

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

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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

## Cite as

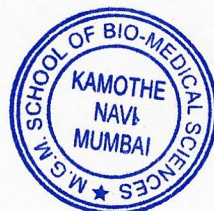
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A handwritten signature in blue ink, appearing to read "Rashmi Hosalkar".

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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.<sup>1</sup> The ALDH NAD(P)<sup>+</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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 (RAR $\beta$ ). When the endogenous concentration of RA is low, exogenous RA can activate the ALDH1A1 promoter to enhance the production of RA.<sup>6</sup>

### 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.<sup>7</sup>

#### 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.<sup>7</sup> 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.<sup>8,9</sup> 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<sup>hi</sup> cells). Besides, stem cells from adipose tissue, being multipotent mesodermal cells, also embrace a ALDH<sup>hi</sup> cell population.<sup>10</sup> 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).<sup>10</sup> 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.<sup>11</sup>

### 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 (RAR $\alpha$ ) prior to entering the nucleus. In order to induce the expression of downstream target RAR $\beta$ , RA binds to RAR $\alpha$  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 (ER $\alpha$ ) and peroxisome proliferator-activated receptors beta/delta (PPAR $\beta/\delta$ ), RA can form heterodimers with these receptors to upregulate pro-survival genes.<sup>6,9</sup>

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/ $\beta$ -catenin, either upregulate ALDH1 transcription or increase its activity in CSCs (Fig. 1).<sup>6,12</sup> 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 evi-

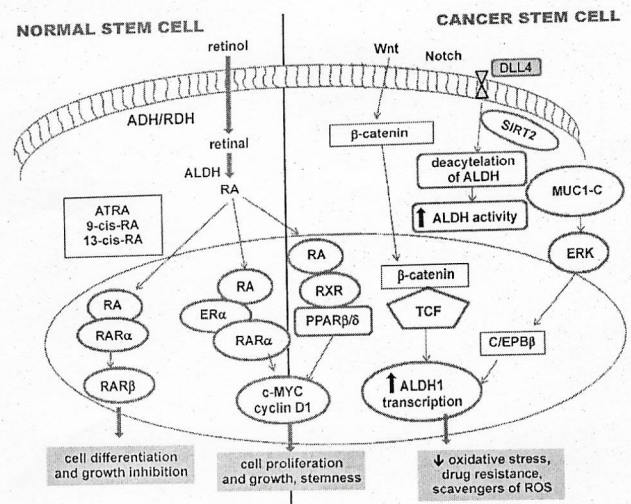


Fig. 1. Potential role of aldehyde dehydrogenase 1 (ALDH1) in normal and cancer stem cells

ALD – alcohol dehydrogenase; ALDH – aldehyde dehydrogenase; ATRA – all-trans-retinoic acid; ER $\alpha$  – estrogen receptor alpha; PPAR $\beta/\delta$  – peroxisome proliferator-activated receptors beta/delta; RA – retinoic acid; RAR $\alpha$  – retinoic acid receptor alpha; RAR $\beta$  – retinoic acid receptor beta; RDH – retinol dehydrogenase; ROS – reactive oxygen species; RXR – X retinoid receptor; TCF – T-cell factor.

dence 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.<sup>6</sup>

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.

