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The Tumor Microenvironment of Oral Squamous Cell Carcinoma: Cellular Components and Their Therapeutic Targets

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Advances in genomic and molecular studies have provided new insights into the complex interactions among various components in the tumor microenvironment (TME) that contributes to cancer growth. Oral squamous cell carcinoma (OSCC), the most common subtype of oral cancer, is characterized by its aggressive local invasion, high recurrence rates, and resistance to conventional therapies. Several alterations in TME, such as hypoxia, acidic environment, and increased tissue stiffness, that were caused by tumor-associated altered mechanism of each of its components, further enchance the malignant properties in tumor cells. Despite these findings, no study to date has comprehensively compiled their effects within a single article, thereby limiting the development of integrative conceptual frameworks capable of generating new hypotheses for optimizing anticancer therapies, particularly in OSCC, that target TME components. This study examines the effects of various TME components, their reciprocal interactions, and their intercorrelation with cancer cells, as well as their collective influence on the dynamic interplay within. This study employed a narrative literature review design to identify relevant studies published between 2015 and 2025 in PubMed, Google Scholar, and ScienceDirect databases. Peer-reviewed international studies investigating specific microenvironmental components, associated molecular mechanisms, and therapeutic implications were included. The articles were categorized into two major sections: those addressing cellular components of the TME, followed by therapeutic targets associated with each component and their potential application as anticancer therapies. Coordinated interactions among cellular components, including tumor-associated macrophages, T lymphocytes, cancer-associated fibroblasts, and natural killer cells, together with non-cellular mediators such as extracellular vesicles, shape a highly dynamic tumor microenvironment in oral cancer that regulates tumor progression, immune responses, and therapeutic sensitivity. These findings underscore the need for personalized therapeutic strategies and the integration of TME-based biomarkers to improve precision and durability of OSCC treatment.

Keywords: *tumor microenvironment, oral cancer, cancer therapy*

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Introduction

Continuous advancement of genomic and molecular studies in the medical field progressively expanded our understanding of cancer progression and evolution. Initially, cancer development was primarily attributed to genetic alterations resulting from exposure to chemical carcinogens.[1,2] However, this paradigm has been challenged by numerous studies demonstrating that these alterations are also closely associated with immune responses occurring within the host.[3] Cancer cells are capable of proliferating through interactions with surrounding cells and further advancing and metastasizing via similar mechanisms, collectively known as intercellular communication. These findings have established the conceptual foundation for a growing research focus on the cancer cell ecosystem, referred to as the tumor microenvironment.[4]

The TME comprises cancer cells surrounded by diverse populations of non-malignant cells, all embedded within a remodeled and vascularized extracellular matrix. The extracellular matrix, endothelial cells, adipocytes, immune cells, fibroblasts, neuroendocrine cells, pericytes, and numerous signaling molecules within the TME interact dynamically during cancer initiation and progression.[5] Furthermore, cancer cells secrete growth factors and cytokines that recruit and reprogram stromal cells such as immune cells and fibroblasts as well as enzymes that degrade and reshape the TME architecture. These modifications generate a microenvironment conducive to cancer pathogenesis. Compared with normal tissues, the tumor milieu exhibits distinct features, including aberrant vascularization, hypoxia, acidic pH, impaired cell adhesion, and increased collagen stiffness.[6] Such insights have led to emerging therapeutic concepts aimed at reprogramming the TME toward a non-malignant phenotype (tumor reversion), thereby restoring tissue homeostasis and concurrently attenuating cancer progression.[7]

