MMPs as Biomarkers of Oral Squamous Cell Carcinoma: Biomarker Identification of Oral Squamous Cell Carcinoma through Transcriptomic Expression Analysis

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Abstract

Background

Due to the high mortality rate of oral squamous cell carcinoma (OSCC), early detection of the disease is critical. Despite previous research on potential diagnostic biomarkers, there is no consensus regarding the role and validity of specific biomarkers for OSCC.

Aims

The purpose of this study was to explore and verify diagnostic biomarkers for OSCC.

Methods and Results

mRNA expression data of 57 oral tissues from OSCC patients and 22 from individuals without OSCC was analyzed using a moderated t-test to determine potential biomarkers.

Statistical analysis revealed 163 differentially expressed genes between OSCC and normal tissues, 68 of which were upregulated in OSCC tissue. The 11 most significantly upregulated genes were determined to be MMP1, MMP3, MMP10, CXCL10, IL8, CXCL11, MMP12, CXCL9, GBP5, RPS4Y1, and MMP13.

Conclusion

This study suggests that MMPs are especially promising diagnostic biomarkers and therapeutic targets for OSCC and identifies 68 upregulated genes for further research.

Key Words: Oral squamous cell carcinoma, biomarkers, MMPs, head and neck cancer, Cancer biomarker(s)

Introduction

Head and neck cancers, including oral malignancies, are one of the most common cancers worldwide (Jemal et al., 2011). Oral squamous cell carcinomas (OSCC) account for over 90% of all oral malignancies (Bray et al., 2018). Oral squamous cell carcinoma poses a significant risk due to its tendency to progress past the initial stages without the production of pain or easily recognizable symptoms (Severino et al., 2015). As a result, it is usually discovered only after it has metastasized to the lymph nodes of the neck (Severino et al., 2015).

Despite advances in cancer treatment, such as surgical resection followed by postoperative radiotherapy and chemotherapy, the five-year survival rate of OSCC patients still remains around 50% due to common neck lymph node metastasis and neighboring tissue invasion (Yang et al., 2016; D'Silva & Ward, 2007). Given the high mortality rate of the disease, the early diagnosis of OSCC is critical. Detection of the cancer in stages I-II raises patients' survival rate to 80% (Mehrotra & Gupta, 2011). Thus, the development of effective diagnosis, risk, and prognosis predictors is of paramount importance.

Biomarkers are measurable indicators that could be useful for early diagnosis of OSCC lesions (Radhika et al., 2016). Ultimately, identifying and analyzing biomarkers associated with oral cancer could aid in early detection and thus decrease the mortality rate for many patients.

Analysis of global protein expression and secretion has gained increasing interest as a method of identifying new biomarkers of OSCC (Almangush et al., 2021; Rodriguez et al., 2021). In recent years, many studies have proposed different biomarkers for the diagnosis and prognosis of OSCC using the analysis of microarray assays (D'Silva & Ward, 2007). A study by Zhang et al. (2021), found GDF15, MCSF, I309, MMP3, CTACK, and AXL as biomarkers

associated with OSCC diagnosis. Other studies identified genes such as ISG15, OASL, IFI6, and RSAD2 as potential biomarkers (Singh et al., 2021).

Although much research has been done on biomarkers, there is a need for validation studies to confirm findings and provide help in identifying biomarkers (Almangush et al., 2021). Furthermore, many biomarkers require additional support and confirmation to fully establish their role and validity in OSCC diagnosis (Almangush et al., 2021).

The purpose of this study was to analyze the transcriptomic expression of genes in OSCC and normal tissue to identify possible diagnostic biomarkers of OSCC.

Methods

Datasets containing gene expression data from patients were examined from NCBI GEO, and the OSCC mRNA expression profile microarray data possessing accession number GSE25099 was chosen for analysis. The dataset consisted of expression data from a genome-wide analysis of transcription with the Affymetrix GeneChip Human Gene 1.0 ST Array of 79 samples: 57 specimens from patients with OSCC and 22 oral tissues from patients without (Peng et al., 2011).

R (www.r-project.org) was used to perform statistical analysis. The oligo package from R was used to perform quantile normalization on the data, and statistical significance was determined by a moderated t-test using the limma package. A moderated t-test was used in order to reduce confounding factors. The t-test allowed for the analysis of differential expression and the identification of significant differences in biomarker expression with the limited data available. Statistically significant genes were chosen as those with an absolute $\log_2$-fold change of greater than or equal to 2 with a p-value less than 0.05. 163 genes were identified as

significant (see Appendix, Figure I), and 68 genes upregulated in OSCC tissue−indicated by a positive $\log_2$-fold change−were determined. Using limma, a topTable of the upregulated significant genes was produced (see Appendix, Table I) and sorted by $\log_2$-fold changes.

