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Original Article

Coexpression of CLPTM1L and TMEM207 as a Strong Prognostic Indicator in Oral Squamous Cell Carcinoma

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ABSTRACT

CLPTM1L is known to enhance the survival of malignant cells by engaging endoplasmic reticulum (ER) stress–associated survival mechanisms, whereas TMEM207 disrupts the tumor-suppressive role of WW domain–containing oxidoreductase (WWOX), thereby increasing the vulnerability of cancer cells to apoptosis triggered by ER stress. This study explored whether these two ER stress–linked proteins could function as prognostic biomarkers in oral squamous cell carcinoma (OSCC). Using immunohistochemistry with antibodies against CLPTM1L and TMEM207, we found that 31 of 89 OSCC cases displayed coexpression of both proteins at the invasive front of the tumor. Survival analysis using Kaplan–Meier curves and the log-rank test demonstrated a significant association between dual expression of CLPTM1L and TMEM207 and unfavorable clinical outcomes ($P = 0.00252$). Their coexpression was also strongly correlated with lymph node involvement ($P = 0.000574$). Results from both univariate and multivariate models further indicated that this combined expression pattern serves as an independent predictor of poor prognosis. Overall, our findings show that simultaneous immunoreactivity for CLPTM1L and TMEM207 is tightly linked to nodal metastasis and holds prognostic relevance in OSCC.

Keywords: OSCC, prognosis, CLPTM1L, ER stress, TMEM207, WWOX

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Introduction

Over the past decade, the global incidence of oral squamous cell carcinoma (OSCC) has shown a steady upward trend. Although conventional treatments such as chemotherapy and radiation therapy have been refined, patients with advanced OSCC continue to face dismal survival rates [1]. This stands in marked contrast to the dramatic prognostic improvements achieved in several other malignancies—including breast, lung, gastrointestinal carcinomas, and lymphomas—largely due to the introduction of precision molecular-targeted agents.

To establish similar therapeutic breakthroughs for OSCC, it is imperative to elucidate the critical molecular events and signaling networks that drive malignant transformation and progression in the oral epithelium.

The endoplasmic reticulum (ER) serves as the primary site for proper maturation of proteins destined for secretion or membrane insertion [2]. A variety of intrinsic and extrinsic stressors can disrupt ER homeostasis, causing the buildup of unfolded or misfolded proteins [3]. Persistent ER stress is cytotoxic and typically culminates in programmed cell death [4]. Malignant cells, however, frequently upregulate adaptive survival mechanisms to cope with chronic ER stress [5], making these protective pathways promising targets for selective anticancer therapy.

CLPTM1L (Cleft Lip and Palate Transmembrane Protein 1-Like) was originally discovered in a screen for genes conferring resistance to cisplatin [6] and has since been linked to the development of lung cancer in

multiple studies [7-10]. Of note, CLPTM1L physically associates with the ER chaperone GRP78 and thereby activates pro-survival Akt signaling during ER stress in pancreatic cancer cells [11].

TMEM207, an ER-resident transmembrane protein, directly binds the tumor suppressor WWOX through a PPxY motif–WW domain interaction [12]. This binding antagonizes the pro-apoptotic and growth-suppressive activities of WWOX, rendering cancer cells more vulnerable to ER stress-triggered cell death [13, 14]. Intriguingly, the ability of WWOX to exert its tumor-suppressive effects has been shown to depend on GRP78 levels in ovarian carcinoma models [15].

The present investigation was designed to evaluate whether combined expression of CLPTM1L and TMEM207 carries prognostic significance in OSCC. We demonstrate that high-level co-expression of these two proteins strongly correlates with regional lymph node involvement and reduced overall survival in affected patients.

Materials and Methods

Clinical samples

This retrospective analysis included formalin-fixed, paraffin-embedded tumor specimens from 89 patients who underwent curative-intent surgical resection for primary OSCC. The study protocol conformed to the 1975 Declaration of Helsinki and received approval from the Ethics Committee of Gifu University Graduate School of Medicine (IRB No. 28-524).

