INPLASY

Biomarkers identification in oral squamous cell carcinoma mi-croenvironment: A systematic review of proteomic studies

INPLASY2023120114

doi: 10.37766/inplasy2023.12.0114

Received: 29 December 2023

Published: 29 December 2023

Pomella, S[1]; Melaiu, O[2]; Cifaldi, L[3]; Bei, R[4]; Gargari, M[5]; Campanella, V[6]; Barillari, G[7].

Corresponding author:
Giovanni Barillari

barillar@uniroma2.it

Author Affiliation:
University of Rome Tor Vergata.

ADMINISTRATIVE INFORMATION

Support - Supported by the Italian Ministry of University and Research (MUR), University Scientific Re-search Projects (RSA) 2021 grant. no. E83C22002040005. S.P. is funded by a grant from MUR, Re-search, and Innovation Projects (PON).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023120114

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 December 2023 and was last updated on 29 December 2023.

INTRODUCTION

Review question / Objective - Summarize and integrates available data on the proteins that are found in OSCC microenvironment, as identified through proteomic and/or phosphoproteomic approaches; - Provide information that could be used to improve the specificity and sensitivity of the diagnostics of OSCC; - Streamline the therapeutic options directed against that tumor.

Rationale A critical determinant of oral squamous cell carcinoma (OSCC) progression and outcome is the composition of the tumor microenvironment (TME). Therefore, the study of the intricate interplay between cancer-associated fibroblasts (CAFs), immune cells, and cancer cells within the heterogeneous TME will contribute to the understanding of OSCC behavior and therapeutic response. Proteomic methodologies, particularly mass spectrometry (MS), have emerged as vital tools, en-abling the characterization of protein markers dictating TME dynamics in OSCC. This review will emphasize the significance of understanding TME protein markers for diagnosing and prognosticating OSCC.

Condition being studied Oral squamous cell carcinoma (OSCC) is an aggressive and highly metastasizing malignancy that originates from the transformation of epithelial cells lining the oral cavity, most frequently in the palate, the floor of the mouth, and the tongue. Nowadays, OSCC accounts for over 90% of oral cancers, and it is witnessing a global increase in annual new cases, prominently in Asia, followed by Western countries: this places OSCC among the top ten most common human malignancies. The onset of OSCC is influenced by host genotype, age and gender, and it is favored by lifestyle-related factors including smoking, alcohol consumption, exposure

to ultra-violet radiation, and the use of betel quid. Infection of oral keratinocytes by human papilloma viruses (HPVs) is another risk factor for OSCC development, this occurring mostly in young individuals. Treatment options for OSCC range from surgery and radiation therapy to chemotherapy or a combination thereof, being selected based on the severity of the disease. However, these approaches have significant side effects. Moreover, OSCC patients, after an initial response, often develop chemo- and/or radio-resistance. Consequently, OSCC has a poor prognosis, and the survival rates of OSCC patients have seen minimal improvement over the last decades. In this context, the understanding of the proteins that drive OSCC progression is limited. Recently, however, two articles have reported that in OSCC tissues, cancer cells, CSCs, CAFs, MSCs and TAMs interact via the proteins they release, thereby establishing a niche that supports tumor progression. It is quite likely that those and other TME proteins could work as biomarkers for diagnostic purposes (possibly allowing OSCC early detection) and/or as targets of novel therapeutic approaches (hopefully more effective that the ones adopted nowadays).

METHODS

Search strategy PubMed/MEDLINE database has been used to perform a systematic search for articles published between January 1st, 2001, and June 30th, 2023, using the following search query: ((tumor microenvironment)) AND ((oral squamous cell carcinoma)) AND ((proteomic)).

Participant or population The data we have retrieved from the 16 selected studies involve OSCC specimens from a total of 94 patients. In 12 of the 16 studies, the cohort of patients with OSCC has been compared to a cohort of healthy individuals, with a total of 45 non-tumoral samples that have been considered herein.

