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# E-cadherin and c-Met expression in actinic cheilitis and lip squamous cell carcinoma

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## ABSTRACT

**Objective:** The aim of this study was to assess epithelial expression of E-cadherin and c-Met in normal lip, in actinic cheilitis and lip squamous cell carcinoma. **Study Design:** Biopsies of normal lip vermilion (NL, n=18), actinic cheilitis (AC, n=37), and lip SCC (n=22) were processed for E-cadherin and c-Met immunodetection. Epithelial and tumor cell expression was scored for each sample considering staining intensity and percentage. **Results:** E-cadherin expression was significantly reduced in AC and lip SCC as compared to normal lip ( $P<0.05$ ), with a significant reduction in lip SCC as compared to AC ( $P=0.003$ ). Expression of c-Met was significantly higher in AC and lip SCC as compared to NL ( $P<0.05$ ), with a significant increase in lip SCC as compared to AC ( $P<0.0001$ ). **Conclusion:** The results showed that epithelial E-cadherin expression is reduced and c-Met expression is increased as lip carcinogenesis progresses, suggesting that these proteins may be useful markers of malignant transformation.

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**Key words:** E-cadherin, c-Met, lip carcinogenesis, UV light, actinic cheilitis, lip squamous cell carcinoma.

## INTRODUCTION

Chronic exposure of the lip vermilion to sunlight and/or artificial ultraviolet irradiation (UV) causes actinic cheilitis (AC), a pre-malignant lesion with the potential to develop into invasive lip squamous cell carcinoma (SCC), the most common form of oral cancer<sup>(1)</sup>.

E-cadherin is a calcium-dependent membranous glycoprotein that plays important roles in the maintenance of cell-cell adhesion, preservation of epithelial tissue polarity, and structural integrity<sup>(2,3)</sup>. The inactivation of the E-cadherin cell adhesion system by both genetic and epigenetic mechanisms plays a significant role during multistage human carcinogenesis<sup>(3,4)</sup>. Several studies demonstrate that reduction of E-cadherin expression occurs in oral dysplasia, with such reduction being proportional to the degree of dysplasia<sup>(5-7)</sup>. E-cadherin expression is frequently down-regulated in a wide variety of human malignancies, including skin cancer<sup>(8)</sup>, oral squamous carcinoma<sup>(4,7,9-11)</sup>, lip SCC<sup>(12)</sup>, gastric cancer<sup>(13,14)</sup>, breast cancer<sup>(15)</sup>, lung cancer<sup>(16)</sup>, and prostate cancer<sup>(17)</sup>. Reduced E-cadherin expression has been shown to be an indicator of unfavorable prognosis in oral squamous cell carcinoma and in other malignancies<sup>(9,10,18)</sup>.

Brouxhon et al.<sup>(6)</sup> demonstrated that during UV-induced skin carcinogenesis in SKH-1 mice, SCC progression produces a significant and progressive down-regulation of E-cadherin protein expression in epidermal keratinocytes as lesions progress from in situ carcinomas to large invasive SCCs.

The proto-oncogene, c-Met, is a transmembrane tyrosine kinase receptor that mediates the oncogenic activities of the hepatocyte growth factor (HGF). Overexpression of c-Met and/or its ligands has been shown to contribute to progression and dissemination of several malignancies, such as gallbladder<sup>(19)</sup>, gastric<sup>(20,21)</sup>, bladder<sup>(22)</sup>, breast<sup>(15)</sup>, and head and neck cancer<sup>(7,18,23,24)</sup>. The overexpression of c-Met frequently has been correlated with poor prognosis in various cancers<sup>(20,22)</sup>.

Several studies have found an inverse correlation between the expression of HGF/c-Met and membranous E-cadherin expression in human tumors<sup>(7,15,18,22)</sup>. A limited number of studies have investigated E-cadherin expression in lip SCC<sup>(12)</sup>. However, E-cadherin expression in AC has not been determined. In addition, the expression of E-cadherin and c-Met has not yet been studied in normal and photodamaged lips. Thus, the purpose of this study was to assess epithelial expression of E-cadherin and c-Met in normal lip, actinic cheilitis (pre-malignant lesion), and lip SCC samples.

