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REVIEW

Stromal Control of Macrophage Dysfunction in Oral Squamous Cell Carcinoma: Mechanistic Barriers and Therapeutic Strategies for Durable Immune Reprogramming

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Abstract

Objective: Oral squamous cell carcinoma (OSCC) is characterized by a highly complex and immunosuppressive tumor microenvironment (TME) that significantly limits the efficacy and durability of immune-based therapies. Among immune populations, tumor-associated macrophages (TAMs) represent a dominant and functionally plastic cell type that critically influences tumor progression, therapeutic resistance, and immune escape. While macrophage reprogramming toward an anti-tumor (M1-like) phenotype has emerged as a promising therapeutic strategy, durable immunoreprogramming in OSCC remains elusive. Increasing evidence suggests that stromal components of the TME play a decisive role in enforcing macrophage dysfunction and constraining sustained phenotypic conversion. **Methods:** This review synthesizes current mechanistic insights into how stromal enforcement shapes macrophage dysfunction in OSCC and identifies key barriers to achieving durable immune reprogramming. **Results:** Metabolic constraints imposed by the stromal milieu further compromise macrophage functionality. Hypoxia-induced HIF-1α stabilization and lactate accumulation drive epigenetic and metabolic reprogramming of TAMs, favoring oxidative phosphorylation and fatty acid metabolism associated with immune suppression. Acidic pH and nutrient deprivation blunt macrophage responsiveness to immunomodulatory agents, limiting the durability of therapeutic reprogramming. In addition, abnormal vasculature and stromal barriers reduce effective drug delivery, leading to heterogeneous and transient macrophage modulation. We highlight the dynamic crosstalk between stromal cells, ECM architecture, and metabolic stressors that collectively undermine sustained macrophage re-education. **Conclusion:** Furthermore, we discuss emerging therapeutic strategies aimed at overcoming these barriers, including stromal normalization, metabolic rewiring, epigenetic modulation, and nanotechnology-enabled targeted delivery systems.

Keywords: Cancer- Human- Health- Illness- Medicine- Oral Squamous Cell Carcinoma (OSCC)

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Introduction

The oral cancer therapy becomes challengeable even after intense research due to chemo resistance, immune escaping and reprogramming of the existing cancer cells at the point of therapy [1]. The immunosuppressive tumor microenvironment (TME) extensively limits the antitumor surveillance by means of different ways including improper cytokine signalling, stromal reprogramming and induced metabolic stress. Tumor-associated macrophages, cancer-associated fibroblasts, and aberrant vasculature collectively promote immune escape, enabling sustained tumor growth, invasion, and resistance to treatment. This complex immunometabolic landscape not only limits the effectiveness of conventional therapies but also undermines emerging immunotherapeutic strategies,

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underscoring the urgent need for approaches that restore immune competence while targeting tumor-supportive stromal networks [2-6].

The reprogramming plays a vital role on determination further the fate of the therapeutic regimes. Rather than uniformity, Oral Squamous Cell Carcinoma (OSCC) is comprised of multiple niches, i.e., patterned by the location, nutrients and availability of oxygen. In further they are limited by composition of stromal cells locally, ECM properties, and cancer signalling clues [1]. These oral tumor niches are a unique microenvironment characterised by its own spatial and functional aspects within the OSCC that play as an executioner of specific biological functions between the cancer cells, fibroblasts, vasculatures and immune cells, extracellular matrix (ECM), endothelial cells, soluble mediators, and a unique oral micro-biome for serving the tumor proliferation, tumor angiogenesis and invasion. As the tumor progress, the "tumor-friendly" niches also tend to increase and becomes complex in nature due to converted signalling mechanisms from the oral cancer cells [2, 3]. The larger tumor produces compartmentalized and functional niches characterized by hypoxia, oxygenated peripheral; immune- inflamed and excluded locations, lesser-dense fibroblastic regions, and steeper and highly pronounced metabolic-gradient regions with lactates, lipids and glucose. This eventually results intense pro-angiogenic, immunosuppressive, metastatic and stem-cell niches within the tumor. Several studies showed that OSCC niches are spatially, mutational characterized by the individual host factors (i.e., immunity, systemic metabolism and reactivity of the stoma) of the patients [4-7].

