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Systematic Review

Tumor Microenvironment Gene Regulation in Oral Squamous Cell Carcinoma: A Systematic Review

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Abstract

Background: The oral squamous cell carcinoma (OSCC) is a very aggressive cancer that is the product of tumor cell interactions with the microenvironment. The tumor microenvironment (TME) has a severe impact on OSCC progression, metastasis, and resistance to treatment by altering gene expression via various cellular and molecular signal transductions. **Aim:** This review systematizes the information on gene regulation in the OSCC TME (cellular components, signaling pathways that regulate tumor progression and resistance). **Methods:** We used PRISMA guidelines to search PubMed, Scopus, Web of Science, and Google Scholar (up to April 2025) with OSCC studies addressing the subject of gene regulation and tumor microenvironment. The quality of human or experimental models was evaluated using the Newcastle–Ottawa Scale and the qualitative synthesis was performed because of heterogeneity. **Results:** The significant regulatory functions of tumor-associated macrophages, cancer-associated fibroblasts, immune cells, and non-coding RNAs were found, especially in the pathways like JAK/STAT, EGFR, Wnt/ -β catenin, and PI3K/AKT/mTOR. **Conclusions:** The conceptualization of gene regulatory networks in the OSCC TME identifies the emerging biomarkers and targets of therapy. Merging multimodal omics and single-cell studies can further contribute to the precision strategies to enhance the outcomes of OSCC.

Keywords: oral squamous cell carcinoma; tumor microenvironment; gene regulation; signaling pathways; epigenetics

1. Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common and aggressive cancers of the oral cavity with an associated poor mortality rate. In the year 2020, 377,713 cases of OSCC were reported with the incidence of 117,757 deaths [1], even though advances in diagnostic and therapeutic procedures have been available. The global burden of OSCC imposes considerable morbidity and mortality depending on the cancer, with its associated risk factors, which include tobacco consumption, alcohol intake, betel nut chewing, and hereditary factors [2]. The development of OSCC is increasingly driven by genetic and epigenetic changes in tumor cells, as well as by complex interactions with the tumor microenvironment (TME), which significantly affect tumor initiation, progression, invasion, and metastasis [3]. The TME is a heterogeneous and well-organized network of various components such as cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), T lymphocytes, tumor-associated neutrophils (TANs), myeloid-derived suppressor

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cells (MDSCs), and dendritic cells as embedded in the extracellular matrix (ECM) milieu [4]. The communication of these components occurs through the secretion of cytokines, growth factors, RNAs, and metabolites, thereby affecting the behavior of the tumor cells and immune response [5]. The interaction of cancer cells with the tumor microenvironment (TME) promotes both tumor growth and angiogenesis. At the same time, such effects also contribute to chemotherapy resistance and immune escape [6].

Recent studies have highlighted the regulatory function of gene expression in the TME, and targeting non-coding RNAs, such as miRNAs, which regulate many cellular functions in OSCC, including cell cycle regulation, apoptosis, migration, and invasion [7,8]. For example, abnormal expressions of miRNAs and their target genes, including MAP2K1, are linked to OSCC progression and poor clinical outcomes [9]. Knowledge of the molecular mechanisms regulating gene expression in the TME is necessary to identify potential novel diagnostic biomarkers or therapeutic targets. This systematic review appraises the literature on gene regulation in the tumor microenvironment of oral cancer, providing an overview of the molecular pathways and gene networks involved. By showing evidence of tumor cell–microenvironment interactions at the genetic and epigenetic levels, this article aims to provide information that can help develop better, more specific treatment modalities for OSCC.

2. Materials and Methods

2.1. Literature Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor in (Supplementary Material) and flowchart as shown in Figure 1. The review was not prospectively registered in PROSPERO or any other public registry. Although protocol registration was initially planned, administrative and supervisory changes during the study prevented completion of prospective registration before the review commenced. Nevertheless, all eligibility criteria, search strategies, study selection procedures, and outcome measures were predefined prior to data extraction and analysis. However, all eligibility criteria, search strategies, study selection procedures, and outcome measures were predetermined prior to data extraction and analysis. A thorough and systematic literature search was conducted using electronic databases, namely PubMed, Scopus, Web of Science, and PubMed Central (PMC). A structured search strategy was used to identify relevant studies up to 2025. To maximize retrieval of relevant studies, keywords were combined with Medical Subject Headings (MeSH) terms with Boolean operators (AND, OR and NOT) related to the tumor microenvironment, gene regulation, and oral cancer. The search strategy was tailored to suit each database to ensure that it covered all the literature available.

2.2. Inclusion and Exclusion Criteria

Studies that satisfied the following criteria were considered eligible for inclusion: (1) original research and review articles that are related to gene regulation in the tumor microenvironment of oral cancer; (2) studies in humans or relevant in vitro or in vivo studies; (3) studies published in the English language; (4) studies available in full text. The exclusion criteria included the following: (1) studies that did not relate to either oral cancer or the regulation of gene expression within a tumor microenvironment; (2) abstract-only publications, conference abstracts, editorials, or letters that did not provide primary data; (3) studies that showed insufficient methodological detail.