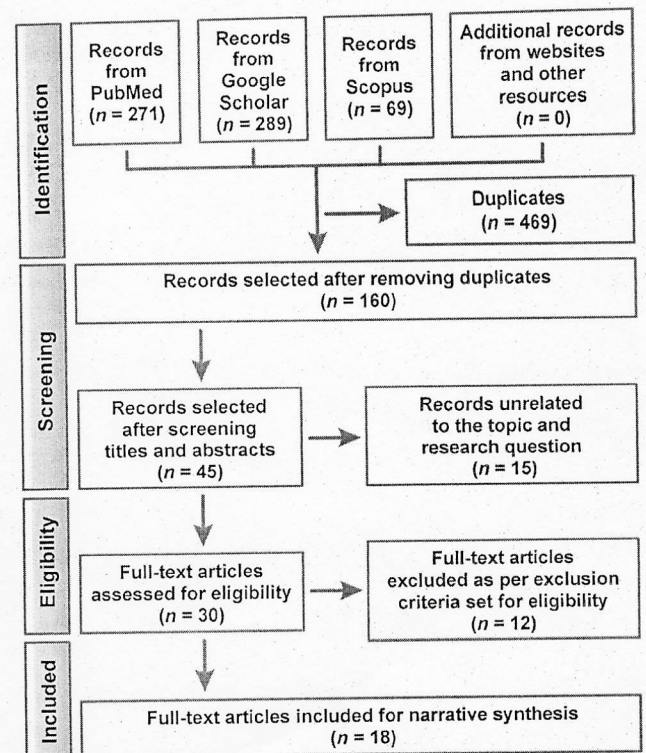


Fig. 2. Flowchart for the selection of articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

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

Authors, year	Details of the sample	Expression pattern of ALDH1
Habiba et al. 2017 <sup>14</sup>	oral leukoplakia (n = 79)	positive expression in 48% of cases 50% and 73% of UT and MT cases exhibit expression, respectively (a 3.02-fold increase in risk)
Feng et al. 2013 <sup>17</sup>	oral erythroplakia (n = 34)	positive expression in 55.9% of cases 29.4% and 82.4% of UT and MT cases exhibit expression, respectively (an 11.20-fold increase in risk)
Feng et al. 2020 <sup>18</sup>		ALDH1 immunoreactivity increased in the multiple transformed group as compared to UT cases, supporting the field cancerization theory
Custódio et al. 2018 <sup>19</sup>	actinic cheilitis (n = 43)	positive expression in 51.1% of cases
Liu et al. 2013 <sup>20</sup>	oral leukoplakia (n = 141)	positive expression in 38.3% of cases 26.9% and 70.3% of UT and MT cases exhibit expression, respectively (a 4.17-fold increase in risk)
Xu et al. 2013 <sup>21</sup>	oral lichen planus (n = 101)	positive expression in 34.6% of cases 30.3% and 66.7% of UT and MT cases exhibit expression, respectively (a 6.71-fold increase in risk)
Mansourian et al. 2017 <sup>22</sup>	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 <sup>23</sup>	oral epithelial dysplasia (n = 40)	positive expression in 35% of cases 25% and 10% cases showed low and high expression, respectively
Abdulmajeed et al. 2013 <sup>24</sup>	oral epithelial dysplasia (n = 61)	increased expression in severe dysplasia as compared to those with minimal dysplasia
Marangon et al. 2019 <sup>31</sup>	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.<sup>8,13–15</sup> An in-depth study conducted by Kato et al. revealed a differential expression pattern of ALDH isoenzymes in human palatal mucosa.<sup>16</sup> 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.<sup>16</sup>

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 <sup>15</sup>	OSCC (n = 80)	positive expression in 50% of cases	ALDH1 expression was positively correlated with lymph node metastasis
Custódio et al. 2018 <sup>19</sup>	LSCC (n = 20)	positive expression in 55% of cases	ALDH1 expression was positively correlated with carcinogenesis in the lip
Rao et al. 2020 <sup>23</sup>	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 <sup>24</sup>	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
Juvenio de Freitas Filho et al. 2021 <sup>25</sup>	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 <sup>26</sup>	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 <sup>27</sup>	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 <sup>28</sup>	OSCC (n = 78)	higher expression observed	higher expression of ALDH1 was not significantly associated with the clinicopathologic status of patients
Ortiz et al. 2018 <sup>29</sup>	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 <sup>30</sup>	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 <sup>31</sup>	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 <sup>32</sup>	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.<sup>14,17–24</sup> All the studies performed an immunohistochemical analysis of ALDH1 in the biopsied tissue samples; only 1 study used an immunosorbent 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).<sup>15,19,23–32</sup> 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<sup>hi</sup> 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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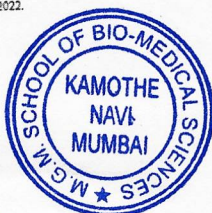
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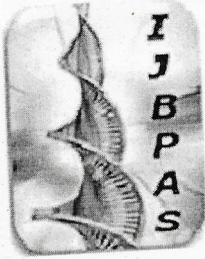
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**EVALUATION OF IMMUNE EXPRESSION OF STAT3 AS EARLY EVENT FOR  
CELLULAR ALTERATION IN TOBACCO STRESSED ORAL MUCOSA**