Previously, the cancer therapeutics aimed primarily on the tumor cells and their intrinsic characters, viz., proliferative signalling, apoptosis, mutations and chemo-resistance. The intended research elaborated the knowledge on tumor microenvironment (TME) as a principal participant as it vitally roles on every aspects of the tumor cell' fate [8]. As described, the TME is a highly complex tumor eco- system and continually influenced by the microbial products, mechanical stress and chronic inflammatory signals. Further, it also anatomically varied with normal oral cavity by having characteristic immune suppression. Hence, the immune dysfunction plays a significant role on progression and the failure of the therapy on OSCC [1, 2, 9-14]. The OSCC tumors have distinguish exhibition by highly immune suppressed environment including the T- cell exhaustion, immune exclusive and suppressed myeloid cell populations. Since, this TME natures shifts continuously according to the OSCC signals, the recent studies showed that without focusing them, the immunotherapies and other related chemotherapeutic regimes could not achieve a rationale success over the OSCC (Table 1). Tumor Associated Macrophages (TAM) is one of the important cell types that profoundly influence the OSCC tumors at behaviour level. The plasticity of the macrophages, particularly, the TAM, made them to respond on switching their dynamic phenotypes to TME clues, as the key drivers for OSCC progression and chemo-resistance [10, 11, 15-18]. The emerging research literatures informed that failure of the therapeutic regimes not only by the macrophage plasticity, but also due to stromal constraint that enforce the immune tolerance at the TME level. Oral Cancer – Associated Fibroblasts (OCAFs) emerges as significant regulators on immunity of TME by modifying the metabolic, and biochemical mechanisms of the tumor cells. The regulation of the M1 (anti-tumor) to M2 (pro-tumor) phenotypes of the OCFs is very essential to integrate the therapeutic strategies for overcoming the tumor barriers [2, 10, 13, 15, 18-21].

Within, OSCC, the OCFs are The macrophages are the innate immune cells that have significant cell plasticity which switch them between two polarized stages called pro- inflammatory (M1- like) and tissue – repairing (M2- like) phenotypes. This macrophage polarization is more important as M1 adopts for pro inflammatory and anti- tumor phenotype, in which, M2 meant for pro- tumor activity [18]. Basically, M1 helps for pro- inflammatory responses, anti- tumor immunity and antigen representation. M2 usually promotes angiogenesis, tissue remodelling, and suppression of the immunity and progression of the tumors. Post, 2022, transcriptonomic studies revealed that OSCC harbours with different macrophage M1 and or M2 categories at TME level. This is highly regulated with the stromal, metabolic interactions, and spatial localizations. Later, it was revealed that the TME of OSCC seemed to be highly heterogeneity in nature and severely limits the successive of the therapeutic regimes by characterizing the polarization of the macrophages in favour of the OSCC (Figure 1). This review critically examines the role of OCAFs in enforcing macrophage dysfunction, with a focus on why M2 → M1 macrophage reprogramming remains unstable in OSCC and how integrated targeting strategies may overcome these barriers.

"State Continua" TAMs at OSCC TME

Based on the single- cell RNA- seq and spatio-transcriptomics on OSCC, the recent studies showed that