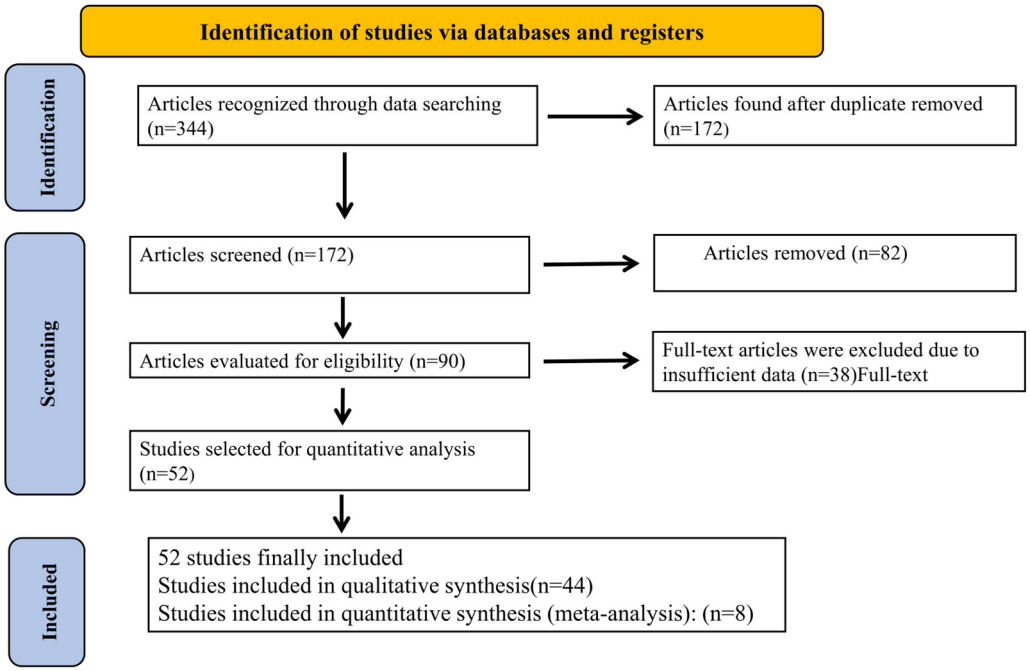

Figure 1. Flow chart of records inclusion and exclusion. Tumor microenvironment gene regulation in oral squamous cell carcinoma.

Relevant studies were defined as those directly investigating gene expression, epigenetic regulation, or signaling pathways within cellular or molecular components of the OSCC tumor microenvironment.

2.3. Study Selection and Data Extraction

A thorough, successful search of four major electronic databases (PubMed, Scopus, Web of Science, PMC) was conducted to identify the studies that were devoted to the tumor microenvironment (TME) in oral squamous cell carcinoma (OSCC). The search condition was a combination of the keywords of the subject under investigation in the background of oral squamous cell carcinoma tumor microenvironment, gene regulation, expression, and epigenetics, and restricted to human-based research in 2016–2025 years. A preliminary database searching with the aid of a search was discovered with 344 records. This resulted in the elimination of duplicates and left 172 unique articles. These were narrowed down by the title and abstracts of which 82 were weeded out as being irrelevant, having a lack of original data, neither TME, nor genes regulation. The two independent reviewers identified and filtered the full texts of 38 articles based on the predetermined inclusion and exclusion criteria. These discrepancies were resolved either through discussion or (where necessary) giving an opinion to a third reviewer. The inclusion criteria allowed forty-four studies to be eligible and included in the qualitative synthesis in Table 1. They comprised original research papers and reviews, which analyzed TME-relevant gene expression, immune signaling, stromal, and epigenetic modulation of OSCC. Out of the studies incorporated, 8 studies had enough quantitative information (i.e., hazard ratios, change of gene expression in the form of a fold change and odds ratios) to incorporate in their meta-analysis as in Table 2. Data were extracted from a standardized form by 2 reviewers, who provided recommendations on the following: author, publication date, study design, study population characteristics, elements of the TME, targeted genes, molecular pathways, and main findings.

Table 1. Summary of studies included in qualitative synthesis (n = 44).

Study Type	Focus Area	TME Component	Target Gene(s)/Pathway	Key Findings	References
Original Research	DNA methylation regulation	CAFs	DNMTs, TET1	Epigenetic regulation of tumor suppressor genes	[10]
Original Research	M2 macrophage polarization	TAMs	eIF5A	Promotes tumor growth via M2 polarization	[11]
Original Research	THBS1-mediated M1 activation	TAMs	THBS1	Enhances migration and immune evasion	[12]
Original Research	Chemerin-JAK2/STAT3 in EMT	Neutrophils	Chemerin, JAK2, STAT3	Promotes OSCC progression	[4]
Original Research	HMGB1 activation	TAMs	NF-κB, IL-6	Promotes migration and invasion	[13]
Original Research	Crosstalk via HMGB1	TAMs	HMGB1	Suppresses TAM–OSCC interaction	[14]
Original Research	IL-6 mediated inflammasome	TAMs, T Cells	IL-6, STAT3, NLRP3	Triggers OSCC progression	[15]
Original Research	VEGFR2/EGFR inhibition	Tumor cells	VEGFR2, EGFR	Suppresses tumor proliferation	[16]
Original Research	TME and gene expression in OSCC	Mixed	IL-6, MMPs	Links inflammation with gene upregulation	[17]
Original Research	miRNA target identification	Tumor Cells	miR-21, PTEN	Controls invasion and growth	[18]
Original Research	Immune escape and metastasis	Immune cells	CXCR4, PD-L1	Suggests immune-based therapeutic targets	[19]
Review	MDSCs as regulators	MDSCs	IL-10, TGF-β	Therapy resistance targets	[20]
Original Research	Cancer stemness and resistance	CSCs	CCNG2, miR-1246	Enhances stemness and chemoresistance	[21]
Review	Epigenetic regulation in TME	Mixed	DNMTs, HDACs	Epigenetic factors modulate OSCC	[22]
Original Research	PD-L1 and survival	Tumor cells	PD-L1	Poor prognosis association	[23]
Original Research	IL-10 in TME	Immune cells	IL-10	Immunosuppressive role of IL-10	[24]
Review	TME mechanisms	General	Various	Mechanistic insights into TME	[7]
Review	Pathogenesis overview	General	ECM, MMPs	TME influence on OSCC	[8]
Review	Prognostic molecular pathways	Mixed	p53, AKT	Prognostic molecular signatures	[9]
Review	EMT gene regulation	Tumor Cells	TWIST, ZEB1	EMT-related progression	[25]
Review	Immune system role	General	ILs, chemokines	Immunity from initiation to metastasis	[26]