Immunohistochemistry

Sections from the invasive tumor front were subjected to immunohistochemical examination. Primary antibodies comprised a commercially available rabbit polyclonal anti-CLPTM1L (1:100; NBP1-84378, Novus Biologicals, Littleton, CO, USA) and an in-house murine monoclonal antibody directed against amino acids 40–50 (VNYNDQHPNGW) of human TMEM207 (used at 5 µg/mL) [12].

After deparaffinization and antigen retrieval, non-specific binding was blocked with normal goat serum. Slides were incubated with primary antibodies overnight at 4°C, then developed using the ImmPRESS™ horseradish peroxidase polymer system (Vector Laboratories, Burlingame, CA, USA) as reported previously [15].

For selected cases (n = 20), dual-label immunohistochemistry was carried out with the MACH 2 biotin-free detection kit (Biocare Medical, Walnut Creek, CA, USA) following the manufacturer's recommended procedure.

Immunohistochemical scoring and statistical analysis

Immunoreactivity was quantified as the percentage of positively stained carcinoma cells at the invasive tumor front. For each case, three non-overlapping high-power fields (×400 magnification) were evaluated, and the mean percentage of stained cells was calculated. Tumors were classified as positive when ≥10% of invasive cancer cells showed staining and negative when <10% did. All slides were scored by a single senior pathologist blinded to clinicopathological information and patient outcome.

Overall survival (OS) curves were generated using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. Associations between categorical clinicopathological variables were tested using the χ^2 test or Fisher's exact test when appropriate. Univariate and multivariate analyses of prognostic factors were performed with the Cox proportional hazards regression model. Statistical significance was defined as $P < 0.05$. All analyses were conducted using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA).

Results and Discussion

Expression of CLPTM1L and TMEM207 in OSCC and its prognostic implications

The clinicopathological characteristics of the 89 patients are summarized in **Table 1**. Representative immunohistochemical staining patterns are presented in **Figure 1**. Normal oral stratified squamous epithelium displayed negligible immunoreactivity for either protein. In contrast, CLPTM1L and TMEM207 expression was observed in 50 (56.2%) and 40 (44.9%) of the 89 OSCC cases, respectively. A highly significant positive correlation was found between CLPTM1L and TMEM207 expression (**Table 2**; P = 0.0002). Thirty-one tumors (34.8%) exhibited co-expression of both proteins. Concurrent expression of CLPTM1L and TMEM207 within the same tumor cells was verified by double-immunofluorescence staining in a subset of cases **(Figure 2)**.

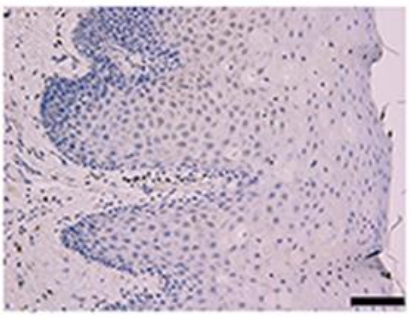
Table 1. Summary of the demographic and clinicopathological characteristics of patients with OSCC.

Characteristic	No. of patients (%)
Gender	
Male	43 (48)
Female	46 (52)
Age (years)	
50<	15 (17)
50≧	74 (83)

Tumor location	
TON	37 (42)
LG	24 (27)
BM	13 (15)
UG	9 (10)
FOM	4 (4)
HP	2 (2)
Histology of SCC	
Well-differentiated	60 (67)
Moderately-differentiated	23 (26)
Poorly-differentiated	6 (7)
Tumor T status	
T1	25 (28)
T2	43 (48)
T3	11 (13)
T4	10 (11)
Tumor N status	
N0	53 (60)
N1	17 (19)
N2	11 (12)
N3	8 (9)
Tumor M status	
M = 0	89 (100)
M = 1	0 (0)
Stage (UICC 8th ED)	
I	19 (21)
II	26 (29)
III	15 (17)
IV	29 (33)
Radiotherapy/Chemotherapy	
None	59 (66)
Radiotherapy only	1 (1)
Chemotherapy only	11 (13)
Radiotherapy+Chemotherapy	18 (20)
Survival status	
Alive	59 (66)
Deceased	30 (34)
Disease-associated death	22 (25)

T and N data based on pathology examination. The time for survival is 5-year.