## MATERIALS AND METHODS

### Biopsies

Biopsies of lower lip vermilion from 37 non-smoking patients with AC (12 women and 25 men, age 22-74 years, mean  $52.4\pm14.2$  years) were obtained from the Archives of the Oral Pathology Laboratory, School of Dentistry, University of Concepción; and biopsies of 22 lip SCC (n=15 well-differentiated, n=6 moderately-differentiated, n=1 poorly-differentiated; 4 women and 18 men, age 35-86 years, mean  $65.7\pm12.1$  years) were obtained from the Archives of the Department of Pathology, School of Medicine, University of Concepción. Eighteen normal lip vermilion biopsies (12 women and 6 men, age 22-63 years, mean  $40.4\pm13.3$  years) were used as controls. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of the University of Concepción.

All specimens were fixed in 10% buffered formalin, pH 7.4, and paraffin embedded within 24 hours. Serial sections, 4- $\mu$ m thick, were obtained from the tissue blocks and processed for histopathologic and immunohistochemical analyses.

### Immunohistochemical Staining

Tissue sections were deparaffinized in xylene and rehydrated in graded alcohol. Endogenous peroxidase activity was blocked by incubation in methanol with 3% hydrogen peroxide for 10 minutes. For antigen retrieval, tissue sections were steamed in EDTA buffer 0.001M (pH 8.0) at 96°C for 30 minutes. After rinsing in phosphate-buffered saline (PBS), slides were incubated overnight with the monoclonal antibody Mouse E-Cadherin Ab-4 (Clone: NCH-38, dilution 1:100, NeoMarkers Laboratories, Fremont, CA, USA) and anti-c-Met monoclonal antibody (Clone: 3D4, dilution 1:100, Invitrogen, ZYMED Laboratories, Carlsbad, CA, USA). The primary antibody was diluted in Antibody Diluent (ZYMED, Carlsbad, CA, USA). This was followed by incubation with the UltraVision ONE HRP Polymer (LAB VISION, Fremont, CA, USA) for 30 minutes. Sections were then washed in PBS and the reaction was developed with DAB (3,3'-diaminobenzidine Mouse/Rabbit Plydetector PDBSA02A7, Bio SB) for 5 minutes at room temperature. Slides were counterstained with Harris hematoxylin. Positive controls were normal skin for E-cadherin, and a papillary thyroid carcinoma for c-Met. The negative controls consisted of replacing the first antibody with buffer and omitting the primary antibody.

Epithelial staining scores for E-cadherin and c-Met were

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obtained for each sample by two calibrated observers, based on the combination of staining intensity and extension in each tissue section as previously described<sup>(25)</sup>. For NL and AC samples, staining extension was evaluated at the basal, parabasal, and suprabasal epithelial layers of each sample. For lip SCC samples, the markers were evaluated in the tumor cells and in the stroma and defined as the percentage of positive cells/field (x40). Staining intensity for each marker was recorded as undetectable (0), weak (1), medium (2), or strong (3). Results were expressed as the mean  $\pm$ SD.

### Statistical Analysis

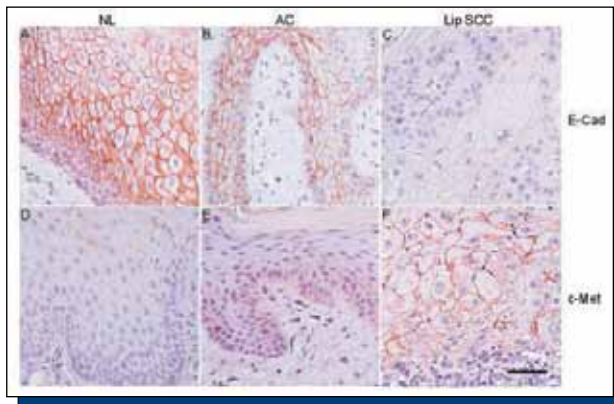
Data were analyzed with statistical software (SPSS, version 16.0; SPSS, Inc, Chicago, Ill, USA). Differences between groups were examined using the Mann-Whitney test; differences were considered statistically significant when  $P < 0.05$ .