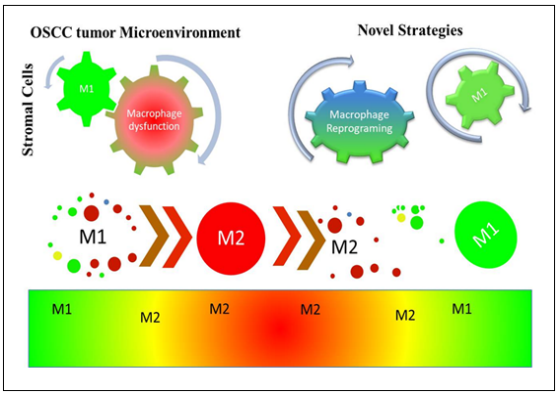

Figure 1. Spatial Reprogramming of Macrophage Polarization in OSCC). In OSCC, immunosuppressive M2 macrophages predominate in the tumor core, whereas pro-inflammatory M1 macrophages are enriched at the tumor periphery. Therapeutic strategies targeting M2-associated signaling and metabolic pathways promote M2-to-M1 repolarization, reinforcing peripheral anti-tumor immune niches and suppressing tumor progression.

Table 1. Stromal Drivers of Macrophage Dysfunction in Oral Squamous Cell Carcinoma (OSCC)

Stromal Component	Key Mediators	Mechanism of Macrophage Dysfunction	Relevant Pathways/ Receptors	References
Cancer-Associated Fibroblasts (CAFs)	Monocyte Chemoattractant Protein-1 (CCL2, MCP-1), C-X-C motif chemokine 12, Stromal Cell-Derived Factor-1 (CXCL12, SDF-1)	Significant for the requirement monocytes to TME of OSCC	C-C chemokine receptor type 2 (CCR2), C-X-C motif chemokine receptor 4 (CXCR4)	[16, 22, 13]
Endothelial Cells / Vascular Niche	Chemokine (C-X3-C motif) ligand 1 (CX3CL1), C-C Motif Chemokine Ligand 2 (CCL2)	Enhancing the migration of the trans endothelial cells and adhesion if the monocytes	C-X3-C motif chemokine receptor 1 (CX3CR1), C-C chemokine receptor type 2 (CCR2)	[19, 15, 8]
	Macrophage Colony-Stimulating Factor (M-CSF) (CSF1 (M-CSF)	Essential for tumor survival, M2 polarization, tumor progression	Colony-Stimulating Factor 1 Receptor) (CSF1R)	[8, 21, 23]
	Transforming Growth Factor-beta (TGF-β)	Inhibition of M1 phenotype and related functions, inducing the M2 types at OSCC TME	TGF-β/ Suppressor of Mothers against Decapentaplegic, (SMAD), Signal Transducer and Activator of Transcription 3 (STAT3)	[24, 9, 10]
	Interleukin- 6 (IL-6), Interleukin- 10 (IL-10)	Enhancing the immune suppression, M2 polarization	Janus Kinase (JAK) family of enzymes and the Signal Transducer and Activator of Transcription 3 (STAT3 (JAK/STAT3), Nuclear factor- kappa B (NF-κB)	[18, 11, 15, 19, 2]
	Lactate, other metabolites	Hypoxia-Inducible Factor 1-alpha (HIF- 1α/2α) stabilization and supports for the M2 polarization, enhancing the tumor angiogenesis at TME of OSCC	HIF-1α, mTORC1, G protein-coupled receptor 132 (GPR132)	[12, 17, 20]

TAMs have not exhibited the segregated phenotypes as M1 and or M2 [18, 25, 26]. Due to intrinsic and extrinsic signals like, interferon response, complex inflammatory pathways, antigen presentation, hypoxia conditions, matrix remodelling, and tissue- wound healing signatures, they overlapping and occupy the same tumor region [27, 28]. Hence, rather than distinct M1 or M2, those macrophages are described by means of metabolic signalling (viz., above mentioned pathways). The spatio-transcriptonomic studies on OSCC revealed that the OSCC exist as micro-anatomical niches. The tumor periphery harboured with highly immune active macrophages (i.e., M1) and these zones as well accessible for anti tumor immunities [28-30]. In these regions,