Table 1. *Cont.*

Study Type	Focus Area	TME Component	Target Gene(s)/Pathway	Key Findings	References
Review	JAK/STAT3 axis	General	IL-6, STAT3	Key pathway in cancer	[27]
Review	PD-1/CTLA-4 pathways	T Cells	PD-1, CTLA-4	Checkpoint regulation	[28]
Review	Immune checkpoint miRNA regulation	T Cells	PD-1, PD-L1	miRNA as immune regulators	[29]
Review	miRNA and TAMs	TAMs	miR-155, miR-21	miRNAs in macrophage function	[30]
Review	CAFs in therapy	CAFs	IL-6, CXCL12	CAF-targeted therapy approach	[31]
Review	Cytokine signaling	General	JAK2, STAT3	Cytokine dynamics in OSCC	[32]
Review	PI3K/AKT in OSCC	Tumor cells	PI3K, AKT	Pathways of resistance and survival	[33]
Original Research	MDSC role in gastric cancer	MDSCs	ARG1	MDSC-mediated immune evasion	[34]
Review	MDSCs in tumor microenvironment	MDSCs	IL-10, TGF-β	MDSCs and regulation	[35]
Review	CXCR2 in cancer	Immune cells	CXCR2	Inflammation and metastasis link	[36]
Review	Notch pathway in OSCC	Tumor cells	NOTCH1	Proliferation and stemness control	[37]
Review	CSF-1R in macrophages	TAMs	CSF-1R	Regulates TAM survival	[38]
Review	CAFs and immune cells	CAFs, immune cells	TGF-β	CAF–immune interaction in OSCC	[39]
Original Research	CSCs and TANs	CSCs, TANs	CD10, IL-8	Reprogramming of neutrophils	[40]
Review	EMT and Wnt signaling	Tumor Cells	Wnt/β-catenin	Invasion and metastasis	[41]
Review	MAPK pathway	Tumor Cells	ERK1/2, JNK	MAPK activation effects	[42]
Original Research	DNMT1 inhibition	Tumor Cells	DNMT1	Epigenetic reactivation	[43]
Review	circRNAs and immunity	Tumor Cells	circRNAs	Checkpoint modulation	[44]
Review	Tumor immunity	General	TGF-β, IL-6	Progression and immune escape	[45]
Review	TME and metastasis	General	VEGFA, IL-10	From initiation to metastasis	[6]
Review	CAF-TAM interaction	CAFs, TAMs	IL-6, CXCL5	CAF–macrophage synergy	[46]
Original Research	Neutrophil–macrophage crosstalk	TANs, TAMs	CXCL1/EGF	Dual immune cell regulation	[47]
Original Research	MALAT1–STAT3 axis	Tumor Cells	MALAT1, STAT3	Enhances OSCC development	[48]

Table 2. Summary of studies included in the meta-analysis (n = 8).

Sample Size	Effect Size (HR/OR/FC)	TME Component	Target Gene(s)/Markers	Outcome	References
1200	HR = 2.10 (95% CI 1.65–2.67)	T cells, macrophages	PD-L1, PD-1	Poor survival with high PD-L1 expression	[49]
1000	OR = 1.85 (95% CI 1.40–2.30)	Immune Cells	CD3+, CD8+ infiltration	T-cell density as survival marker	[50]
300	FC = 3.4	Macrophages	Circ-ILF2, eIF5A	Promotes cisplatin resistance, M2 macrophage polarization	[51]
350	OR = 2.9	Hypoxic TME	HIF-1α, VEGFA	Angiogenesis and poor survival	[52]
400	HR = 1.80	T cells	PD-1/PD-L1 Axis	Immune evasion and therapy response	[53]
500	OR = 1.75	CAFs	CAF density, α-SMA	CAF density correlated with recurrence	[54]
800	OR = 2.20	Systemic immune response	Neutrophil-to-lymphocyte ratio	Predicts poor overall survival	[55]
600	HR = 2.00	Tumor tissue	miRNA profile (e.g., miR-21, miR-31)	Prognostic role of miRNA in TSCC	[56]

2.4. Quality Assessment

The quality of methodological aspects of the included studies was assessed systematically by the Newcastle–Ottawa scale (NOS) which is a scale created specifically to appraise observational studies. All studies were selected, compared, and determined for inclusion or exclusion by 2 independent reviewers (MA and NT) according to the NOS domains. Ranking then followed, with the studies rated as high, moderate, or low quality based on the number of stars awarded, as a result of disagreements resolved by consensus.