Oral cancer remains a significant global health concern, accounting for approximately 188,438 deaths in 2022 and contributing markedly to the worldwide cancer burden.[8] Oral squamous cell carcinoma (OSCC) represents the predominant subtype, responsible for the majority of these cases. Much of this mortality stems from late diagnosis, as patients often present only after experiencing severe pain and discomfort symptoms typically associated with advanced-stage disease. Conventional strategies that remain widely applied to date include surgical procedures, radiotherapy, and systemic therapy (chemotherapy). The curative effects of these three treatment modalities have not demonstrated significant outcomes, largely due to the emergence of therapeutic resistance and post-treatment adverse effects.[9,10] Although considerable progress has been made in developing novel therapeutic strategies, the overall five-year survival rate still falls below 50%.[11] The clinical management of oral cancer is further complicated by the distinct characteristics of the oral cavity, which harbors a uniquely dynamic TME in different individuals. This microenvironment, shaped by constant exposure to mechanical stress, microbial interactions, parafunctional habits, lifestyle, and inflammatory stimuli, fosters remarkable tumor heterogeneity and cellular plasticity features that enable cancer cells to adapt, evade therapy, and sustain malignant progression.[12,13]

Although many studies have examined individual cellular and molecular components of the TME, most have evaluated these factors separately. This fragmented approach has limited our understanding of how interactions among stromal, immune, and cancer cells collectively drive OSCC progression and affect therapeutic response. This review explores the TME as a dynamic and multifaceted system, examining both its overall structure and the specific contributions of its constituent elements to cancer progression. TME represent a promising therapeutic landscape, offering opportunities to eliminate malignant cells more effectively by targeting the ecosystem as a whole rather than focusing on isolated components. By narrowing the scope to oral cancers, this work highlights how targeting the TME may offer new opportunities for therapeutic intervention and improved clinical outcomes.

Cellular Components in OSCC TME: Tumor-Associated Macrophage (TAM) Elucidating Tumor Progression and Immune Modulation in OSCC

Macrophages represent the most abundant immune cell population within the TME and are closely associated with various processes that promote primary tumor growth, progression, and subsequent metastasis. Based on their functions and responses to polarizing stimuli, macrophage phenotypes are categorized as M0 (naïve), M1 (classical), and M2 (non-classical).[14,15] The M1 and M2 subtypes possess distinct surface markers, which define their divergent roles within the TME.[16] M1 macrophages are

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typically activated by pro-inflammatory signals mediated by T helper (Th)-1 cells, while M2 macrophages arise in response to anti-inflammatory cues and matrix-remodeling activity driven by Th-2 cells. Although this polarization varies across microenvironments and individuals, the TME of oral carcinoma is generally dominated by macrophages exhibiting the M2 phenotype.[17]

Complement C1q subcomponent-binding protein (C1QBP) has been identified as a key regulator in promoting the polarization of macrophages from the M1 to the M2 phenotype via the tumor necrosis factor receptor-associated factor (TRAF)–chemocine ligand 2 (CCL2) axis, thereby contributing to the malignant progression of oral cancer.[18] TAM play a central role in transforming the TME into an immunosuppressive state, thereby facilitating immune evasion in cancer cells, including those in oral malignancies. In particular, M2-polarized macrophages contribute to this process by suppressing the cytotoxic activity of T cells and sustaining the immunosuppressive milieu through the secretion of regulatory cytokines.[19]

Contrast to previous reports, the TME of oral leukoplakia creates a Th1-enriched milieu, which promotes the polarization of TAM toward an M1 phenotype through the expression of STAT1 in $CD163^+$ macrophages.[20] This could be explained by several studies proving cancer progression doesn't stand solely on higher level of M2, rather the imbalance of both phenotype in the TME. Moreover, the pro-inflammatory effects M1 posseses could cause chronic inflammation in TME in which an ideal place for tumor to grow and invade.[21] Supporting this notion, polarized M1 macrophages have been show to drive OSCC metastasis by regulating EMT and maintaining cancer stem cell-like traits (CSCs) through IL6/Jak/Stat 3 signalling loop.[22]