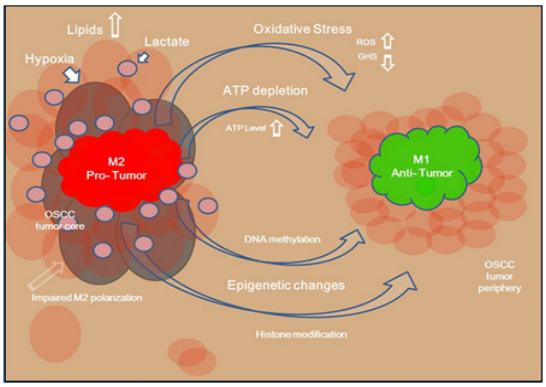

Figure 2. Metabolic Barriers to Durable Macrophage Reprogramming in Oral Squamous Cell Carcinoma (OSCC). Schematic showing how hypoxia-driven metabolic constraints in OSCC promote M2 macrophages in tumor cores, while peripheral niches support M1 polarization, revealing metabolic targets for reprogramming.

oxygen tension, vascularity and immune cell filtration are being relative preserved than the inner core of OSCC niches. The macrophages in these regions represent the M1 types, but, not complete M1 classical polarization. In contrast, the inner region is characterized by its hypoxia responsiveness, angiogenic modulators, extracellular interactive molecules and high lactate concentrations. Further, a dense collagen is found rather than intrinsic macrophage lineage differences [8, 15, 13, 19, 20, 24, 25, 27]. From outer to inner core, these niches have increased concentrations of several cell proliferative modulators, cytokines, mechanical signalling instructors that eventually modify the macrophage behaviour. At these scenario, a tumor associated mecrophage' fate is highly influenced by the spatial exposure cum transient signals. Further, transcriptonomic studies also revealed that a macrophage exhibited "M1" type, could be converted as severe immune suppressive M2- like, it travels upon migration to deep regions of same niches [1, 16, 20, 22, 23, 27]. Recent studies supported this spatial constrained model and existence of asymmetric plasticity of the macrophages within OSCC. Further, they revealed that even achieved M1 conversion from the therapeutic regiments, could be overrides by the TAMs from the immune suppressive niches. These studies showed that plasticity of the macrophage as an important vulnerable factor for determining the therapeutic flexibility on OSCC treatments and highly influenced by the tumor metabolites also, along with the spatio-transcriptomics [8, 11, 15, 16, 18, 21, 24, 28-30].

Classically, the tumor metabolites were assumed as a rudiment of their growth output, but, at present, several studies showed that they are no longer, as passive

Table 2. Metabolic Barriers to Durable Macrophage Reprogramming in OSCC

Metabolite / Pathway	Source in OSCC TME	Effect on Macrophages	Mechanism of Reprogramming Barrier	Potential Therapeutic Target	References
Lactate	OSCC cells, CAFs (Warburg effect)	Stabilizes HIF-1α/2α; promotes M2 polarization; inhibits M1 functions	Inhibits prolyl hydroxylation of HIF-1α; induces histone lactylation of M2 genes	Lactate Dehydrogenase (LDH) inhibitors (e.g., oxamate, gossypol), Monocarboxylate Transporter (MCT) inhibitors	[2, 32, 33]
Adenosine	Hypoxic tumor cells, CAFs, ECs (via CD39/CD73)	Promotes M2 polarization; suppresses M1 polarization; induces immunosuppression	adenosine receptors (A2A/A2B) signaling → ↑ cyclic adenosine monophosphate (cAMP) → transcription factor cAMP response element–binding protein (CREB) activation	CD73 inhibitors (e.g., oleclumab), A2A antagonists (e.g., AZD4635)	[34, 35]
Succinate	Hypoxic OSCC cells, CAFs	Stabilizes HIF-1α; promotes M2 polarization and pro-angiogenic phenotype	succinate receptor 1 (SUCNR1), G protein-coupled receptor 91 (GPR91) → P hosphatidylinositol 3-kinase (PI3K)/HIF-1α axis	SUCNR1 antagonists (e.g., 4-(4-chloro-6-((4-(phenylsulfonyl) phenyl)amino)-1, 3,5-triazin-2-ylamino)-N, N-bis(tetramethylene)-3-carboxamidophenyl) acetic acid (NF-56-EJ40)	[36]
PGE_2	OSCC cells, TAMs (via COX-2/ mPGES-1)	Promotes M2 polarization; induces immunosuppression and angiogenesis	EP2/EP4 → cAMP/PKA → CREB; JAK/STAT6	COX-2 inhibitors (e.g., celecoxib), EP4 antagonists	[37-39]
Sphingosine-1-phosphate (S1P)	OSCC cells, apoptotic cells	Promotes M2-like polarization and s urvival	S1PR signaling → PI3K/AKT, ERK	S1PR modulators (e.g., fingolimod analogs)	[40, 41]
Lipid accumulation	OSCC cells, CAFs (via exosomes, lipoproteins)	Promotes M2 polarization and foam-cell-like phenotype	PPARβ/δ, LXR activation	PPAR/LXR modulators, lipid metabolism inhibitors	[42, 43]
Glucose/ amino acid depletion	High tumor and stromal consumption	Suppresses M1 differentiation; promotes M2 polarization	mTORC1 inhibition, ROS accumulation in M1	Metabolic support (e.g., glutamine, serine)	[44-46]
Hypoxia	Poorly organized vasculature, high O_2 consumption	Stabilizes HIF-1α/2α; promotes M2 polarization and immunosuppression	HIF-1α → VEGF, IL-10, PD-L1; NF-κB activation	HIF inhibitors, oxygen carriers, anti-angiogenics	[47-49]