2.5. Data Synthesis

A qualitative assessment was performed due to the study design and outcome variability. The fundamental principles and molecular mechanisms of gene regulation in the oral cancer tumor microenvironment have been identified and constructed. Findings are shown in Table 1 where relevant to enhance clarity.

3. Result

3.1. General Information

The published articles numbered 52 and spanned the years 2016–2025. The number of articles published per year has fluctuated significantly over the years. The majority of the articles were published in 2024, and the highest number of articles in a single year was 12. The following 2020 (eight articles) and 2018, 2022, and 2023 (seven articles) years are notable, as they appear to have a more active research activity. Two published articles were in 2016 and 2017 and increased to its highest point of six in 2018. Nonetheless, over the years, the number of articles has steadily declined: three in 2019, and then a slight increase to six in 2020. Significantly, the sole six articles were published in 2022, and 2023. This decrease was significant over the previous year, with four articles in 2025. This tendency suggests that studies on the topic have fluctuated, with significant peaks in 2018 and 2023 and an apparent increase in 2024, as shown in Figure 2.

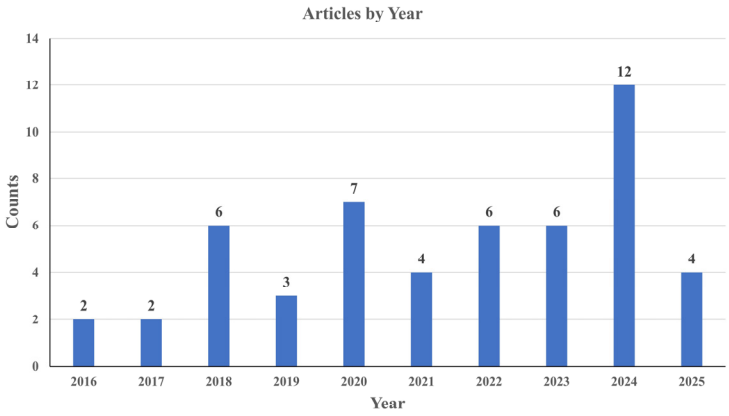

Figure 2. Number of publications on different cancers from 2016 to 2025.

3.2. Risk of Bias Assessment

In five major areas, namely, randomization process (D1), deviations of the intended interventions (D2), missing outcome data (D3), the measurement of the outcome (D4), and selection of the reported result (D5), the evaluation of risk of bias was undertaken in 52 studies (5 out of 52). Potential bias was also taken into consideration overall. The findings indicated that domains that exhibited a difference in methodological quality between the studies had a variation. The outcome of the bias created by the randomization process (D1) showed the highest outcome, as most of the studies (85–100) were rated as low risk, indicating that appropriate and well-described randomization strategies were applied. Only a very few (about 10 per cent) were high risk due to randomization processes that were inappropriate or vague. The more varied deviations that led to bias D2 were slightly over 40 per cent of the studies that were low risk. Comparatively, about 25–30% of them had certain reservations in the back of their minds, and up to 30–35% fell under the high-risk group, which indicates possible problems, such as non-adherence to the protocol or lack of blinding. Missing outcome data bias (D3) was also addressed reasonably well, with the majority (75–100) of studies receiving low-risk ratings, indicating low attrition and loss to follow-up. There were only a small percentage (about 25 per cent) of studies of a specific interest and a significantly smaller number of high-risk studies. Prejudice in the outcome measure (D4) was a concern. Approximately 30–35 per cent of the studies were of concern, and nearly 50–70 per cent were at high risk, mainly due to subjective outcome measures or inadequate blinding of the assessors. The proportion that was considered low risk was low in this area (approximately 15 per cent). Most of the studies (approximately 65–80) in which results were prespecified and selectively reported discriminated based on the chosen outcome (D5) (Figure 3). However, it was found that around 20–35% of the studies were deemed to be of high risk, which may be a sign of reporting bias. In a large part of the research, the possibility of bias was considered low, but it was judged to be high in a quarter of the studies. These studies had higher proportions of high-risk areas (more than one). The results above point to the overall high quality of the methodology of the studies included, yet are simultaneously premised on the studies lacking one specific aspect, i.e., intervention fidelity and outcomes measurement—one of the primary means of enhancing the internal validity of the upcoming research is to strengthen the validity of the areas under consideration as well.