Results

163 differentially expressed genes between OSCC and normal tissues were found through statistical analysis using R, 68 of which were upregulated in OSCC tissue. The 11 most upregulated genes were determined to be MMP1, MMP3, MMP10, CXCL10, IL8, CXCL11, MMP12, CXCL9, GBP5, RPS4Y1, and MMP13. The majority of these genes (IL8, CXCLs, MMPs) were immune system genes, and a large portion were MMPs.

Discussion

Matrix Metalloproteinases

Many of the most upregulated genes (MMPs, CXCLs, IL8) play a key role in the regulation of immune response. The presence of a suppressed immune system, including changes in cytokines and the balance of immune cells, is an established phenomenon in OSCC patients (Nosratzehi et al., 2017).

Of the 68 upregulated genes, MMPs were an especially promising candidate due to their prevalence among the significantly upregulated genes in OSCC tissues. MMPs (matrix metalloproteinases) are a gene family which code for MMP endopeptidases that are responsible for tissue remodeling and degradation of the extracellular matrix (ECM) in normal physiological processes (Verma & Hansch, 2007). They also contribute to immune system function by regulating inflammatory processes (Kessenbrock et al., 2010).

Increased expression of MMPs has been reported to play an important role in cancer development (Kessenbrock et al., 2010). High concentrations of MMP14 on the cell membrane of metastatic cancer cells contribute to cell migration, and MMPs can cause proteolytic acceleration of cell growth, leading to unregulated cell growth and proliferation in many tumors (Kessenbrock et al., 2010). MMPs are also involved in promoting tumor development by blocking receptor-transmitted or lymphocyte-mediated apoptosis, as well as by deregulating signaling pathways responsible for controlling cell growth, inflammation, and angiogenesis, causing unregulated tumor growth, inflammation, and metastasis (Kessenbrock et al., 2010).

However, the complex role of MMPs hinders the use of widespread matrix metalloproteinase inhibitors as an effective tool against cancer. MMPs can generate both angiogenesis-inhibiting and angiogenesis-promoting signals, and in certain cancer models in mice, MMPs such as MMP9 can generate ECM fragments like tumstatin, which suppress tumor vasculature formation (Kessenbrock et al., 2010). In one study, mice that were MMP9 deficient had increased tumor growth compared to those with normal MMP9 levels (Kessenbrock et al., 2010).

Role of MMPs in Oral Cancer Detection

Nonetheless, there seems to be no established consensus on the role of MMPs in oral cancer detection. Many previous studies found significant increases in levels of MMPs in the serum of OSCC patients (Andisheh-Tadbir et al., 2014; Baker et al., 2006; Lee et al., 2008; Tadbir et al., 2012; Schiegnitz et al., 2017). One study found that MMPs had a role in the immune escape mechanism of cancer since NK cell cytotoxicity was significantly reduced against OSCC when pretreated with MMPs (Lee et al., 2008).

However, results have not been consistent. A study in 2014 concluded that MMP3 could be useful for OSCC diagnosis (Andisheh-Tadbir et al., 2014). However, its utility for prognosis was deemed limited because there was no correlation in serum MMP-3 concentration with clinicopathologic features such as tumor stage, tumor size, nodal status, and histological grade (Andisheh-Tadbir et al., 2014). The study was corroborated by another study done earlier, which also found no apparent correlation between serum MMP3 concentration and clinicopathological features of the OSCC tumor (Tadbir et al., 2012).

Conversely, certain earlier studies established an association between MMP3 expression and OSCC tumor clinicopathological features (Kusukawa et al., 1995; Kurahara et al., 1999). In particular, Kurahara et al. (1999) observed a correlation between MMP expression and lymph node metastasis and tumor invasion.

Moreover, another study found that there were no significant differences in saliva concentration of MMP3 among control groups and head and neck cancer squamous cell carcinoma groups, concluding that salivary MMP3 levels might not be accurate enough to detect early stages of OSCC (Nafarzadeh et al., 2018). This was supported by a meta-analysis of Asian and European populations in 2013, which found no significant association between MMP levels and the risk for head and neck cancer in overall comparisons (Zhang et al., 2013). However, the study found that in some subgroups a MMP3 polymorphism was significantly correlated to the risk of head and neck cancer (Zhang et al., 2013).

In summary, this study finds that MMPs, along with other immune genes, may play important roles in the metastatic, angiogenic, and immunosuppressive abilities of OSCC.

Limitations and Further Research

Due to the limited sample size of the study, results may be limited in their ability to contribute to general findings. Further experiments should be conducted with larger sample sizes.

Another limitation is that the study only analyzed expression data at the transcriptional level. Further experiments should be conducted at the protein level to verify the results of this experiment.