products, but, as instructive molecular clues that shaping the fate of TAMs on OSCC (Table 2) . Similar to lactate, the tumor niches are also characteristically having different concentrations of adenosine, succinate, PGE_2, Sphingosine-1-phosphate (S1P), accumulated lipids, depleted level of glucose and or various amino acids [31]. Lactate accumulation, hypoxia and altered nutrient availability are significant changes at tumor niches and directly reprogram the transcriptional, functional and epigenetics of the existing macrophages. Among them, lactates and hypoxia are the direct influencers of the TAMs behaviour (Figure 2). The glycolytic flux and chronic oxygen deprivation were showed to increase the vascular abnormality and rapid tumor expansion on OSCC. These increase the acidity of the niches and activate the macrophages by sensitizing the redox pathways those results in tissue repair, immune tolerance and angiogenesis. Hence, hypoxia and lactates act as primary destructive clues that evade the macrophages from cytotoxic and or antigen- presenting ones [2, 4, 8, 10, 12, 13, 18, 23-25, 31]. Lactate could alter mitochondrial activity, chromatin processes and redox potential for favouring the tumor growth. Further, it sustains the macrophage survival even at the hostile environments such as tumor niches by enhancing the pro- inflammatory transcriptional networks [2, 13, 17, 19, 24, 26, 30, 31].

In contrast, metabolically permissive peripheral niches allow partial M1 activation, highlighting spatial heterogeneity in TAM function. Understanding how metabolic barriers regulate TAM plasticity in OSCC provides critical insight into resistance mechanisms and identifies metabolic intervention strategies to restore antitumor macrophage activity. Integrating metabolic modulation with immunotherapy or nanomedicine-based delivery systems may restore macrophage plasticity, enhance immune activation, and improve therapeutic efficacy in OSCC [9, 13,16, 20, 22, 24, 32, 38, 39, 44].