## RESULTS

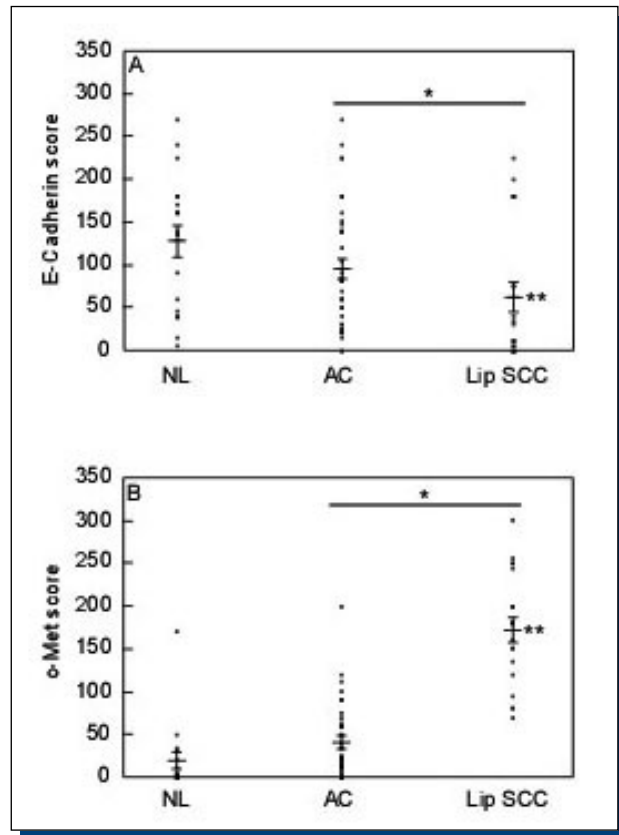
Figure 1 shows representative microphotographs of serial sections from normal lip, AC, and lip SCC biopsies immunostained for E-cadherin and c-Met. Strong membranous E-cadherin staining was found in nearly all the epithelial layers of normal lip, excluding the most superficial cells (Figure 1A). For AC specimens, moderate and weak membranous and non-membranous E-cadherin staining was found in basal, parabasal, and middle spinous cells but not in the superficial layers (Figure 1B). For lip SCC samples, the E-cadherin staining was weaker or lost (Figure 1C). Table 1 shows the cellular localization of E-cadherin expression in NL, AC, and lip SCC samples. E-cadherin expression was significantly reduced in AC and lip SCC as compared to normal lip ( $P < 0.05$ , Mann-Whitney test), with a significant reduction in lip SCC as compared to AC ( $P = 0.003$ ) (Figure 2A).

Immunohistochemistry showed that c-Met expression in NL was negative or occasionally weak at the basal and parabasal epithelial layers (Figure 1D). Weak positive c-Met staining was observed at basal, parabasal, and suprabasal epithelial layers of AC samples (Figure 1E).

In lip SCC samples c-Met was expressed at the membrane and cytoplasm of tumor cells (Figure 1F). Table 2 presents the cellular localization of c-Met expression in NL, AC, and lip SCC samples. Expression of c-Met was significantly higher in AC and lip SCC as compared to NL ( $P < 0.05$ , Mann-Whitney test), with a significant increase in lip SCC as compared to AC ( $P < 0.0001$ ) (Figure 2B). In addition, c-Met expression was found in stromal cells from AC (2.3%) and lip SCC lesions (50.3%) (not shown).