TAM also play a vital role in the invasion of OSCC through through peritumoral interactions, as shown by findings that gingival connective tissue cells (GCTCs) enhance, whereas periodontal ligament cells (PDLCs) suppress M0 macrophage infiltration into TME.[23] Comparable effects have been observed in stromal cells of distinct subtypes, such as SCC-associated stromal cells and verrucous squamous cell carcinoma-associated stromal cells.[24]

The invasion and migration of squamous cell carcinoma (SCC) have been shown to increase in parallel with elevated expression of CD40 (an M1 macrophage marker), CD163 (an M2 macrophage marker), IL-1β, and TNF-α in macrophages. In the same study, treatment with melatonin was found to modulate the interaction between tumor-associated macrophages (TAMs) and SCC-15 tongue cancer cells, attenuating these effects through downregulation of related gene expression and modulation of the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF).[25] Communication between OSCC and macrophages is mediated by multiple genes within the TME. One study reported that HMGB1, which is highly expressed in tongue cancers, shows a positive correlation with macrophage infiltration and polarization. Targeting HMGB1 expression in macrophages reduced the growth of CAL-27 and SCC-25 cancer cells in a time-dependent manner, accompanied by decreased expression of MMP-9, p-p65, TLR4, and TGF-β.[26]

The interaction between TAMs and the TME that drives this condition is mediated by chemokines that promote the recruitment and differentiation of monocytes into macrophages.[27,28] This was demonstrated in a study where inhibition of eIF5Ahpu in oral squamous carcinoma cells using GC-7 suppressed M2 polarization and activation within the TME. GC-7 treatment decreased the expression of immunosuppressive molecules such as Arg1, IL-10, RELMα, PD-1, and PD-L1, while simultaneously increasing the expression of pro-inflammatory markers including CD86, TNF-α, CXCL9, CXCL10, IL-1β, and CCL5.[29] Moreover, CXCL2 was found to be upregulated during squamous cell carcinoma progression via activation of the NF-κB signaling pathway.[28] Therapeutic approaches targeting M2 macrophages have also been explored, such as the use of Prussian blue nanoparticles, which successfully reprogrammed M2 macrophages toward an M1-like phenotype. This shift was evidenced by decreased CD206 expression and increased CD86 expression, thereby disrupting TAM–TME communication in oral squamous carcinoma and subsequently suppressing tumor proliferation and migration.[30]

T Cells Drive Immune Modulation in OSCC

Lymphocyte infiltration into the TME represents a host immune response to tumors and consequently alters tumor cell biology. Among these lymphocytes, $CD8^+$ T cells function as key anti-tumor effectors, whereas regulatory $CD4^+$ T cells (Tregs) suppress the cytotoxic activity of these effector cells. The dynamic balance between these two subsets is crucial for immune evasion, anti-tumor immunity, and immune homeostasis. The presence of $CD8^+$ T cells

has been consistently associated with a more favorable clinical prognosis.[31] In contrast, Tregs play a critical role in regulating various immune responses, including antitumor immunity and immune escape, contributing to the establishment of an immunosuppressive TME and resulting in poorer cancer prognosis.[32]

A high density of $CD8^+$ T cells observed at the invasive front and peripheral stroma of primary OSCC specimens has been correlated with better overall, disease-specific, and recurrence-free survival, suggesting their potential role as an independent prognostic indicator.[33,34] It is associated with no lymph involvement and smaller tumor size, serving good prognosis in OSCC.[34,35]