Major drug discovery strategies to overcome durability barriers in OSCC

The identification of durability barriers within the OSCC tumor microenvironment (TME) has fundamentally reshaped oral cancer drug targeting strategies (Table 3). Post transcriptonomic era of cancer therapy, witnessed that targeting the TAMs is one of the major break-through, but, at present the drugs are targeted to nullify the epigenetic and or metabolic memory imposed by the TME [2, 8, 9, 44, 12, 49]. This method aimed to focus on dismantling

Table 3. Major Drug Discovery Strategies on OSCC based on Macrophage Reprogramming

Epigenetic Mechanism	Key Enzymes/ Modifiers	Affected Genes/ Pathways	Effect on Macrophage Phenotype	Potential Therapeutic Target	References
DNA Methylation	DNMTs (DNMT1, DNMT3A/B)	Silencing of M1-promoting genes (e.g., IRF5, NOS2)	Promotes M2 polarization; suppresses M1 functions	DNMT inhibitors (e.g., 5-azacytidine, decitabine)	[50, 51]
Histone Acetylation	HDACs (HDAC1–11), HATs (e.g., p300/CBP)	Repression of M1 genes; activation of M2 genes	Enhances M2 polarization and immunosuppression	HDAC inhibitors (e.g., vorinostat, panobinostat)	[52, 53]
Histone Methylation	HMTs (e.g., EZH2), HDMs (e.g., JMJD3, UTX)	H3K27me3 (repressive) on M1 genes; H3K4me3 (activating) on M2 genes	Stabilizes M2 phenotype; resists M1 reprogramming	EZH2 inhibitors (e.g., tazemetostat), JMJD3 activators	[53]
Histone Lactylation	Unknown "writers"/ erasers	Lactylation of H3K18, H3K9 on M2 genes (e.g., Arg1, VEGFA)	Links metabolism to M2 gene expression; promotes pro-tumor functions	Lactate reduction, lactylation pathway inhibitors	[54, 55]
Non-coding RNAs	miRNAs (e.g., miR-21, miR-155, miR-146a), lncRNAs	Targeting of M1 transcription factors (e.g., IRF5, STAT1) and signaling	Fine-tunes M2 polarization and immunosuppression	miRNA antagonists (antagomirs), lncRNA inhibitors	[56, 57]
Chromatin Remodeling	SWI/SNF, ISWI complexes	Altered accessibility of M1/M2 gene promoters	Reinforces M2 chromatin state; limits plasticity	SWI/SNF modulators (under investigation)	[58, 59]

the molecular significances that characterizing the immune tolerance rather than single transient macrophages. Blockade of lactate signalling is a central process that modifies the epigenetic and or metabolic reminds on TME of OSCC [1, 2, 26, 36, 19, 49]. Accumulation of lactates in OSCC helps for alteration of redox balance, mitochondrial metabolism, histone modification that enhances the immune tolerance. Inhibition of monocarboxylate transporters (MCT1/ MCT4) that blocks the lactate export at OSCC cells seemed to be a promising strategy. This method indirectly helps for the removal of metabolic brakes that induce the immune tolerance on macrophages [1, 2, 4, 11, 13, 20, 26, 38, 44].

Modulators of AMPK pathway rewire the macrophage reprogramming for restoration of normal function and metabolic stability of the mitochondria at TAMs. They are effective on rewiring the redox oxygen species signals and sustain the inflammatory functions on macrophage level. Further, these agents reduce dependency on lactate and glycolytic pathways [8, 11, 15, 16, 35, 36, 41- 43, 47]. Targeting the HIF-1α and HIF- 2α are important strategies for interrupting hypoxia adaptive transcriptional networks on OSCC. These agents could inhibit the transcriptional suppressive states on fibroblast- rich invasive fronts of OSCC niches [2, 8, 13, 15, 20, 36, 42, 43]. The residues of OSCC niche metabolites become a significant reason for stabilization of tumor- favourable epigenetic modifications. The lactate accumulation further, induces the tumor- friendly plasticity that induces beyond short- term stimulation. The histone deacetylase inhibitors and modulators of chromatin functions widely help to prevent epigenetic modifications including lactate induction in OSCC. To overcome these chemo-resistance, recurrence of the OSCC, the drugs should be integrated with the durability barrier oppositions [12, 13, 20, 26, 32-34, 44, 46, 47, 37-40].