**Figure 1.** Immunohistochemical detection of E-cadherin and c-Met in normal lip (NL), actinic cheilitis (AC) and lip SCC. (A-C) Representative microphotographs of epithelial E-Cadherin (E-Cad) expression in NL (A), AC (B), and lip SCC (C) sections. (D-F) Representative microphotographs of epithelial c-Met expression in NL (D), AC (E), and lip SCC (F) sections. Bar represents 50µm.



**Figure 2.** Expression score for E-cadherin and c-Met in normal lip (NL), actinic cheilitis (AC), and lip SCC. A combined expression score of staining intensity and extension was obtained for E-Cadherin (A) and c-Met (B) from each sample.

\* $P < 0.05$  (Mann-Whitney test), for E-cadherin and c-Met expression in AC and lip SCC as compared to NL. \*\* $P < 0.001$  for E-cadherin and c-Met expression in AC as compared to lip SCC.

**Table 1.** Cellular localization of E-cadherin expression in normal lip, actinic cheilitis, and lip SCC

E-cadherin	Normal Lip		Actinic Cheilitis		Lip SCC	
	n	%	n	%	n	%
<b>Strong Membranous</b>	18	100	12	33.3		
<b>Mild Membranous</b>			21	58.4	8	36.7
<b>Membranous /Cytoplasmatic</b>			3	8.3	6	27.3
<b>Cytoplasmatic</b>					1	4.2
<b>Loss</b>					7	31.8
<b>Total</b>	<b>18</b>	<b>100</b>	<b>36</b>	<b>100</b>	<b>22</b>	

**Table 2.** Cellular localization of c-Met expression in normal lip, actinic cheilitis, and lip SCC.

C-Met	Normal Lip		Actinic Cheilitis		Lip SCC	
	n	%	n	%	n	%
<b>No expression</b>	11	61.1				
<b>Mild Membranous</b>	7	38.9				
<b>Membranous /Cytoplasmatic</b>			2	5.5		
<b>Cytoplasmatic</b>			34	94	22	100
<b>Total</b>	<b>18</b>	<b>100</b>	<b>36</b>	<b>100</b>	<b>22</b>	

## DISCUSSION

E-cadherin and its associated intracellular catenins are a key cell-cell adhesion protein in epithelial cells<sup>(9)</sup>. The loss of E-cadherin expression and/or function reduces cell-cell contacts and has been correlated with enhanced tumor progression and invasion<sup>(12,16)</sup>. E-cadherin inactivation may also occur early in some premalignant lesions, and the loss of expression is thought to induce intracellular signaling that promotes tumor development and progression<sup>(5,10,13)</sup>.

The present study showed that the progression of actinic cheilitis, a premalignant lesion caused by chronic exposure to UV radiation, to lip SCC is closely associated with a significant reduction or loss of E-cadherin expression. The expression of E-cadherin was significantly decreased in lip SCC as compared to AC and normal lip. The data also showed that E-cadherin was significantly decreased in AC compared with normal lip. This is in agreement with other studies that found elevated expression of E-cadherin in normal oral epithelium<sup>(4,11)</sup>, but weaker staining for E-cadherin in the dysplastic areas<sup>(5,6,9,11)</sup> as well as the infiltrating neoplastic islands of the invasive SCC carcinoma<sup>(5-7,9,11,12)</sup>.

Previously, we reported a significant increase in MDM-2 epithelial expression in AC compared to normal lip<sup>(26)</sup>. The use of immunohistochemical methods in breast cancer has led to lower levels of E-cadherin associated with higher expression of MDM-2<sup>(27)</sup>. Yang et al.<sup>(27)</sup> identified E-cadherin as a new substrate for MDM-2, demonstrating that MDM2 ubiquitinates E-cadherin and decreases its protein levels.

On the other hand, reduction or loss of E-cadherin expression together with increased COX-2 expression has been reported previously in HCA-7 colon carcinoma cells<sup>(28)</sup>, in non-small cell lung cancer<sup>(16)</sup>, and in prostate cancer<sup>(17)</sup>.