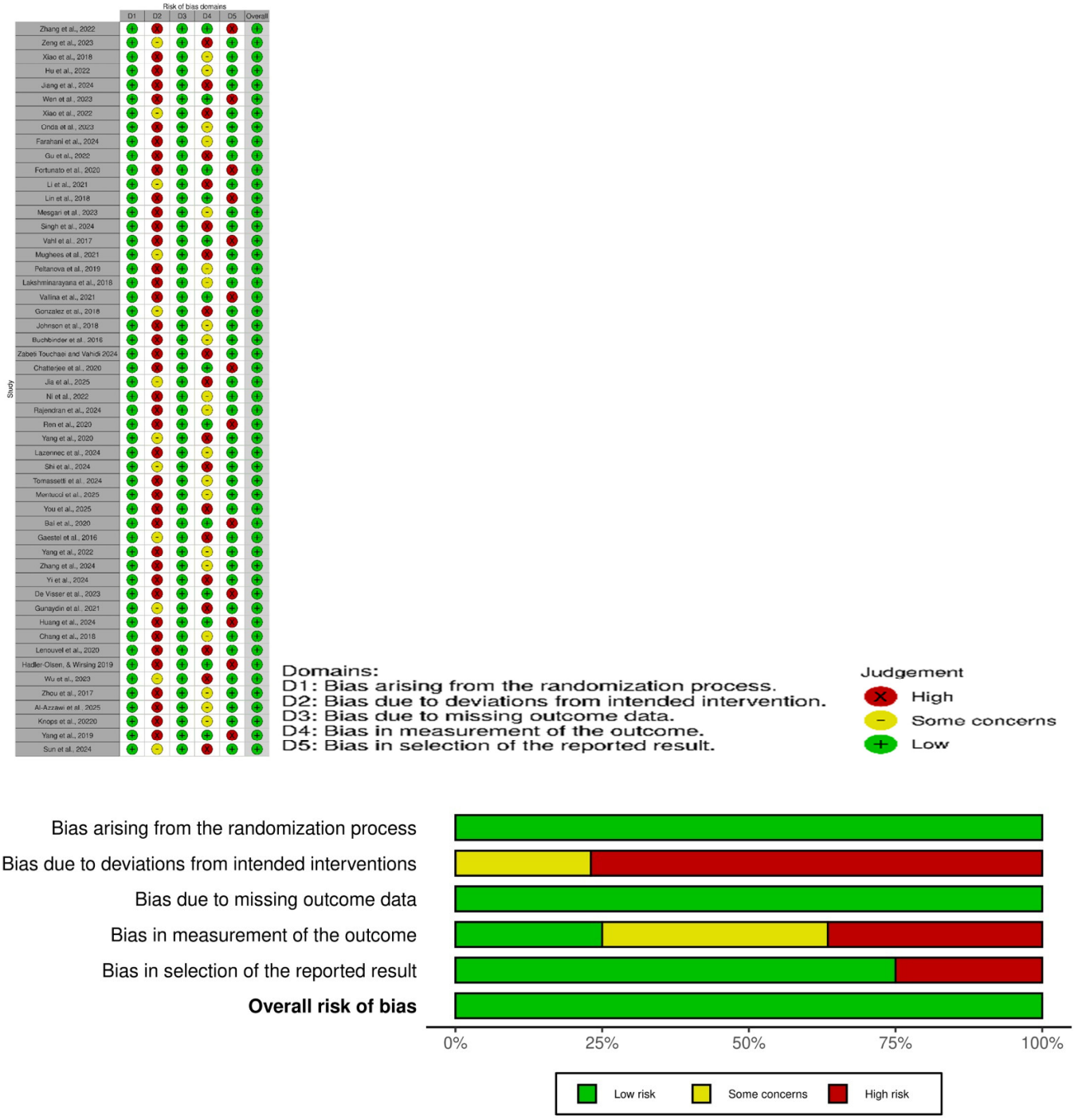

Figure 3. Risk of bias assessment using the Newcastle–Ottawa score. Risk-of-bias assessment for each study according to the NOS. Plots created using the risk-of-bias visualization, Cochrane RoB 2 (Version 2).

4. Discussion

In the case of OSCC, TME is an organized system of malignant and heterogeneous stromal and immune cells, such as cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), T lymphocytes, tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs) [4]. These cells are widely communicative by the activities of cytokines, chemokines, growth factors, and extracellular vesicles and metabolites that interactively promote tumor growth, invasion, angiogenesis, and immune-evasion gene expression programs. The ratio of immune effector cells (e.g.,

cytotoxic T lymphocytes) to immune inhibitory cells (e.g., regulatory T cells (Tregs) and M2-polarized TAMs) is predominant regarding tumor growth and patient outcome in the case of OSCC [57]. One of them is that the increase in tumor size can be caused by the release of substances by TAMs and the regulation of the invasion and metastasis-linked genes [46]. Likewise, CAFs mediate tumor behavior, including changes in gene expression, paracrine signaling by tumor cells, extracellular matrix remodeling, and immunosuppression.

4.1. TAMs and Their Gene Regulatory Roles

Tumor-associated macrophages (TAMs) are critical immune cells that comprise the OSCC tumor microenvironment, exhibiting functional plasticity and polarizing into either a pro-inflammatory M1 or pro-tumoral M2 phenotype. Recent research has shown that OSCC cells directly contribute to TAM polarization via multiple molecular mediators, thereby affecting tumor progression. Zeng et al. (2023) have demonstrated that eIF5Ahpu, which is expressed by OSCC cells, has a proliferative effect on M2 polarization of TAMs, which supports tumor growth as well as immune evasion [11]. Similarly, a circular RNA (Circ RNA) from an OSCC biopsy, Circ-ILF2, has been found to cause M2 macrophage polarization by activating immune system targets [58]. Other factors involved in M2 polarization such as SOAT1, which are under the control of ETS1 and HDAC6 in OSCC cells, also support M2 polarization through different signaling, such as AP-1/IL-13. A damage-associated molecular pattern molecule, HMGB1, has a dual role through IL-10/TGF-β and TLR4/NF-κB signaling pathways, which result in the opposite phenotypes, i.e., M2 and M1 polarization (seen to be a complex regulation of macrophage phenotypes in OSCC) [14].