A previous study reported a significant increase in Treg prevalence within the OSCC microenvironment, predominantly consisting of $CD4^+CD25^+$, $CD4^+FoxP3^+$, $CD8^+FoxP3^+$, and $CD4^+CD25^+FoxP3^+$ subtypes. This elevation shows a positive correlation with OSCC progression, where higher Treg levels were observed in advanced-stage cancers, lymph node involvement, and larger tumor sizes. The accumulation of Tregs masks the presence of pro-immune T cell subsets, thereby fostering an immunosuppressive milieu that enables cancer cells to evade immunosurveillance.[36] Conversely, another study reported that $CD4^+$ Tregs serve as immune biomarkers associated with favorable prognosis, showing a positive correlation with better clinical outcomes. The double-edged observation keeps the role of $CD8^+$ and $CD4^+$ T cells within the TME controversial, leading researchers to further investigate their interplay with other T cell subsets rather than considering them as a single, uniform population.[37,38] T cells are also able to communicate with TAM via the TME, as how both $CD4^+$ and $CD8^+$ T cells were observed in the intraepithelial lesions of moderate and severe dysplasia of leukoplakia an oral premalignant lesions samples. This communication goes bothway, as T-helper-1 cells produce IFN that induces M1 macrophages.[20]

$CD8^+$ T cells have long been the central focus of cancer immunotherapy, either through direct activation or indirect modulation.[31] Indirectly, these cells can be enhanced by inhibiting MED-1 expression in metastatic oral squamous carcinoma cell lines SCC-9 and UPCI-SCC-154. Suppression of MED-1 downregulates PD-L1 expression via the Notch signaling pathway, thereby inducing cytotoxic $CD8^+$ T-cell activity.[39] Additionally, inhibition of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) has been shown to increase the population of $CD8^+$ T cells in 4MOSC cells, producing an antitumor effect through the induction of pyroptosis.[40] In another study demonstrated that treatment with plumbagin restored T-cell proliferation after 96 hours of co-culture, accompanied by increased expression of pro-immunity cytokines such as Granzyme B and IFN-γ, and decreased levels of immunosuppressive cytokines including TGF-β and IL-10. This indirect enhancement of cytotoxic T-cell function effectively suppressed tongue cancer cell proliferation in vivo.[4]

Treg cells exhibit antagonistic effects on $CD8^+$ T cells by inhibiting the cytotoxic activity of T lymphocytes, natural killer cells, dendritic cells, and B cells. They attenuate antitumor immunity through the expression of co-receptors and immunosuppressive cytokines such as TGF-β, IL-10, and IL-35. The accumulation of Tregs within the TME contributes to the establishment of an immunosuppressive ecosystem that promotes tumor growth and invasion.[3] The interplay between Tregs and $CD8^+$ T cells poses a major challenge in cancer therapy, as both cell types share overlapping surface molecules, making it difficult to selectively target one without affecting the other. For instance, mogamulizumab an antibody designed to deplete Tregs was also found to reduce cytotoxic T-cell numbers, necessitating the use of trametinib as an adjuvant to prevent $CD8^+$ T-cell depletion.[21] In another study, Notch2 knockout in Tregs resulted in reduced Treg populations and a simultaneous increase in $CD8^+$T-cell numbers, leading to tumor pyroptosis and inhibition of OSCC growth.[41]

The antitumor activity of T cells in the TME is often impaired due to elevated expression of immune checkpoint molecules such as programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), lymphocyte activation gene 3 (LAG-3), and T-cell immunoglobulin mucin-3 (TIM-3). Among these, PD-1 plays a predominant role in mediating T-cell exhaustion.[42] Several immunotherapeutic agents have been developed for the treatment of oral cancers, including immune checkpoint inhibitors (ICIs). These agents function by blocking PD-1, which physiologically suppresses T-cell activation.[43] In cancer, this pathway is co-opted by tumor cells to evade immune surveillance. Thus, ICI therapy reactivates cytotoxic $CD8^+$ T cells, allowing effective tumor cell elimination. Pembrolizumab and nivolumab have also been utilized as immunotherapeutic agents for patients with recurrent disease.[44] Meanwhile, blockade of LAG-3 has been shown to significantly restore T-cell function, particularly through the modulation of IL-10 production. This cytokine exerts dual roles promoting immunosuppression within

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the TME while simultaneously enhancing $CD8^+$ T-cell activation and antitumor responses.[45]

Cancer-Associated Fibroblasts (CAF) Mediate Tumor Invasion and Immune Suppression