Furthermore, the experiment only analyzed biomarkers in relation to the diagnosis of OSCC; the prognosis of such a disease, another important facet, was not taken into account. Future experimentation could use biomarkers to make predictions on the prognosis of patients.

Additionally, the current method of screening for OSCC by taking random biopsies of clinically normal and suspect oral tissue is impractical due to the serious discomfort experienced by the patient, and the unsuitability for repeated sampling at multiple sites (Trimarchi et al., 2017). One alternative is salivary biomarkers (Trimarchi et al., 2017). Many previous studies indicated a correlation between salivary MMPs and OSCC diagnosis and prognosis, although no conclusive, widely-agreed upon, and accurate methods or results have been found (Song et al., 2020). In the future, further research should be done on salivary MMPs to provide valuable insights into their use as noninvasive biomarkers for the diagnosis, prognosis, and potential treatment of OSCC.

Conclusions

In this study, by using a comparative analysis of genome-wide transcriptomic expression data of OSCC and normal tissues, 163 significant genes and 68 upregulated genes were identified as potential diagnostic biomarkers for OSCC. In particular, MMPs were identified as especially promising diagnostic biomarkers and therapeutic targets for OSCC.

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Data Availability

The data that support the findings of this study are openly available in NCBI GEO at 10.1371/journal.pone.0023452, reference number GSE25099.

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Appendix

Figure I. Volcano plot of significant genes.

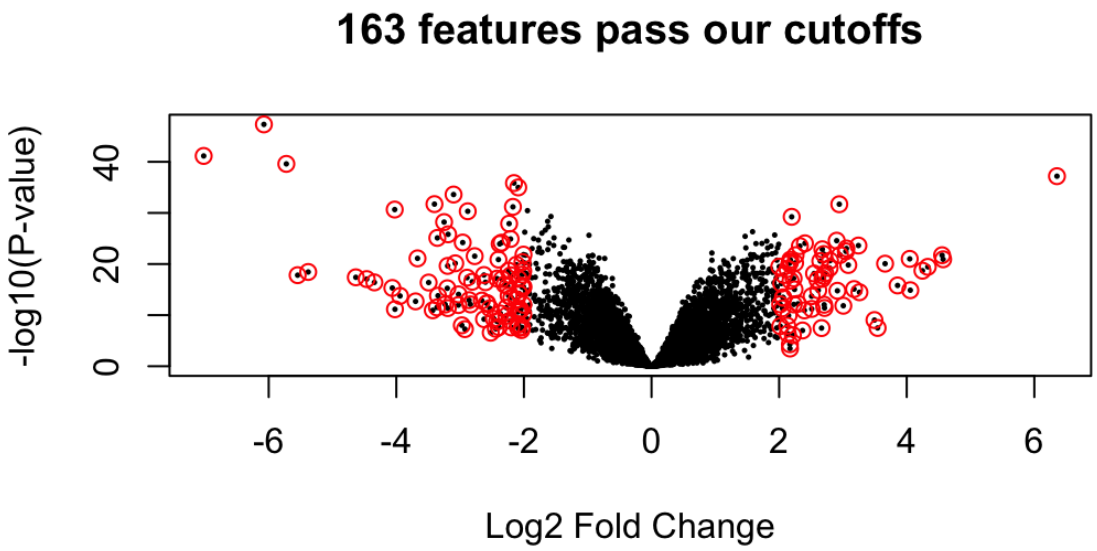

Table I. Sorted table of genes with a positive log fold change value.

probe_id	logFC	AveExpr	P.Value	adj.P.Val	gene_assignment
3388807	6.354774933	8.770374108	6.46E-38	3.55E-34	MMP1
3388830	4.570398794	7.598941287	1.18E-21	2.88E-19	MMP3
3388785	4.554129576	7.322304996	1.90E-22	5.51E-20	MMP10
2773958	4.330296051	8.418709443	3.58E-20	5.84E-18	CXCL10
2731332	4.246756595	7.98302588	2.03E-19	2.65E-17	IL8
2773972	4.056157737	7.159238817	1.33E-15	8.00E-14	CXCL11
3388859	4.047199119	8.023728497	9.76E-22	2.44E-19	MMP12
2773947	3.856334397	7.287738484	1.55E-16	1.10E-14	CXCL9
2422035	3.660777005	7.573664765	8.49E-21	1.61E-18	GBP5
4028512	3.543598475	7.386712848	3.22E-08	3.58E-07	RPS4Y1
3388893	3.494236919	7.640560368	9.21E-10	1.50E-08	MMP13
2735027	3.25877467	7.705410433	3.34E-15	1.82E-13	SPP1
3047581	3.243063079	7.155595439	2.41E-24	1.18E-21	INHBA