Functionally, M2 tumor-associated macrophage infiltration induced by SPP1 overexpression is correlated with lymph node metastasis in head and neck cancers, including OSCC [59]. Lactate produced by OSCC cells induces M2 polarization, and this drives tumors [60]. Moreover, macrophage-secreted factors, such as IL-6, create positive feedback with tumor cells in promoting colony formation, migration, and xenograft growth through the IL-6/STAT3/THBS1 axis [12].

4.2. CAFs and Gene Expression Modulation

Cancer-associated fibroblasts (CAFs) constitute a significant portion of the stroma of OSCC and they engage in cancer progression by remodeling the extracellular matrix (ECM) and regulating the expression of genes of cancer and immune cells by the matrix cell. Growth factors, cytokines, and extracellular vesicles released by CAFs regulate various signaling pathways [61]. Research shows that CAFs express more genes encoding TGF-β, fibroblast activation protein (FAP), and chemokines that attract immunosuppressive cells, thereby establishing a pro-tumoral microenvironment (micromilieu). For example, CAF exosomal miRNAs are associated with epithelial-to-mesenchymal transition (EMT) in OSCC cells, which stimulate invasion and metastasis [40]. The crosstalk between CAFs and OSCC cells involves complex gene regulatory loops that contribute to the persistent maintenance and resistance to therapy of cancer.

4.3. Role of T Lymphocytes and Immune Checkpoint Gene Regulation

The cytotoxic T cells (CD8+ T cells) and regulatory T cells (Tregs) T lymphocytes are involved in the immune response development of the OSCC microenvironment. The traffic of effector and suppressive T-cell groups is one of the factors that influence the course and prognosis of the patient [26]. PD-1 and CTLA-4, as well as their ligands PD-L1/PD-L2, are also significant genes in immune escape in OSCC. Via the JAK2/STAT3 signaling pathway that contributes to immunosuppression, the OSCC cells express granulocyte–macrophage colony-stimulating factor (GM-CSF) which increases the expression of PD-L1 in TAM [28]. These checkpoint genes are highly expressed and are associated with poor clinical outcomes

and resistance to immunotherapy. The non-coding RNAs also contribute to the expression and activity of T-cell genes. MicroRNAs in the regulation of the expression of checkpoint genes is one more example of immune regulation that can be utilized both as a biomarker and therapeutic target [29].

4.4. Cytokine-Mediated Gene Regulation and Signaling Pathways

Cytokines and chemokines are also essential components of cell–cell communication in the OSCC tumor microenvironment, and they control gene expression programs that govern inflammation, angiogenesis, and immune cell recruitment. Cytokines control genes and abnormally regulate key signaling pathways in OSCC, such as the JAK/STAT, NF-KB, and MAPK [32]. Indicatively, TAMs release IL-6 that prompts tumor cells to proliferate, survive, and invade by regulating the development of an extended signaling pathway, known as the JAK-STAT pathway [27]. Indicatively, a study has shown that IL-6 is increased in OSCC tissues and that IL-6 enhances tumor growth and progression by activating a signaling pathway between JAK2/STAT3, which subsequently regulates other downstream genes, including Sox4. The authors also showed that the addition of pathway inhibitors inhibits tumor growth, and that the IL-6/JAK/STAT3 pathway is a vital pathogenic pathway in OSCC [15]. On the same note, tumor-secreted HMGB1 causes the amplification of the activation of the pro-inflammatory NF-kB pathway in the macrophages to facilitate tumor progression [13].

4.5. Epigenetic Regulation and Non-Coding RNAs

The OSCC tumor microenvironment is regulated by epigenetic processes, including DNA methylation, histone modifications, and non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Aberrant methylation of tumor suppressor genes and the miRNAs have been reported to influence the involvement of the immune response and interaction with the stromal environment in OSCC tissues. One of them is miR-21 and miR-155, which are upregulated in TAMs and promote M2 polarization in order to increase tumor-promoting functions [13]. Exosomal miRNAs of CAF also participate in the gene expression alterations of tumor invasion and metastasis [40].

4.6. Myeloid-Derived Suppressor Cells (MDSCs)

To report a new example, myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that exert significant immunosuppressive effects in the OSCC microenvironment. MDSCs inhibit T cells and natural killer (NK) cell capacities that lead to the inhibition of anti-tumor immunity, and facilitation of tumor growth [20]. These signaling events include the release of immunosuppressive cytokines, including IL-10 and TGF-β, the production of reactive oxygen species (ROS), and the depletion of the T cell of essential amino acids that support T-cell functions. According to a number of recent findings, a high degree of MDSC correlates with the latter tumor stage and poor prognosis of the OSCC patient [62]. Other chemokines released by tumors include VEGF and GM-CSF that contribute to the maintenance of MDSCs in the tumor microenvironment. Gene expression studies are found to be upregulated during the differentiation of MDSCs and their functional activity and in this way, play a significant part in remodeling the OSCC microenvironment to an immunosuppressive one.