TON, tongue; LG, lower gum; BM, buccal mucosa; UG, upper gum; FOM, floor of mouth; HP, hard palate.



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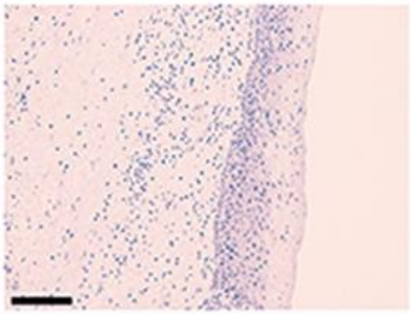

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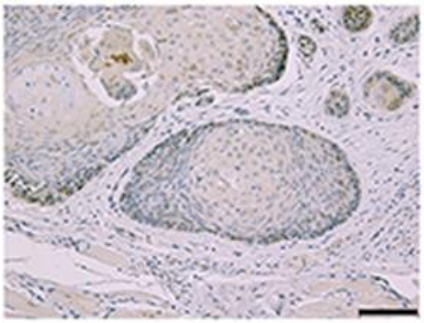

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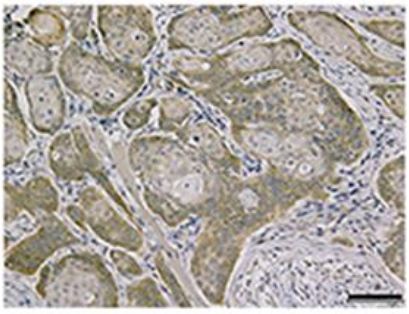

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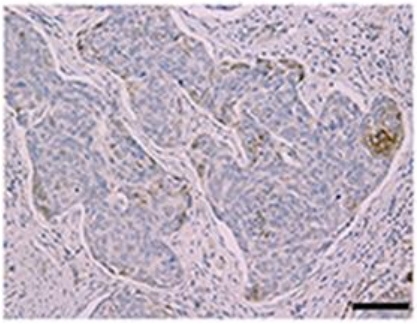

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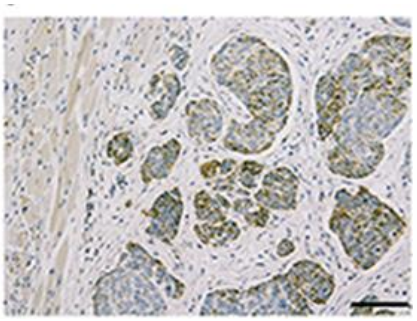


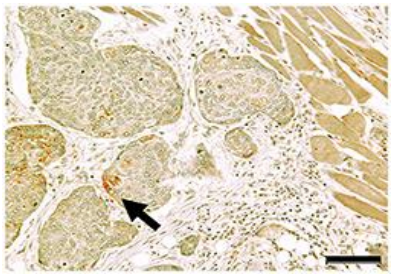
f)

Figure 1. Representative immunohistochemical staining for CLPTM1L and TMEM207 at the invasive front of oral squamous cell carcinoma (OSCC). (a, b) Normal non-neoplastic oral stratified squamous epithelium showing minimal or absent immunoreactivity for CLPTM1L (a) and TMEM207 (b). (c, d) CLPTM1L staining in OSCC specimens from patients with favorable (C) and poor (D) clinical outcome. (e, f) TMEM207 staining in OSCC specimens from patients with favorable (e) and poor (F) clinical outcome. Strong membranous and cytoplasmic immunoreactivity for both CLPTM1L and TMEM207 is evident in tumors associated with adverse prognosis (d, f). Original magnification ×400.

