

A Comprehensive Review of the Immunoexpression of Cancer Stem Cell Markers in Oral Lichen Planus

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ABSTRACT

The cancer stem cell (CSC) hypothesis proposes that a small cluster of tumour cells with stem-cell like properties have unrestricted proliferative potential, aberrant differentiation potential and may be responsible for initiation, progression and aggressive behaviour of tumours. Increase in expression of certain CSC markers and their interactions with the microenvironment could correlate with the biological behaviour of oral potentially malignant disorders (OPMDs) like oral lichen planus (OLP). This article highlights the studies that evaluate the expression of various cancer stem cell markers in OLP in order to emphasise the role of CSC markers in predicting its biological behaviour. An electronic search of PUBMED was conducted to find studies published in English language on CSC marker expression in OLP. After thorough screening of the search results, 11 studies were identified. The overall analysis of the included studies suggested that CSC-positive OLP carries significantly high risk of developing Oral Squamous cell carcinoma (OSCC). Expression of CSC markers showed dominance over other factors such as age, gender and smoking habits, in predicting progression of OLP to OSCC. It was also inferred that owing to the variability of CSC

population, it is difficult to establish malignant potential of OLP based on a single CSC marker investigation.

Keywords: Cancer stem cells, Oral Lichen Planus, Oral Cancer, cancer stem cell biomarkers, oral potentially malignant disorders.

1. INTRODUCTION

Stem cells are a unique subset of cells distinguished by their abilities of self-renewal and differentiation into multi-lineage cellular constituents of a specific tissue or organ.¹ This favours the possibility that some of the clinical features of human tumours may be due to converted stem cells. These rare transformed stem cells, labelled cancer stem cells, could have an influence on the process of tumourigenesis due to their potential for self-renewal.²

The cancer stem cell (CSC) hypothesis has attracted a lot of attention to understand tumour initiation, progression as well as to correlate it with aggressive tumour behaviour. It proposes that a small cluster of cancer cells with stem-cell like properties have unrestricted proliferative potential and anomalous differentiation potential and could thus be responsible for tumour formation. This stem cell population is differentiated from other tumour cells by the

expression pattern of stemness related markers such as CD133, CD44, CD24, Oct4, Sox-2, ALDH1, NANOG, ABCG2, Bmi-1 etc. Existence of CSCs has been correlated with aggressiveness and increased radio-chemotherapeutic resistance in many malignancies including oral squamous cell carcinoma (OSCC).³

Oral squamous cell carcinoma is often preceded by with clinical changes in the oral epithelium known as oral potentially malignant disorders (OPMDs).³ Reports evaluating the expression of CSC markers specifically in OPMDs are still scarce considering the already established significance of CSCs in OSCC. It has been hypothesized that increase in expression of certain CSC markers and their cross talk with the microenvironment could correlate with progression of OPMDs.⁴ These markers, if validated in OPMDs like oral leukoplakia, submucous fibrosis and oral lichen planus, could prove valuable for predicting malignant transformation and as targets for chemoprevention.

Oral lichen planus (OLP) has been defined as one of oral potentially malignant disorders by the World Health Organization, with the reported rate of malignant transformation being 1.37%.^{5,6} The clinical and histologic features of OLP lesions have limited prognostic value for malignant progression.⁵ Thus, numerous studies have sought to identify robust cancer stem cell markers that could help to predict the malignant potential of OLP lesions. Therefore, this review attempts to highlight the studies undertaken to evaluate the expression of various cancer stem cell markers in OLP in order to emphasise the role of cancer stem cells and their markers in predicting the biological behaviour of OLP.

2. OBSERVATIONS

All the selected studies (N= 11) were systematically analysed. Table 2 illustrates the total no of OLP cases (n=600) included in different studies, the CSC marker employed, the comparison groups and the resultant p values. Out of all the studies

(N=11) evaluated, follow-up was recorded in most (N=7). Out of the total number of OLP cases (n=600) included in all the studies (N=11), follow up studies (N=7), with a follow up period ranging from 2.5 years to 5 years, included (n=478) OLP cases. Out of these (n=478), 16.7%(n=80) showed transformation into OSCC. Majority of the investigations showed statistically significant differences in expression of cancer stem cell markers in OLP as compared to control groups. The p values ranged from highly significant (<0.001) to not significant (0.237).