2359691	3.174348027	8.443945384	7.91E-16	4.93E-14	S100A7A
2809399	3.0842637	8.051596885	1.55E-20	2.78E-18	FST
2403261	3.054775548	9.985593244	9.08E-24	3.66E-21	IFI6
2371139	3.04595411	9.65391747	3.26E-23	1.24E-20	LAMC2
3451814	3.006100912	6.981464329	1.45E-12	4.31E-11	NELL2
3257204	2.954247713	9.211927732	1.75E-22	5.34E-20	IFIT3
3252036	2.943130076	9.134988661	1.98E-32	4.84E-29	PLAU
2343473	2.913476673	8.342209656	1.72E-15	9.87E-14	IFI44L
2421883	2.902388355	8.123684905	2.70E-25	1.75E-22	GBP1
2439554	2.798549861	6.140569817	2.20E-21	4.93E-19	AIM2
2343511	2.79164299	7.302985505	6.07E-20	9.35E-18	IFI44
3898355	2.722543466	6.912531696	6.33E-19	7.45E-17	FLRT3
3095223	2.711572856	6.70479792	3.99E-12	1.09E-10	IDO1
2749011	2.70578522	5.42204434	9.20E-13	2.84E-11	TDO2
3257246	2.701186533	9.228078536	2.24E-18	2.32E-16	IFIT1
3511698	2.698600741	7.396319734	1.11E-22	3.70E-20	EPSTI1
3016148	2.679746984	8.691677464	7.77E-18	7.01E-16	SERPINE1
2829947	2.677342333	10.32044375	1.29E-23	5.08E-21	TGFBI
4030162	2.665202037	7.899380894	3.43E-08	3.80E-07	DDX3Y
2468351	2.64530738	7.135736879	2.59E-21	5.65E-19	RSAD2
2955827	2.613796411	6.683789177	1.36E-15	8.09E-14	PLA2G7
2792800	2.600795003	7.38993592	1.23E-17	1.05E-15	DDX60
3448744	2.547347607	8.310308339	7.12E-19	8.08E-17	PTHLH
3587553	2.510971895	7.65634223	6.11E-12	1.62E-10	GREM1
2967276	2.508849145	5.577704201	1.98E-14	9.06E-13	POPDC3
3178147	2.404508037	8.212950036	8.86E-25	5.00E-22	CTSL1
2584134	2.396138008	6.23974246	1.19E-11	2.96E-10	FAP
4031136	2.367289602	5.533151651	1.00E-07	9.96E-07	EIF1AY
3058759	2.324899217	8.080038657	3.11E-24	1.49E-21	SEMA3C
2731381	2.29553552	8.562314162	6.08E-13	1.95E-11	CXCL1
3041816	2.257841989	7.205128777	1.81E-22	5.46E-20	DFNA5
3222170	2.250788573	9.17476481	6.04E-21	1.20E-18	TNC
3275729	2.241265464	6.919897689	9.30E-16	5.72E-14	IL2RA
2598261	2.228962844	9.986691235	7.94E-13	2.50E-11	FN1
3021377	2.226993662	7.206252246	6.40E-18	5.90E-16	PTPRZ1

2730465	2.216206951	4.166406909	8.52E-07	6.50E-06	AMTN
2635906	2.197193142	7.472063065	5.78E-30	8.48E-27	PHLDB2
3579546	2.179047425	9.436588637	1.91E-17	1.58E-15	WARS
2583465	2.1750113	8.950316259	1.44E-21	3.44E-19	ITGB6
3722338	2.171084252	7.988564394	3.67E-21	7.61E-19	IFI35
3617719	2.170587735	6.069600917	3.46E-04	1.20E-03	ACTC1
3142381	2.168785042	4.933877786	5.06E-05	2.32E-04	FABP4
2700585	2.162000436	8.094656611	7.55E-21	1.46E-18	PFN2
2377035	2.147865725	6.082137657	1.22E-10	2.39E-09	IL24
3718902	2.135286088	7.63107986	4.36E-07	3.66E-06	CCL18
2697863	2.130431149	8.241873909	9.38E-20	1.38E-17	RBP1
3388673	2.127795296	5.969134976	1.19E-08	1.50E-07	MMP7
3422855	2.073957259	8.918240755	1.45E-18	1.54E-16	GLIPR1
3257192	2.064899767	7.508218992	4.19E-14	1.79E-12	IFIT2
2440943	2.060645275	7.240816033	3.28E-14	1.44E-12	FCGR3A
2530713	2.052220278	5.885996106	4.77E-12	1.29E-10	CCL20
3061456	2.034160674	7.293877636	6.77E-17	5.07E-15	SAMD9L
3455388	2.018354813	7.0436557	1.45E-08	1.78E-07	KRT75
2523874	2.016691664	6.15890933	7.73E-13	2.44E-11	ICOS
3454892	2.002405561	7.457637683	3.21E-20	5.35E-18	GALNT6