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STROMAL MONOCARBOXYLATE TRANSPORTER MCT4 IS A POOR PROGNOSTIC FACTOR IN SQUAMOUS CELL CARCINOMA

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ABSTRACT

Introduction: Monocarboxylate transporter 4 (MCT4) is the main exporter of lactate out of cells. It is also a critical component in the glycolytic metabolism of cancer cells. In this study, stromal MCT4 in oral SCC was correlated with risk of recurrence (ROR), extent of primary tumor (pT) and nodal metastasis (pN), perineural invasion (PNI), lymphovascular invasion (LVI), HPV status, extracapsular extension (ECE) and positive margin.

Methods: Clinical data were collected for 86 consecutive patients with oral HNSCC. Tissue microarrays (TMA) were constructed from paraffin blocks of resection specimens and stained for MCT4. Immunohistochemistry (IHC) staining was assessed and quantified by digital image analysis with Aperio software. Using a co-localization algorithm we assessed the intensity of staining and the percentage of positive cells in the tumoral stromal cells. Correlations of MCT4 expression with clinicopathological features and survival were studied. **Results:** Increased IHC staining for MCT4 was strongly associated with an increased risk of recurrence, OR 1.96 (95%CI: 1.17-3.40), presence of PNI, OR 2.25 (95%CI: 1.33-3.95), higher pT, OR 1.68 (95%CI: 0.99-2.89), higher pN, OR 2.07 (95%CI: 1.25-3.57) and presence of LVI, OR 2.21 (95%CI: 1.11-4.67). We didn't find any significant association between stromal MCT4 expression and HPV status, presence of ECE or positive margin. Conclusions**:** This study demonstrates that MCT4, a marker of glycolysis in cancer-associated stroma, is highly expressed in oral SCC. The IHC staining pattern of stromal MCT4 suggests that high MCT4 expression appears to be a useful marker for tumor progression and prognosis. We propose MCT4 serves as a new prognostic factor in oral SCC and can act as a potential therapeutic target marker considering pharmacological development of MCT4 inhibitors.

INTRODUCTION

Metabolic dysregulation is a critical process that leads to tumorigenesis and altering the tumor microenvironment in many cancers.

Recent studies suggest that distinct metabolic compartments exist in HNSCC and other cancers. That metabolic coupling between compartments promotes tumorigenesis.

Normal cells rely on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes where tumor cells are highly glycolytic despite the presence of oxygen. This phenomenon is called "*the Warburg effect*".

A *Reverse Warburg Effect* has been recently showed that tumor cells take advantage of the adjacent non-cancerous stromal cells to become glycolytic and the metabolic products such as lactate and pyruvate are then shuttled by monocarboxylate transporters (MCT1 and MCT4) to provide fuel for tumor growth and aggressive behavior.

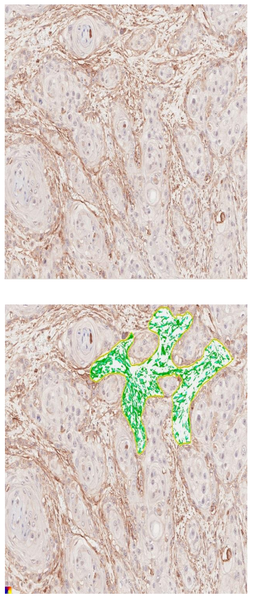
Peritumoral staining of MCT4, as a functional biomarker, has been associated with poor outcomes in HNSCC. The full significance of metabolic coupling has not yet been cleared for oral cavity squamous cell carcinoma.

METHODS

After IRB approval, records of 86 consecutive patients treated surgically for oral cavity squamous cell carcinoma were reviewed. Clinical data were collected for each patient, and each primary tumor sample was processed onto a tissue microarray (TMA) for immunohistochemistry (IHC) staining. IHC staining was performed for MCT4 antibody (Santa Cruz Biotechnology) . Intensity of IHC staining for each sample was acquired using digital pathology interpretation by Aperio. Intensity scores were compared against clinical data to identify potential biomarker for favorable or unfavorable tumor behavior.

RESULTS

Patient demographics and characteristics are shown in Table 1. An example of typical IHC staining for MCT4 and annotated region by Aperio is shown in Figure1. MCT 4 staining Immunohistochemistry (top), Note that the stroma adjacent to the tumor has stained strongly positive for MCT4. Annotated region by Aperio (bottom)



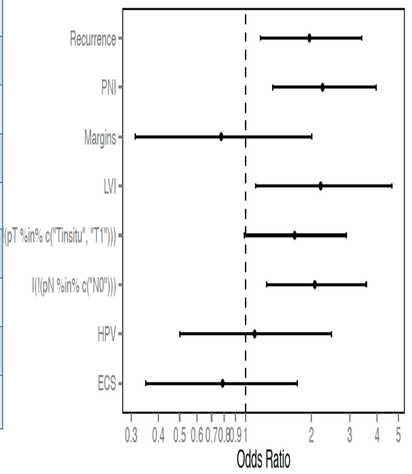
Demographic				
Sex	m 49/f 32			
Mean age (yr)	62.9 (29-90)			
Tobacco Use	64			
Alcohol Use	31			
Mean Follow-up (mos.)	20.4 (2-83)			
Subsite				
Oral Cavity				
Oral Tongue	33			
RMT	12			
Hard Palate	10			
FOM	12			
Alveolar ridge	7			
Buccal mucosa	5			
Lip	2			
Differentiation				
Well-moderate	76			
Poor	4			
Staging				
Tumor Stage	T1	T2	T3	T4
	24	20	5	32
Nodal Stage	N0	N1	N2	N3
	49	11	21	0
Prognositc Factors	Pos	Neg	No Data	
HPV	0	75	6	
PNI	45	28	8	
LVI	16	41	24	
ECS	13	19		
Surgical Margins	6	75		
Adjuvant Treatment				
XRT	49	32		
Systemic Therapy	35	46		

Table 1. Patient demographics

IHC staining showed that the adjacent noncancerous cells stained strongly for MCT4. Higher intensity MCT4 in peri-tumoral stroma was significantly associated with recurrence, higher nodal stage, lymphovascular invasion and perineural invasion ($p<0.05$), (Table 2, Figure 2).

	OR	95% CI of OR	P-value
Recurrence	1.96	1.17-3.40	***0.013***
PNI	2.25	1.33-3.95	***0.003***
Margins	0.77	0.31, 2.01	0.584
LVI	2.21	1.11-4.67	***0.029***
T1 vs.T3-T4	1.68	0.99-2.89	0.057
N0 vs. N1-3	2.07	1.25-3.57	***0.006***
HPV	1.10	0.50- 2.47	0.811
ECS	0.79	0.35- 1.72	0.549

Table 2. Statistical analysis



CONCLUSION

Oral cavity squamous cell carcinoma showed strong MCT4 staining pattern that suggests metabolic compartmentalization in peritumoral stroma, which is associated with disease recurrence and other poor prognostic indicators; thus they may serve as a functional biomarkers for more aggressive oral cavity cancers. Furthermore, therapies to target metabolic coupling may be beneficial in patients with oral cavity cancer.

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