CAFs play a pivotal role in tumor initiation and progression through the secretion of various soluble factors, including growth factors, kinases, cytokines, and chemokines into the TME. One of the key mediators involved is lysyl oxidase (LOX), which promotes extracellular matrix (ECM) remodeling and stiffening, rendering the tissue more susceptible to cancer cell invasion. The increased stiffness of the ECM has been shown to promote oral cancer progression via activation of the focal adhesion kinase (FAK) signaling pathway.[46]

CAF represent a heterogeneous cell population within the oral TME, typically characterized by the expression of alpha-smooth muscle actin (α-SMA). In tongue cancer specimens, the predominant phenotype observed is $CD86^+$/$\alpha\text{-SMA}^+$, whose higher density has been associated with increased cancer recurrence and poorer survival outcomes.[47] CAFs may originate from gingival fibroblasts that undergo phenotypic transformation within the TME shaped by oral squamous cell carcinoma. This transformation is marked by elevated expression of α-SMA and vimentin, which subsequently facilitates epithelial–mesenchymal transition (EMT).[48]

The multidirectional communication within the OSCC TME components was stated in previous study that showed CAF goes in hand with TAM (by polarizing M2 macrophages) to establish an immunosuppresive TME that poses a major obstacleto effective cancer therapy. Supporting this, elevated CAF levels have also been shown to suppress T cell proliferation by producing immunosuppresive cytokines such as TGF-β, IL-10, and arginase I.[49,50] Furthermore, CAF activation contributing to cancer cell progression has been described in another study, primarily mediated through IL-6 signaling.[51]

In a cohort study of patients with OSCC, elevated expression of epiregulin (EREG) was observed and was linked to the transformation of normal fibroblasts into CAFs through activation of the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2–STAT3) pathway. CAFs are commonly characterized by the expression of several markers, including α-smooth muscle actin (α-SMA), vimentin, and N-cadherin.[1] Several experimental studies have explored therapeutic strategies targeting CAFs. Previous study reported that subcutaneous administration of carbon dioxide reduced intratumoral hypoxia, suppressed the expression of CAF markers (α-SMA and fibroblast activation protein/FAP), and modulated communication between HSC-3 tongue cancer cells and stromal cells.[52]

Natural Killers (NK) Regulate Antitumor Immunity

CAFs Natural killer (NK) cells are lymphoid cells derived from the bone marrow and secondary lymphoid organs such as the spleen, tonsils, and lymph nodes. These cells function in both innate and adaptive immune responses without undergoing receptor recombination, allowing them to recognize and eliminate abnormal or infected cells in an antigen-independent manner. NK cells play a central role in the elimination of virus-infected and pathologically transformed cells, making them a promising target for immunomodulatory therapies, including cancer immunotherapy.[53]

The presence of natural killer (NK) cells within tumor tissues is indicated by a high abundance of the CD57 marker, including in oral squamous cell carcinoma (OSCC) specimens. Increased NK cell infiltration has been shown to correlate with improved patient survival, underscoring their critical role in tumor cell eradication.[54] NK cells participate in both innate and adaptive immune responses through cytokine secretion and direct cell–cell interactions with dendritic cells.[55] Furthermore, evidence suggests that tumor cells capable of evading cytotoxic T lymphocyte–mediated immune responses remain susceptible to recognition and subsequent elimination by NK cells, thereby reinforcing the considerable therapeutic potential of NK cells in cancer treatment strategies.[54]

