermatol*. 2017;92(2):168–171. doi:10.1590/abd1806-4841.20174964
23. Rao RS, K LR, Augustine D, Patil S. Prognostic significance of ALDH1, Bmi1, and OCT4 expression in oral epithelial dysplasia and oral squamous cell carcinoma. *Cancer Control*. 2020;27(1):1073274820904959. doi:10.1177/1073274820904959
24. Abdulmajeed AA, Dalley AJ, Farah CS. Putative cancer stem cell marker expression in oral epithelial dysplasia and squamous cell carcinoma. *J Oral Pathol Med*. 2013;42(10):755–760. doi:10.1111/jop.12073
25. Juvencio de Freitas Filho SA, Coutinho-Camillo CM, Oliveira KK, et al. Prognostic implications of ALDH1 and Notch1 in different subtypes of oral cancer. *J Oncol*. 2021;2021:6663720. doi:10.1155/2021/6663720
26. Huang CF, Xu XR, Wu TF, Sun ZJ, Zhang WF. Correlation of ALDH1, CD44, OCT4 and SOX2 in tongue squamous cell carcinoma and their association with disease progression and prognosis. *J Oral Pathol Med*. 2014;43(7):492–498. doi:10.1111/jop.12159
27. Tamatani T, Takamaru N, Ohe G, Akita K, Nakagawa T, Miyamoto Y. Expression of CD44, CD44v9, ABCG2, CD24, Bmi-1 and ALDH1 in stage I and II oral squamous cell carcinoma and their association with clinicopathological factors. *Oncol Lett*. 2018;16(1):1133–1140. doi:10.3892/ol.2018.8703
28. Wu TF, Li YC, Ma SR, Zhang WF, Sun ZJ. Expression and associations of TRAF1, BMI-1, ALDH1, and Lin28B in oral squamous cell carcinoma. *Tumour Biol*. 2017;39(4):1010428317695930. doi:10.1177/1010428317695930
29. Ortiz RC, Lopes NM, Amôr NG, et al. CD44 and ALDH1 immunoexpression as prognostic indicators of invasion and metastasis in oral squamous cell carcinoma. *J Oral Pathol Med*. 2018;47(8):740–747. doi:10.1111/jop.12734
30. Qian X, Wagner S, Ma C, et al. Prognostic significance of ALDH1A1-positive cancer stem cells in patients with locally advanced, metastasized head and neck squamous cell carcinoma. *J Cancer Res Clin Oncol*. 2014;140(7):1151–1158. doi:10.1007/s00432-014-1685-4
31. Marangon H Jr., Moreira Melo VV, Caixeta ÂB, et al. Immunolocalization of cancer stem cells marker ALDH1 and its association with tumor budding in oral squamous cell carcinoma. *Head Neck Pathol*. 2019;13(4):535–542. doi:10.1007/s12105-018-0985-4
32. Prudente de Moraes FP, Lourenço SV, Fraga Ianez RC, et al. Expression of stem cell markers in oral cavity and oropharynx squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123(1):113–122. doi:10.1016/j.oooo.2016.09.009