Intervention Of the 16 selected articles, 7 have performed proteomics studies on the entire tumor mass. Specifically, 5 have focused on the proteome (i.e. entire set of proteins expressed by the selected tissue), 1 has analyzed both proteome and phosphoproteome (i.e. set of proteins that contain a phosphate group as a posttranslational modification), and 1 has analyzed the proteome and secretome (i.e. set of proteins expressed by the selected tissue and secreted into the extracellular space in vivo and in the supernanant when cells are grown in vitro) of human OSCC specimens. Concerning the other 9 papers analyzed in this review, 7 have focused exclusively on OSCC stroma, with CAFs and/or MSCs being the first matrices to be sorted. Of these 7 papers, 2 have carried out studies on the secretome, 2 on both the secretome and the proteome, 2 on the proteome, and 1 on the phosphoproteome. The remaining 2 papers have performed studies on the secretome by analyzing the tumor interstitial fluid (TIF).

Comparator In 12 of the 16 studies, the cohort of patients with OSCC has been compared to a cohort of healthy individuals, with a total of 45 non-tumoral samples that have been considered herein.

Study designs to be included Case Reports, Case Control Studies.

Eligibility criteria Inclusion criteria have been article published in the English language, reporting results of human patient samples, describing cases of OSCC. Exclusion criteria have been reviews, conference abstracts, letters, in vitro or in vivo preclinical studies. Two reviewers (S.P. and O.M.) have performed an independent review of the abstract and full text of the retrieved articles. Articles meeting the inclusion criteria have been selected for a comprehensive final systematic review.

Information sources PubMed/MEDLINE database has been used to perform a systematic search for articles.

Main outcome(s) The main outcome of this systematic review is to identify proteins that are differentially expressed in OSCC, as compared to normal oral mucosa by retrieving data from proteomic studies. The literature search strategy has resulted in 56 articles published between 2001 and 2023. Upon duplicate removal and following the screening process, 16 articles have been chosen for revision. Among the 40 excluded articles, 5 are reviews, 1 is a retracted article, 14 are preclinical studies, 13 articles do not report data from proteomic and/or phosphoproteomic analyses, and 7 articles do not focus on OSCC.

Data management Two independent reviewers (S.P. and O.M.) have extracted the data and evaluated their quality. The Authors of the present review have addressed potential disagreements through discussions. The screening of the articles, duplicate exclusion, and the reasons for exclusion have been documented and recorded using Rayyan. The following information have been extracted: Author(s), year of publication, sample

characteristics and numbers, and techniques involved in proteomics and phosphoproteomics.

Quality assessment / Risk of bias analysis The present study has relied on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The screening of the articles, duplicate exclusion, and the reasons for exclusion have been documented and recorded using Rayyan. Two reviewers (S.P. and O.M.) have performed an independent review of the abstract and full text of the retrieved articles.

Strategy of data synthesis Qualitative analysis of data retrieved from proteomic studies. Comprehensive synthesis of proteins that have been identified as differentially expressed in OSCC primary samples.

Subgroup analysis OSCC patients vs healthy patients; OSCC tumor tissues vs non-neoplastic peritumoral tissues.

Sensitivity analysis Two independent reviewers (S.P. and O.M.) have extracted the data and evaluated their quality. The Authors of the present review have addressed potential disagreements through discussions.

Language restriction English.

Country(ies) involved Italy.

Keywords biomarkers; tumor microenvironment; oral squamous cell carcinoma; proteomic; phospho-proteomic; stroma; CAFs.

Contributions of each author

Author 1 - Silvia Pomella - S.P. contributes to conceptualization, methodology, validation, formal analysis, investigation, data curation, original draft preparation.
Email: silvia.pomella@uniroma2.it
Author 2 - Ombretta Melaiu - O.M. contributes to conceptualization, methodology, validation, formal analysis, investigation, data curation, original draft preparation.
Email: ombretta.melaiu@uniroma2.it
Author 3 - Loredana Cifaldi - L.C. contributes to formal analysis and investigation.
Email: cifaldi@med.uniroma2.it
Author 4 - Roberto Bei - R.B. contributes to review and editing the manuscript.
Email: bei@med.uniroma2.it
Author 5 - Marco Gargari - M.G. contributes to review and editing the manuscript.
Email: marco.gargari@gmail.com
Author 6 - Vincenzo Campanella - V.C. contributes to review and editing the manuscript.
Email: vincenzo.campanella@uniroma2.it
Author 7 - Giovanni Barillari - G.B. contributes to review and editing and supervise the entire work.
Email: barillar@uniroma2.it