In some studies (N= 5)^{5,8-11}, CSC marker expression in transformed and untransformed cases of OLP for assessment of risk of malignant transformation. The immunoexpression of the CSC markers was significantly higher in transformed cases (n=50) as compared to the untransformed cases (n=386) as represented graphically in figure 1. Out of the total cases showing malignant transformation (n=50) in the relevant studies (N=5), Table 3 illustrates only those cases of OLP (n=426) which calculated the p-value and the odds ratio, using various CSC markers (ALDH1, Bmi1, CD133, podoplanin, c-MYC and ABCG2). Out of these (n=426), 9.3%(n=50) showed transformation into OSCC. The odds ratios ranged from averages of 4.59 to 20.75.

A comparison of other parameters (follow up period, age, gender, history of smoking and consumption of alcohol) with the immunoexpression of CSC markers used in all the relevant studies (N=5) was done to establish their association as an independent risk factor. The p values obtained by the Univariate analysis is tabulated in Table 4. In all of the studies(N=5) evaluated for different parameters, it was observed that only age was significantly associated with the risk of malignant transformation. The mean age in transformed cases (n=50) was significantly higher than the mean age in untransformed cases (n=386) as demonstrated graphically in figure 2. All other parameters studied showed no statistically significant

differences between transformed and untransformed cases.

TABLE 2: Studied that evaluated CSC marker expression in OLP

year	author	CSC marker	normal mucosa cases	OLP cases	Comparison groups	p Value
2010	Shi P et al	Podoplanin	~	119	9 transformed and 110 untransformed OLP cases	0.012
2010	Shi P et al	ABCG2	~	119	9 transformed and 110 untransformed OLP cases	0.006
2014	Qiao B et al	SOX2	20	8	precancerous lesions, epithelial non-cancer tissues adjacent to the OSCC and OSCCs	~
2014	Qiao B et al	Oct-04	20	8	precancerous lesions, epithelial non-cancer tissues adjacent to the OSCC and OSCCs	~
2013	Segura S et al	c-MYC	~	22	10 transformed and 12 untransformed OLP cases	0.003
2011	Klosek SK et al	c-Met	12	34	Normal mucosa and OLP cases (with and without smoking habit)	<0.05
2018	Zargaran M et al	CD44	~	20	epithelial hyperplasia, OLP and OSCC cases	<0.01
2020	Ghazi N et al	CD44	10	30	Normal mucosa and OLP cases (with and without dysplasia)	<0.001
2017	Mansourian et al	ALDH1	30	30	Normal mucosa and OLP cases (reticular and non-reticular)	0.237, 0.019
2018	Ezzatt, Helmy	CD133	~	30	OLP cases before and after topical steroid treatment	<0.001
2013	Sun L et al	CD133	10	110	Normal mucosa, OLP (progressing and non progressing) and OSCC	0.001, 0.002
2013	Ma L et al	Bmi1	10	96	Normal mucosa, OLP (progressing and non progressing) and OSCC	<0.001, 0.004
2013	Xu Z et al	ALDH1	10	101	Normal mucosa, OLP (progressing and non progressing) and OSCC	<0.001, 0.021