Table 2. Relation of Clptm1L and TMEM207 expression in OSCC.

TMEM207 positive	TMEM207 negative
Clptm1L positive	30
Clptm1L negative	19

Clptm1L and TMEM207 expression is significantly related to each other. (P = 0.0002).



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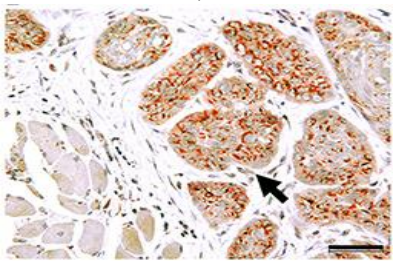

b)

Figure 2. Double immunohistochemical staining demonstrating co-expression of CLPTM1L and TMEM207 in OSCC. (A) Tumor from a patient with favorable prognosis showing negligible staining for either protein. (B) Tumor from a patient with poor prognosis revealing extensive co-localization of CLPTM1L (brown, membranous/cytoplasmic) and TMEM207 (red, membranous/cytoplasmic) in the same invasive cancer cells at the tumor front. Arrows highlight representative double-positive cells. Scale bar: 50 µm. Original magnification ×400.

Co-expression of CLPTM1L and TMEM207 (double-positive status) was significantly associated with advanced primary tumor category (pT1/T2 vs. pT3/T4; P = 0.0148), lymph node metastasis (pN status; P = 0.000574), and history of smoking (P = 0.0032) **(Table 3).**

Kaplan–Meier survival analysis demonstrated that patients whose tumors were double-positive for CLPTM1L and TMEM207 had markedly shorter overall survival compared with those lacking co-expression (log-rank test, P = 0.00252; **Figure 3**).

Univariate Cox regression analysis identified lymph node metastasis (P = 0.0005), UICC stage III/IV versus I/II (P = 0.0089), and double-positive CLPTM1L/TMEM207 status (P = 0.0046) as significant predictors of adverse outcome **(Table 4)**.

On multivariate Cox proportional hazards analysis, double-positive expression of CLPTM1L and TMEM207 emerged as an independent prognostic factor, conferring a hazard ratio for death of 2.466 (95% CI: 1.085–6.386; P = 0.032).

Table 3. Correction between Clptm1L and TMEM207 immunoreactivity and clinicopathological factors.

Clpmt1L2.TMEM207			
Immunoreactivity	**Others**	***P*- value**	**Double positive**
Gender			
Male	26		17
Female	32	0.384	14
Age			
<50	9		6
≧50 years	49	0.768	25
Histology of SCC			
Well-differentiated	38	0.643	22
Moderately-poorly differentiated	20		9
Stage (UICC 8th Ed)			
I+II	35		10
III+IV	23	0.0148	21
Lymph node metastasis			

No	43		11
Yes	15	0.000574	20
Smoking			
No	43	0.0032	16
Yes	15		15

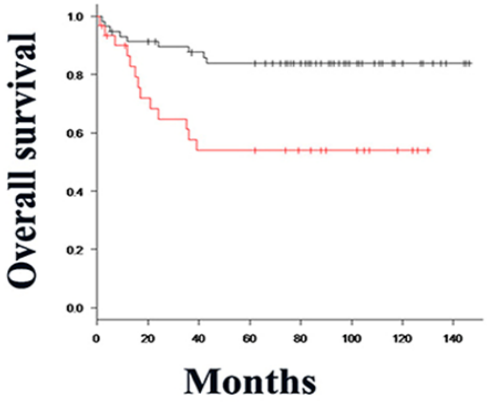

Figure 3. Kaplan–Meier overall survival curves stratified by CLPTM1L and TMEM207 co-expression status in patients with oral squamous cell carcinoma. Patients whose tumors exhibited concomitant expression of both CLPTM1L and TMEM207 (double-positive, red line) had significantly worse overall survival compared to those lacking co-expression (double-negative or single-positive, black line) (log-rank test, P = 0.00252).