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**ABSTRACT**

**Background:** Tobacco contains various known chemical component which act as direct or indirect carcinogenic agent in development oral cancer. Toxins presence in tobacco has a immunomodulatory effect. Signal transducer and activator of transcription-3(STAT3) regulates inflammation through transmitting signals from cytokines and growth factor receptor to target the genes. It has been proposed that due to tobacco carcinogen there is dysregulation and constant activation of STAT3 signaling pathway concerned in malignant transformation. In the present study, we observed expression of STAT3 in tobacco stressed mucosa and in oral Leukoplakia. To the author's knowledge, the STAT3 expression was first time analyzed in oral mucosa stressed under various forms of tobacco and oral leukoplakia.

**Methods:** Tissue sample of normal oral mucosa without tobacco habit (n=50) and with tobacco habit (n=50) were selected for the study to analyze STAT3 expression. Paraffin embedded tissue sections were



processed for immunohistochemistry. Hematoxylin and eosin stained slides and the presence of STAT3 in nucleus as well in cytoplasm was analyzed by two independent observers.

**Results:** Among the 50 samples of tobacco stressed mucosa all slides shows variation in immunoreactivity. On the basis of immunoreactivity score, 70% cases shows no staining i.e. score 0-2 and 30% cases shows weak expression i.e. 3-4 immunoreactive score. In comparison in different tobacco form smoking form observed to be high expression score of mean than mixed followed by smokeless which was 2.8, 2, and 0.002 respectively. No immunoreexpression were observed in sample without tobacco habit. Statistical analysis were calculated by using one way ANOVA with post hoc and unpaired 't' test.

**Conclusion:** The STAT3 expression in tobacco stressed mucosa suggests its participation in modulation of molecular mechanism is the early event before obvious cellular structural changes occurs, which may further transform in to malignancy.

**Keywords:** Signal transducer and activator of transcription-3, STAT3, tobacco habits, oral carcinogenesis, leukoplakia

### INTRODUCTION:

Oral Mucosa undergoes various symptomatic and asymptomatic tribulations due to constant exposure to numerous toxic and non toxic agents. Constant irritation affects the structural and molecular mechanism of mucosal lining leading to serious oral health problem like precancerous and cancerous lesions. The occurrence of oral lesions is usually related to various factors like stress, tobacco related habits, inflammation and genetic. Globally, the use of tobacco is among largest factor responsible for cancer where tobacco products are consumed worldwide and also remain as addiction throughout life.<sup>1</sup> Worldwide estimated prevalence of oral lesions are ranging from 15% in the Gizan, Saudi Arabia<sup>2</sup> and 5 to 51.1% in Spain.<sup>3</sup> In India prevalence of regular use of smoking tobacco is 16.2% and

chewing tobacco is 14%.<sup>4</sup> The overall prevalence of smoking, drinking alcoholic beverages and chewing were 15.02%, 8.78% and 6.99% respectively.<sup>5</sup> These habits have been associated with oral lesions like oral submucous fibrosis (OSF), leukoplakia and oral lichen planus, which has great potential for malignant transformation.<sup>6</sup> Tobacco and its related products are known to be carcinogenic due to its chemical composition. This tobacco related disorders have received great research attention due to transformation in to oral cancer and it is known that oral squamous cell carcinomas generally occur with a history of smokeless tobacco, smoking and/or alcohol abuse. The young patients with these histories have a greater potential to develop these disease