It has been demonstrated that COX-2 overexpression is a crucial event in the initial stage of UV-induced skin cancer<sup>(29)</sup>. Our previous study found that in early lip carcinogenesis, COX-2 protein and mRNA expression increased in AC<sup>(30)</sup>. Brouxhon et al.<sup>(6)</sup> using chronically UV-irradiated SKH-1 mice, showed a sequential loss of E-cadherin from dysplasia to SCCs; those authors also demonstrated that E-cadherin levels declined at the same time PG2 synthesis was enhanced.

In several neoplasias, c-Met expression has been elevated in the tumor as well as in endothelial and inflammatory cells<sup>(7,15,19,20,22,23)</sup>. These findings are corroborated in this study because the expression of c-Met increased significantly as lip carcinogenesis progressed. The result showed that in the early and later stages of lip carcinogenesis, c-Met expression was significantly increased in lip SCC as compared with the epithelium of AC lesions and normal lip. In addition, increased c-Met expression was found in stromal cells of lip SCC.

Other studies from this group have shown that p53 epithelial expression is significantly increased in actinic cheilitis as compared to normal lip<sup>(26,31)</sup>. Induction of p53 by UV irradiation in RKO cells that express wild-type p53 increases the level of endogenous c-Met gene product. Seol et al.<sup>(32)</sup> demonstrated that c-Met is induced by UV light and that p53 plays a role in this activation process.

Conversely, HGF is well-known to be secreted by fibroblasts surrounding the tumor, helping cancer cells invade the all-around stroma<sup>(23,34)</sup>. Chen et al.<sup>(23)</sup> observed that in oral SCC, parenchymal cells expressed high amounts of HGF and c-Met, as did stromal fibroblasts, endothelial cells, and inflammatory cells. Therefore, cancer cells are being stimulated to proliferate by autocrine and paracrine mechanisms. In the present study, we found that c-Met was expressed by stromal cells, some fibroblasts, endothelial cells, and inflammatory cells in AC (2.3%) samples and in lip SCC (50.3%).

It has been shown that HGF regulates the expression of COX-2 and increases synthesis of prostaglandins (PG) in gastric mucosal cells. Overexpression of COX-2 and increased PG secretion are involved in the regulation and growth of gastric cancer. Chen et al.<sup>(21)</sup> found 30 cases of gastric cancer overexpression of c-Met (93.3%) and COX-2 (53.3%). The expression of c-Met was positively correlated with COX-2 ( $r=0.41$ ,  $P=0.024$ ). Scarpino et al.<sup>(24)</sup> suggest that the increased expression of c-Met protein in thyroid papillary carcinoma played a role in up-regulating the expression of COX-2, which, in turn, contributes to the invasive capacity.

Taken together, the reduction or loss of E-cadherin expression with increased c-Met expression in AC and lip SCC shown in our data agree with other studies that have demonstrated that the activation of c-Met by HGF is associated with decreased E-cadherin<sup>(7,13,18,33,34)</sup>. Murai et al.<sup>(7)</sup> found a significant increase of c-Met expression in oral SCC as well as in dysplastic epithelium adjacent to tumor, and they suggest that the overexpression of c-Met interacts with E-cadherin to facilitate the disruption of intercellular junctions, thereby promoting invasion and metastasis. Shimabukuro et al.<sup>(34)</sup> reported that HGF produced by stromal cells influences the mode of stromal invasion of uterine squamous cervical cancer by decreasing E-cadherin.

In summary, the results showed that epithelial E-cadherin expression is reduced and c-Met expression is increased as lip carcinogenesis progresses (normal lip>AC>lip SCC), suggesting that these could be useful markers of malignant transformations in the lip. Future research should be performed to demonstrate the correlation of COX-2, c-Met, and E-cadherin in photodamaged lip.

## CONFLICT OF INTEREST STATEMENT

None declared.

## ACKNOWLEDGMENTS

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