Metformin has emerged as a potential therapeutic agent for oral cancer by restoring the impaired NK cell function of tongue cancer cell line commonly observed in cancer patients. This effect is mediated through activation of phosphorylated STAT1 (pSTAT1) by metformin via the NF-κB signaling pathway, regulated by the cytokine CXCL1. Blocking the CXCL1 receptor (CXCR2) reinstates NK cell cytotoxic activity against tumor cells.[56] Furthermore, combination therapy involving NK cells and cetuximab has demonstrated a significantly enhanced and synergistic antitumor effect compared to either treatment alone. This synergy is attributed to the ability of cetuximab to bind

epidermal growth factor receptor (EGFR) on tumor cells, thereby flagging them for destruction by NK cells.[57] In previous studies, NK cells were activated through co-culture with interleukin-2 (IL-2) derived from peripheral blood, osteoclasts, and probiotic bacteria to enhance cytokine secretion that promotes NK cell survival and exerts anticancer effects in both in vitro and in vivo models.[58]

Non-Cellular Components in Oral OSCC TME Extracellular Vesicles (EVs) Shape TME Intercorrelation

EVs are lipid bilayer-enclosed particles secreted by almost all cell types. Based on their biogenesis, EVs are classified into three major categories: exosomes, microvesicles, and apoptotic bodies.[59] EVs contain a wide range of bioactive molecules, including cell-derived DNA, mRNA, microRNAs (miRNAs), other nucleic acids, proteins, and lipids. Both cancer-derived and non-cancer-derived EVs interact with other components of the TME, influencing cancer progression and therapeutic response by serving as mediators of intercellular communication that deliver molecular "messages" in the form of proteins or RNAs.[60] Because the cargo carried by EVs often reflects the molecular signature of their cells of origin, this section emphasizes the role of EVs as carriers of biological information within the TME.

The cellular components originating from within the TME actively shape tumor progression through intricate intercellular interactions, often mediated by exosomal secretion. Among them, CAFs exemplify this mechanism by releasing miR-34a-5p, which carries regulatory signals that influence the proliferation and motility of OSCC cells through the protein kinase B/glycogen synthase kinase-3 beta/beta-catenin/zinc finger protein SNAI1 (AKT/GSK-3β/β-catenin/Snail) signaling cascade.[61]

In non-cancer-derived exosomes, overexpression of hypoxia-inducible factor-1α (HIF-1α) a master regulator of cellular response to hypoxia was shown to induce miRNA-5100 expression in tongue cancer cells. This information was then transferred to both local and distant stromal cells via exosomes.[42] Another study revealed that miRNA-134, delivered by EVs derived from cancer stem cells, induced M2 macrophage polarization, thereby promoting pro-tumorigenic activity. Moreover, the same miRNA inhibited $CD4^+$ T-cell proliferation and IFN-γ production both in vitro and in vivo through the PI3K/AKT signaling pathway, contributing to an immunosuppressive TME.[62] Additional miRNAs implicated in oral tumorigenesis include miR-1307-5p63, miR-21064, miR-146a65, miR-125b, miR-17-5p, miR-200b-3p, and miR-23a-3p.66 their reports have shown that EVs contribute to metastasis in HSC-4 and SAS oral cancer cell lines through their interaction with transforming growth factor-β (TGF-β).[67]

Tumor-derived exosomes (TDEs) are particularly important in driving ECM remodeling, angiogenesis, drug resistance, invasion, and metastasis within the TME by delivering a variety of proteins, mRNAs, and miRNAs.68 TDEs can induce epithelial mesenchymal transition (EMT) in neighboring normal cells marked by increased vimentin expression and a spindle-like morphology via epidermal growth factor (EGF) secreted by oral squamous carcinoma cells. This transition enhances tumor invasiveness and metastatic potential, making it an attractive therapeutic target. Notably, the same study demonstrated that cetuximab, an anti-EGFR monoclonal antibody, inhibited this EMT process, underscoring the value of exosome-based research in elucidating tumorigenic mechanisms and identifying therapeutic interventions.[69]

The evidence above has spurred increasing interest in targeting EVs for cancer therapy. In oral cancer cell lines (SAS, HSC-3, and HSC-4) exhibiting elevated ATP7B expression, a marker associated with higher malignancy, treatment with the EV-secretion inhibitor GW4869 enhanced the antitumor efficacy of cisplatin by suppressing EV release and downregulating ATP7B expression.[70]