Table 4. Cox multivariate analysis in OSCC.

Variable	Hazard Ratio (95% CI)	P-value
Univariate analysis		
Gender (male vs. female)	1.799 (0.768–4.214)	0.176
Age (<50 vs. ≥50 years)	1.028 (0.995–1.061)	0.093
Histological differentiation	1.065 (0.434–2.612)	0.891
(well vs. moderate/poor)		
UICC stage (I+II vs. III+IV)	3.508 (1.370–8.983)	0.009
Lymph node metastasis (absent vs. present)	3.472 (1.455–8.288)	0.005
CLPTM1L/TMEM207 co-expression	3.431 (1.462–8.048)	0.005
(double-positive vs. others)		
Multivariate analysis		
UICC stage (I+II vs. III+IV)	2.721 (1.023–7.234)	0.045
CLPTM1L/TMEM207 co-expression	2.466 (1.085–6.386)	0.032
(double-positive vs. others)		

This study revealed a significant association between co-expression of CLPTM1L and TMEM207 and a history of cigarette smoking in patients with OSCC. Numerous reports have established that cigarette smoke is a potent inducer of endoplasmic reticulum (ER) stress in both normal and malignant cells [16]. It is therefore plausible that elevated CLPTM1L and TMEM207 levels enable oral squamous cells to withstand smoking-induced ER stress, thereby facilitating carcinogenic progression. Conversely, chronic ER stress triggered by tobacco exposure may upregulate expression of these proteins in emerging cancer cells. Additional functional studies are warranted to clarify the bidirectional interplay between tobacco carcinogens and CLPTM1L/TMEM207 expression in OSCC.

Kaplan–Meier analysis demonstrated that concomitant CLPTM1L and TMEM207 expression was strongly associated with reduced overall survival (log-rank P = 0.00252). Importantly, multivariate Cox proportional hazards regression confirmed that double-positive status represents an independent adverse prognostic factor (HR = 2.466, 95% CI: 1.085–6.386, P = 0.032), even after adjustment for established clinicopathological variables.

The mechanistic basis linking co-expression of these proteins to increased lymph node metastasis remains to be fully elucidated. Of interest, GRP78 overexpression has been consistently correlated with enhanced metastatic potential across multiple malignancies [17-19]. Given the documented physical and functional interactions of CLPTM1L and TMEM207 with GRP78 and the GRP78–WWOX axis, respectively, it is tempting to speculate that GRP78 serves as a central node driving the aggressive phenotype observed in double-positive OSCC tumors.

Previous comprehensive reviews of prognostic immunohistochemical markers in OSCC have primarily emphasized proteins involved in cell cycle regulation, apoptosis, angiogenesis, cell adhesion, and extracellular matrix remodeling [20]. The current findings expand this framework by identifying two ER stress-response proteins—CLPTM1L and TMEM207—as novel, clinically relevant biomarkers capable of predicting adverse outcomes. These observations suggest that therapeutic strategies aimed at disrupting adaptive ER stress responses may hold promise for patients with aggressive, metastasis-prone OSCC.

Conclusion

In summary, concomitant expression of the ER stress-associated proteins CLPTM1L and TMEM207 is significantly correlated with lymph node metastasis and independently predicts unfavorable prognosis in

oral squamous cell carcinoma. These proteins may therefore serve as valuable prognostic biomarkers and potential targets for future molecularly directed therapies.

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Conflict of Interest: None

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Ethics Statement: The studies involving human participants were reviewed and approved by Institutional Review Board of the Gifu University Graduate School of Medicine (specific approval number: 28-524). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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