4.7. Tumor-Associated Neutrophils (TANs) and Their Gene Regulatory Impact

It can also be characterized by tumor-associated neutrophils (TANs), which are of increased significance in the pathogenesis of OSCC progression. The TANs may adopt an anti-tumor (N1) or pro-tumor (N2) phenotype depending on the information provided by microenvironmental cues. N2 TANs prevail in the case of OSCC and promote tumor

growth, angiogenesis, and metastasis2. Gene expression profiling of TANs in OSCC has demonstrated a higher concentration of pro-inflammatory cytokines (e.g., IL-8), matrix remodeling enzyme (e.g., MMP-9), and angiogenesis-promoting factors (e.g., vascular endothelial growth factor [VEGF]) [63]. For example, it was shown that neutrophils infiltrate OSCC tissues and stimulate tumor migration and invasion, as well as the epithelial–mesenchymal transition (EMT), via the JAK2/STAT3 pathway induced by Chemerin. It also determines the pro-tumoral (N2-like) type of TANs that also contribute to the development of OSCC [4]. TANs also communicate with other immunological cells and stroma elements to control gene regulatory networks in an attempt to permit tumor penetration and evasion of the immune system.

4.8. Oral Cancer Stem Cells (OCSCs) and Their Role in Gene Regulation

Oral cancer stem cells (OCSCs) are a part of the tumor that have abilities of self-renewal and differentiation with the implication of tumor initiation, metastasis, and therapy resistance. OCSCs residing within specific niches of the tumor microenvironment interact with stromal cells and immunomodulatory cells. Gene expression research has discovered that OCSCs are born with unique regulator profiles: he upregulation of stemness-associated genes (Eg SOX2, OCT4), resistance genes to therapy, and genes associated with epithelial–mesenchymal transition (EMT) [25]. The TME exerts its effect on OCSC behavior through cytokine and growth factor secretion, which it induces and that boosts tumor aggressiveness by modulating these gene networks.

4.9. Molecular Signaling Pathways and Gene Regulation

Several oncogenic signaling pathways are typically maladjusted in OSCC, which contribute to maladjusted gene expression patterns in the tumor microenvironment and tumor progression. These include, among others, the epidermal growth factor receptor (EGFR) signaling pathway, which is often overexpressed or mutated in OSCC and mediates increased proliferation, survival, and resistance to therapy. Activation of epidermal growth factor receptor (EGFR) initiates the downstream signaling pathways, which include one of the most important, the autophagy-mediated pathway referred to as the mitogen-activated protein kinase. PI3K/AKT/mTOR and (MAPK) pathways are involved in the control of growth, metabolism, and apoptosis of cells [64].

The Wnt/β-catenin signaling pathway, which controls the expression of genes involved in cell adhesion and motility, is another key regulator of OSCC, where abnormal activation promotes epithelial–mesenchymal transition (EMT), invasion, and metastasis [41]. It has been correlated that improperly regulated Wnt signaling correlates with an unfavorable prognosis and aggressiveness of OSCC tumors. It is essential that the JAK/STAT signaling pathway, which is mediated by cytokines, plays a role in regulating immune and tumor development within the OSCC microenvironment as shown in Figure 4. Such is the nuclear protein kinase, abbreviated as STAT3 by the tumor cells and triggered by the IL-6 of the macrophages of the tumor, leading to the expression of genes promoting cell growth, cell survival, and evasion of the immune system [27]. The effect of JAK/STAT signaling on tumor progression and resistance to chemotherapy was aberrant. The PI3K/AKT/mTOR pathway is generally disrupted in OSCC and has been shown to significantly contribute to several crucial cell processes, including metabolism, cell growth, and survival. The components of this pathway contribute an oncogenesis and treatment resistance through mutations or overexpression of one or more components 33. The pathogenesis of OSCC also involves the NOTCH and MAP kinase signaling pathways, which regulate cell differentiation, proliferation, and apoptosis. The survival and proliferation of cells in response to COX activation by the MAP kinase pathway and the presence of

an aberrant signaling of the NOTCH protein in response to COX activation have been proposed to sustain the populations of the cancer stem cells and tumor aggressiveness [42].