A recent study successfully encapsulated cisplatin within exosomes derived from chorionic mesenchymal stem cells for in vivo cervical cancer therapy, demonstrating a significant reduction in tumor growth compared to control groups.[71] This strategy presents a promising research avenue for oral cancer as well. It is important to note that targeting a single or limited number of components within the TME may not provide durable therapeutic outcomes due to the high heterogeneity observed across cancer types, and even among tumors of the same histological type in different individuals. Moreover, such targeted approaches may impose substantial economic burdens. Future research should aim to design therapeutic strategies that simultaneously target multiple components or ideally, the entire landscape of the TME using the minimal number of therapeutic agents necessary to achieve maximal efficacy.

TME in oral cancer is a complex ecosystem where distinct cellular and non-cellular components independently

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and collectively drive malignant progression and therapeutic resistance. TAMs, predominantly of the M2 phenotype, establish an immunosuppressive milieu and promote invasion through peritumoral interactions and cytokine signaling. Concurrent with this, the balance of T lymphocytes specifically the interplay between cytotoxic $CD8^+$ T cells and regulatory Tregs dictates the host's anti-tumor response and clinical prognosis. Structural and metabolic shifts are further driven by CAFs, which facilitate epithelial–mesenchymal transition (EMT) and extracellular matrix remodeling through increased tissue stiffness. While natural killer (NK) cells offer a promising avenue for tumor cell eradication, their function is often impaired within the OSCC landscape. Integrating these cellular dynamics, extracellular vesicles (EVs) act as vital mediators of intercellular communication, utilizing bioactive cargo like miRNAs to reprogram the TME and facilitate metastasis (Table 1). In summary, OSCC orchestrated reciprocal interactions with its surrounding stromal and immune components through tumor-driven signaling (red arrows). TAM, particularly through M2 activation, are recruited via mediators (CCL2 and HMGB1), further increasing immunosuppressive and pro-tumorigenic activities. Concurrently, CAFs contributed to ECM remodeling and increased tissue stiffness, hypoxia, acidic pH, and metabolic reprogramming. The said conditions enhanced tumor activation, invasion, and progression. CD8+ T and NK cells exerted antitumor effects (blue arrows), but their activity is supressed by regulatory T cells and other inhibitory signals in the TME. At the same time, the transfer of microRNAs from EV (gray arrows) supported the intercorrelation between each components found in OSCC TME (Figure 1).

A key limitation of this article lies in the inherent complexity and heterogeneity of the oral cavity tumor microenvironment. In vivo, multiple biological, mechanical, and environmental factors such as microbial dysbiosis, inflammatory signaling, immune cell infiltration, mechanical stress, parafunctional habits, and lifestyle-related exposures occur simultaneously and dynamically within the oral cavity. Consequently, therapeutic strategies targeting a single component of the TME may elicit variable or unintended responses from other interacting components, complicating the prediction of treatment outcomes. Moreover, the oral cavity is highly individualized across patients, with substantial inter-individual variability in microbiota composition, immune landscape, and local tissue responses. This personalized nature of the oral TME limits the generalizability of findings derived from simplified experimental models or cohort-level analyses. Therefore, further studies incorporating patient-specific profiling and integrative multi-component approaches are required to better translate TME-targeted therapies into effective and predictable clinical interventions.

Table 1. Key components of the TME in oral cancer.