Table 3: Studies that assess prognostic value of CSC markers

Year	Author	csc marker	No. of normal mucosa cases	total no. of OLP cases	Mean follow up	transformed cases	untransformed cases	Immunoexpression of csc marker			p value	odds ratio
								normal	transformed	untransformed		
2013	Xu Z et al	ALDH1	10	101	5 years	12	89	0 (0%)	8 (6.7%)	27 (30.3%)	0.021	OR, 4.59; 95% CI, 1.27-16.56
2013	Ma L et al	Bmi1	10	96	4.5 years	9	87	0 (0%)	8 (8.9%)	32 (36.8%)	0.016	OR, 20.75; 95% CI, 2.21-194.57
2013	Sun L et al	CD133	10	110	4.5 years	10	100	0 (0%)	80%	29%	0.002	OR, 9.79; 95% CI, 1.96-48.92
2010	Shi P et al	podoplanin	~	119	5.1 years	9	110	~	8 (8.9%)	48 (43.6%)	0.016	OR, 17.13; 95% CI 1.71-171.22
2010	Shi P et al	ABCG2	-	119	5.1 years	9	110	~	6 (66.7%)	23 (20.9%)	0.029	OR, 6.04; 95% CI, 1.20-30.36
2013	Segura S et al	c-MYC	~	22	5 years	10	12	~	86.70%	44.40%	0.003	~

Table 4: p values for clinical features

Sr. No	Clinical Characteristic	ALDH1 ⁸	CD133 ⁹	Bmi1 ¹⁰	Podoplanin ¹¹	ABCG2 ¹¹
1	Follow up period	0.737	0.993	0.808	0.943	0.943
2	Age	0.014*	0.062	0.038*	0.036*	0.036*
3	Gender	0.451	0.447	0.341	0.682	0.682
4	Smoking History	0.677	1.00	0.648	0.536	0.536
5	Alcohol Intake	0.442	1.00	1.00	1.00	1.00
6.	Expression of CSC marker	0.021*	0.002*	0.004*	0.016*	0.029*

* - Statistically Significant. P values less than 0.05 were considered to be statistically significant

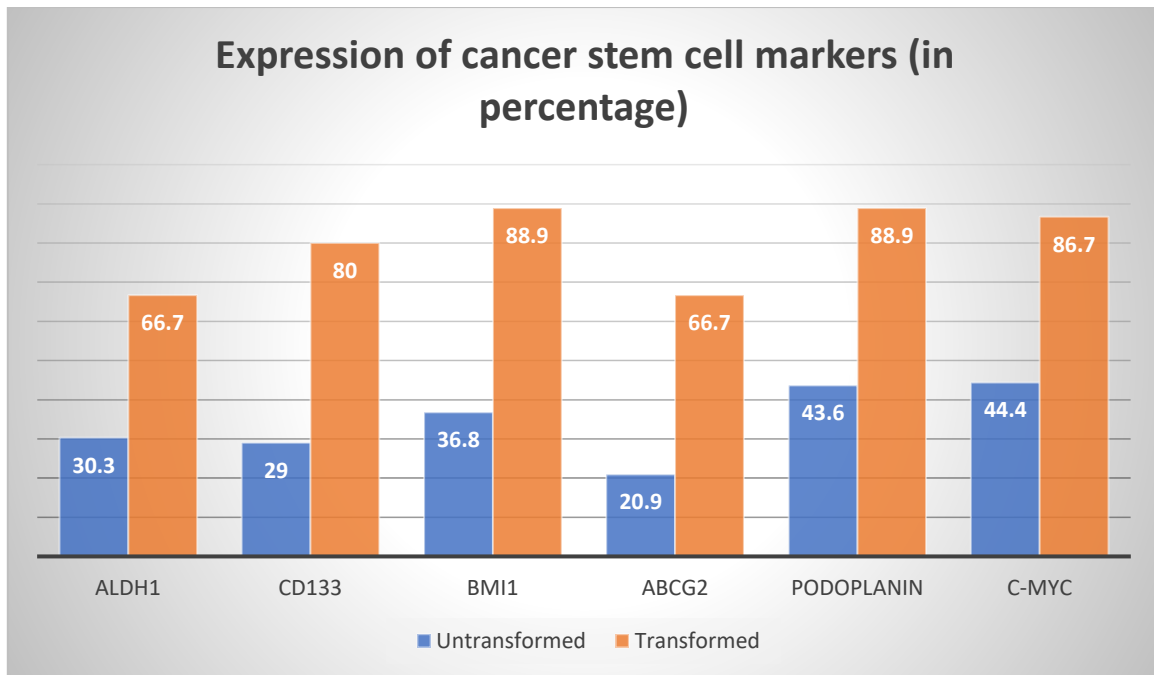


FIGURE 1:

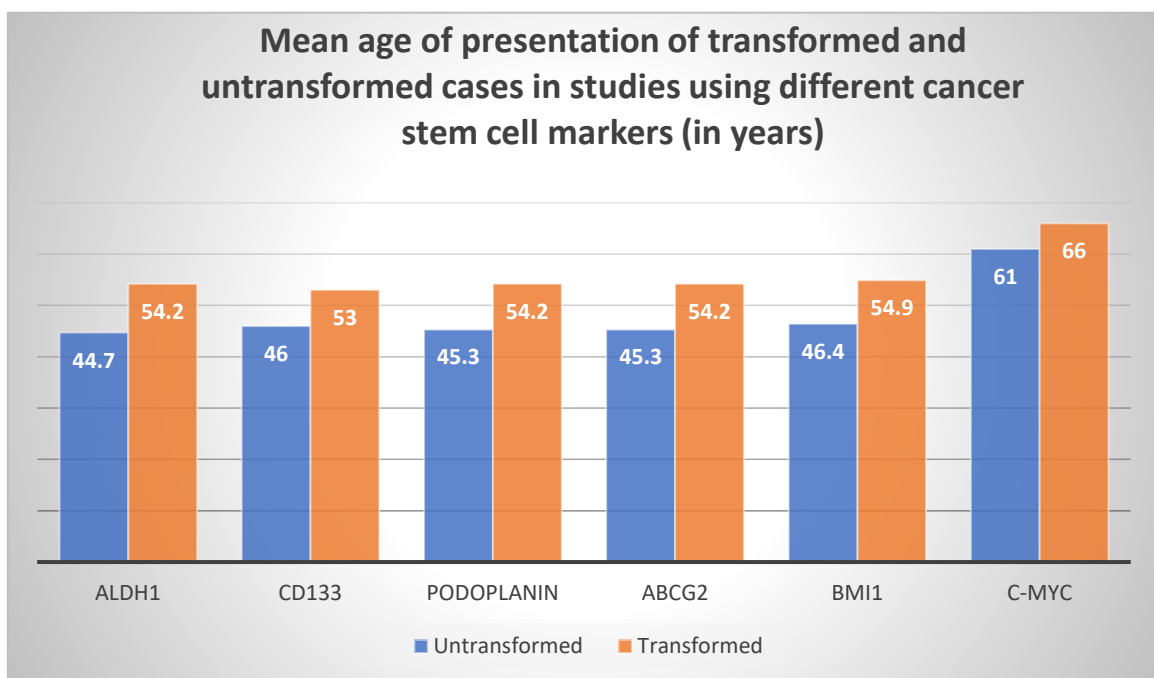


FIGURE 2:

3. DISCUSSION

The Cancer stem cell (CSC) hypothesis is a new but well-proven concept in various stages of oral carcinogenesis.⁶ These CSCs can be detected by various cell surface markers, which can prove to be beneficial for improving treatment selection, predicting the treatment response and improving the disease outcome.¹ Prediction of biological behaviour of Oral Potentially Malignant

Disorders (OPMDs) like leukoplakia, erythroplakia, oral submucous fibrosis and oral lichen planus, based solely on their clinical and histological features, is difficult because these have limited prognostic value. Evaluation of the expression of these biomarkers can be used as a valuable tool for determining their malignant potential or as an adjunct to the conventional method of assessing dysplasia. Thus, this review aimed

to collectively evaluate those studies that demonstrate the expression and prognostic significance of cancer stem cell markers in Oral Lichen Planus.