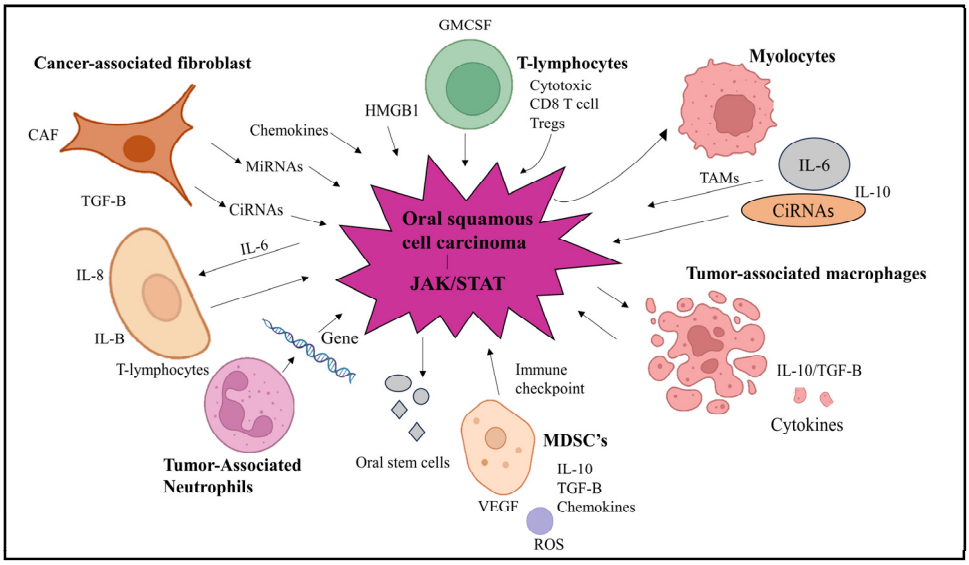

Figure 4. Schematic representation of gene regulation within the tumor microenvironment (TME) of oral squamous cell carcinoma (OSCC). The diagram illustrates the interactions between key cellular components, including tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), T lymphocytes, myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils (TANs). These components regulate tumor progression through major signaling pathways such as JAK/STAT, PI3K/AKT/mTOR, NF-κB, and Wnt/β-catenin. Cytokines, chemokines, and non-coding RNAs (e.g., miRNAs and lncRNAs) mediate intercellular communication, contributing to immune evasion, angiogenesis, metastasis, and therapeutic resistance in OSCC.

4.10. Therapeutic Perspectives

TME in OSCC is a very complicated as well as dynamic system which plays a vital role in tumor evolution, metastasis, and tumor reaction to treatment. One of the most crucial components of other cells in the TME is the ability to target gene activity; hence, the ability to regulate these molecular pathways offers a positive perspective for therapeutic intervention. Greater contributions to this are found in current advances that seek to harness the potential of immunomodulatory therapy capable of retraining tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) to help develop their immunosuppressive environment [20]. This has already been demonstrated with the assistance of such strategies as blockade of colony-stimulating factor 1 receptor (CSF1R) signaling as a way of reducing TAM infiltration and also repositioning the macrophage to an anti-tumor phenotype [38]. In the same way, the activity of the chemokine receptor, such as CXCR2, can be suppressed, and this will prevent the reaction of MDSCs, which will lead to a positive response to anti-tumor immunity [36].

Immune checkpoint blockers targeting PD-1/PD-L1 and CTLA-4 have proven to be a viable intervention in OSCC, particularly when many PD-L1-positive cells are found in the TME [65]. Still, it remains a challenge to utilize mediators of resistance through the signaling pathways of cytokines, such as the JAK/STAT and NF-κB. Small-molecule inhibitors of these pathways, such as JAK inhibitors and NF-κB modulators, are now being evaluated in clinical trials and improve clinical outcomes [66]. In addition, modulation of TAM polarization from a pro-tumoral (M2) to an anti-tumoral (M1) phenotype represents a novel immunotherapeutic approach.

Epigenetic therapies may also be a possible intervention in the specific case of OSCC TME, since aberrant histone modifications and DNA methylation induce them and result in

uncontrolled gene expression. Histone deacetylase and DNA methyltransferase inhibitors have been shown to reproduce epigenetic silencing of tumor suppressor genes and to control immune-regulatory gene expression, and they may sensitize tumors to immunotherapy [10]. Moreover, a cancer-related fibroblast (CAFs) and their secretory attack approach can disrupt the supportive stromal network. Inhibitions of tumor–stroma crosstalk are becoming targets of strategies such as fibroblast activation protein (FAP) inhibitors and inhibition of CAF-exosomal signaling [31]. Because gene regulation is complicated in the OSCC microenvironment, combination therapies that use an integrated approach to the simultaneous action of immune cells, signaling pathways, and stromal factors are anticipated to be necessary to overcome tumor heterogeneity and the problem of therapeutic resistance. In the future, it will be imperative to implement multi-omics profiling alongside functional studies to identify new targets and optimize individualized treatment methods. Moreover, ongoing clinical investigations are evaluating small-molecule inhibitors, monoclonal antibodies, and combination regimens that simultaneously target tumor cells and the surrounding microenvironment. Such integrated therapeutic strategies are expected to overcome tumor heterogeneity, reduce therapeutic resistance, and ultimately improve overall survival outcomes in patients with OSCC.

5. Conclusions

The TME in OSCC is a complex of different cells, namely tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils, cancer-associated fibroblasts, T lymphocytes, and cancer stem cells, that form a complex and interact with each other to control tumor development and progression. These cells are communicated by the network of cytokines, chemokines, and signaling networks (JAK/STAT, EGFR, Wnt/β-catenin, PI3K/AKT/mTOR) that modulate the expression pattern of genes that are vital to tumor growth, immune evasion, metastasis, and therapy resistance. In addition, other relevant roles in the regulation of the expression of genes in the TME condition include tumor behavior and aggressiveness, as well as epigenetic alterations and non-coding RNAs. Although there has been substantial progress in studying these mechanisms, the intricate spatial and temporal interactions of gene regulation in the OSCC microenvironment remain poorly understood. Future studies that need to be conducted are research that combines multi-omics and single-cell methods, to answer the question of heterogeneity and functional status of TME constituents at a high-resolution level. The insights will be invaluable in the discovery of new biomarkers and therapeutic targets. And, lastly, in order to convert this accruing body of knowledge into viable clinical practices, one will be forced to institute those strategies that may best tune-in the TME and avoid the issue of tumor heterogeneity. Thus, with additional knowledge on gene regulation within the OSCC microenvironment, enormous prospects of optimizing patient outcomes via designing novel treatment procedures that are more personalized and effective are present.

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