Component	Subtype / Key Markers	Effect on TME	Targeted Pathways / Mechanisms	Established Antitumor Evidence
Tumor-associated macrophages (TAM)	M1 (CD86, CD40); M2 (CD163, CD206)	Promotes tumor growth, invasion, and immunosupression	TRAF-CCL2 axis; IL-6/Jak/Stat 3 signaling; NF-κB pathway	Prussian blue nanoparticles reprogram M2 to M1; GC-7 suppresses M2 activation
T lymphocytes	CD8+ (cytotoxic); CD4+FoxP3+ (Tregs)	CD8+ cells act as anti-tumor effectors; Tregs mask pro-immune subsets	PD-1/PD-L1; CTLA-4; Notch signaling; LAG-3	Pembrolizumab/ Nivolumab block PD-1; plumbagin restores T-cell proliferation
Cancer-associated fibroblasts (CAF)	α-SMA, vimentin, N-cadherin, FAP	Drives ECM remodelling, tissue stiffening, and EMT	FAK signaling; JAK2-STAT3 pathway; IL-6 signaling	Subcutaneous CO2 suppresses CAF markers; notch 2 knockout reduces Treg-related growth
Natural killer (NK) cells	CD57	Recognizes and eliminates abnormal or infected cells	pSTAT1 activation; CXCL1/CXCR2; EGFR binding	Metformin restores NK function; cetuximab synergy flags tumor cells for destruction
Extracellular vesicles (EVs)	Exosomes, microvesicles, apoptotic bodies	Mediates intercellular communication; drives drug resistance	AKT/ GSK-3β/ β-catenin/ snail; PI3K/ AKT signaling	GW4869 enhances cisplatin efficacy; exosome-encapsulated cisplatin reduces tumor growth

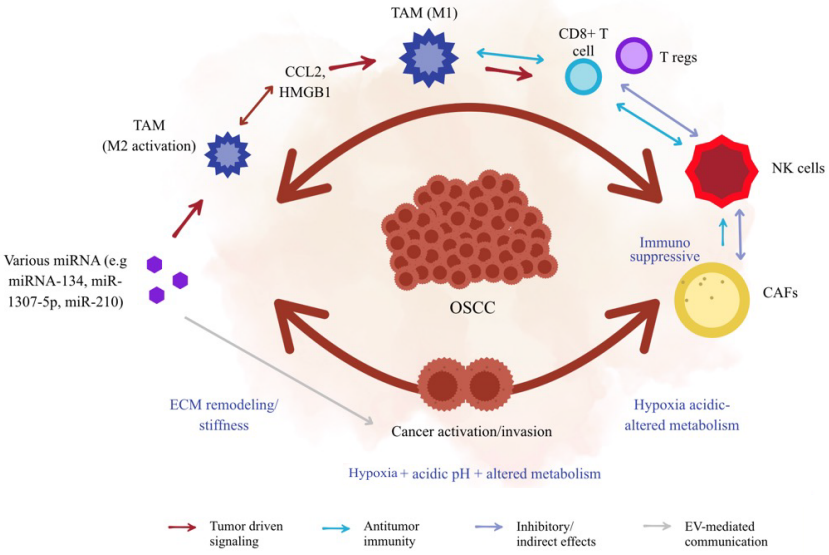

Figure 1. Intercorrelation between OSCC and TME components.

Conclusion

The tumor microenvironment represents a complex ecosystem composed of diverse cellular and non-cellular components that dynamically interact through multiple mechanisms, including signaling pathways, paracrine secretion, and autocrine feedback. This multidirectional communication among components not only drives tumor development and progression but also provides potential therapeutic targets. Accordingly, the TME is considered a broad and integrated biological landscape that can be comprehensively targeted to regulate and improve cancer therapies. Shifting the therapeutic paradigm toward an integrative framework that simultaneously targets these multifaceted interactions rather than isolated components is essential for enhancing the precision and durability of oral cancer treatments.

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Authors' Contributions

NT and FS were involved in concepting the topic of the manuscript, NT and FS prepared the manuscript draft, NT and MIR designed the figures and tables. All authors took parts in giving critical revision of the manuscript.

Ethical Statement

This article is based exclusively on the review and analysis of previously published literature. No primary data were collected, and no human participants, human biological materials, or animals were involved in this study. Therefore, ethical approval from an institutional review board or ethics committee was not required.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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