Univariate analyses of these studies showed that age and expression of cancer stem cell markers have a statistically significant difference between transforming and non-transforming OLP except in the study involving CD133 where age was not a significant factor. The mean age of the transformed cases was observed to be higher than that of the untransformed cases in majority of the studies with the difference being statistically significant. To assess influence of patient's age on malignant transformation, multivariate analysis was also done by the investigators of these studies. Despite adjusting for age, the cancer stem cell marker expression retained statistical significance. This signifies that expression of CSC markers is an independent prognostic factor for malignant transformation of OLP.

Clinical characteristics like gender, follow up period, history of smoking or alcohol intake did not show statistical significance in any of the studies. Diet of the patients was also included in the univariate analysis by Shi P. et al¹⁰ but no statistically significant difference was found between transformed and untransformed cases consuming bland or spicy food.

Expression of cancer stem cell markers showed statistically significant differences in all the investigations without exception. Highly significant differences were found in investigations concerning CD133 and Bmi1 (0.002 and 0.004 respectively). Logistic regression analysis was also done by the researchers in these 5 investigations where cancer stem cell marker expression had the highest odds ratios as compared to other clinical characteristics.

In the present systematic review, it was found that the CSC marker Bmi1 has the highest odds ratio (20.75) for prediction of malignant transformation of OLP as compared to other CSC markers like ALDH1(4.59), CD133(9.79), podoplanin (17.13) and

ABCG2(6.04). Unlike other CSC markers included, c-Met (50%)¹⁶ and CD44(70%)¹⁷ showed expression even in normal oral mucosa and ALDH1 was detected in saliva of normal patients in the study conducted by Mansourian et al.¹¹

While majority of the transformed OLP cases showed significantly high expression of CSC markers, there were a few cases of transformed OLP in all the studies which did not express the particular CSC marker. The only exception was the study by Ghazi N et al¹⁴ where 100% of dysplastic and non-dysplastic OLP cases showed expression of CD44. These results support the fact that CSCs are heterogenous in nature and that there is no universal marker common to all the CSCs. In contrast, few untransformed OLP cases also showed CSC marker expression in the relevant studies.⁸⁻¹¹ This suggests that expression of CSC markers cannot be used as a sole guide to determine malignant potential of a particular case of OLP; though they certainly have a significant prognostic value. This mirrors the inferences drawn by a systematic review conducted by Saluja et al³ on prognostic value of CSC markers in OPMDs.

4. CONCLUSION

The overall assessment of the included studies suggested that CSC-positive OLP carries significantly high risk of developing into OSCC. Most of the studies included in this systematic review showed dominance of CSC markers over other factors such as age, smoking habits and histology in predicting progression of OLP to OSCC. Individual multivariate analysis of these studies suggests that presence of CSC population in OLP points to an unfavourable clinical outcome.

Thus, identifying a diverse and heterogenous population of CSCs by their specific markers can play a critical role in predicting the biological behaviour of OLP. Considering the variability in CSC population and the possibility of recognizing the existence of more than one subset or type of cancer stem cells, it is difficult to establish malignant

potential of Oral Lichen Planus based on a single CSC marker investigation. Therefore, instead of relying on a single or couple of CSC markers, a panel of multiple markers could have a better chance of identifying high risk cases of OLP thereby helping in early intervention and preventing the development of OSCC.

Limitations:

- Six^{11,12, 14-17} studies did not follow up the OLP cases to check for malignant transformation. Thus, the prognostic value of the CSC markers studied cannot be assessed for these investigations.
- Other clinical characteristics and their influence on malignant transformation was not evaluated in 7¹¹⁻¹⁷ of the studies.
- 9^(7-11, 13-17) studies did not mention the clinical type of OLP; hence no inference can be drawn based on which type of OLP has greater potential for malignant transformation.

Future Prospects:

- More follow up studies need to be done on cancer stem cell markers in OLP so as to evaluate their prognostic significance in assessing malignant transformation.
- A multiple CSC marker panel needs to be utilised in future studies to improve detection of cancer stem cells in OLP due to the heterogenous nature of cancer stem cells.
- Other cancer stem cell markers and their exact role in tumourigenesis and progression of OPMDs should be of interest for future research.

Declaration by Authors

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