Macrophage targeted Drug Discovery in OSCC

OSCC are characterised asymmetric plasticity similar to various tumor types and it also expresses spatially heterogenic regions as different niches. These regions strongly varied by the immunomodulation, metabolism, and tissue-remodelling and different macrophage phenotypes across the tumor sites [60]. This macrophage plasticity offers a valuable therapeutic flexibility and vulnerable niche- disrupting strategies. Recent studies on OSCC revealed that the macrophages are not on single state, rather than unique polarization, they are existing as a collection of overlapping functional programs. In response to spatial concern, they are dynamically engaged by transcriptional and metabolic modules collectively influenced by M1 and or M2 phenotypes [2, 13, 15, 16, 20, 30, 31, 33, 51, 60]. These programs are co-existing, interact each other depending on the niche. The macrophages isolated from the OSCC tumor niches transiently induced toward the inflammatory states by cytokines, toll- like receptor agonists, and metabolic modulator approaches [2, 9, 20, 32, 44]. These findings support the research trend to change the state of immune-suppressive tumor favour phenotype into anti- tumor immune macrophage phenotype in OSCC drug discovery strategies. Based on the findings, a number of macrophages reprogram have been developed for substantiating the OSCC growth [12, 15, 16, 36, 52].

The tumor margins are vulnerable for interferon- stimulated macrophage programs, since, they are enriched with the immune- assessable macrophages. These macrophages can be influenced by the interferon regulation, antigen processing, inflammatory mediators and so on. However, due to stromal proximity and immune exclusion, this program often faces limitations and seemed to be incomplete, partially activated and or transient than tumoricidal functions [33-35]. Antigen-presenting macrophage programs aimed to activate the antigen stimulation by influencing the MHC class I and II molecules in tumor niches. Eventually, this might lead to expression of co- stimulatory receptors, phagocytic machineries. This might results in T- cell priming and immune orchestration [61]. Many recent studies revealed that the antigen- presenting programs are diminished by the excessive cytokine production from the tumor and stromal para-signalling, particularly at fibroblast- rich

cores of OSCC niches. Under excessive cytokines, the niches express poorly vascularised, oxygen depleted hypoxia conditioned niche properties on OSCC. This up regulates the hypoxia- responsive genes, results in elevated angiogenesis and stress- adoptive pathways rather than immune elimination [18, 62, 63]. Hypoxia- adapted macrophage programs aimed to reduce the inflammatory responsiveness, for reducing the metabolic stress on OSCC niches. Lipid signalling of the TAMs at niches plays a pivotal role for favouring the tumor growth [8, 64, 65]. Lipid- associated macrophage programs as a prominent strategy to reduce the lipid uptake, storage, and fatty- acid metabolism of the tumor associated macrophages [66, 67]. Combined with the Hypoxia related programs, these are very useful to inhibit the immune suppression, and retrieval of the immune surveillance of OSCC niches [68]. Indirectly, the matrix- remodelling macrophage programs weakens the invasive tumor fronts and fibroblast- dense stroma. These programs reshape the niche environment favourable for the OSCC therapeutics. These micro-environmental changes further restrict the immune infiltration and the stromal dominance [69, 70]. The accumulation of the tumor by- products severely play enhancing the OSCC favour niches, hence, phagocytic and scavenger programs aimed to removes tumor metabolic debris and to enhance the wound- healing functions [71, 72]. Further, this strategy supports immune' phagocytosis over the tumor cells and also the antigen presentation. This also enhances the apoptosis, immune surveillance, and anti- inflammatory signalling of OSCC niches [71-73].

Even though, many macrophage reprograms strategies have been proposed, concurrent usage of altogether in a single patient advised as unsafe and or clinically impossible at the current scenario. Sequence reprogramming activation is better than additively process for reducing the risk of systemic inflammation in OSCC. Therefore, durable macrophage immune-reprogramming will require temporally sequenced, spatially controlled, and biomarker-guided combination strategies that dismantle stromal enforcement mechanisms before immune activation [73, 74]. Meanwhile, the reverted macrophages suffer from a number of limitations including short- life at the tumor niches, instability at OSCC niches. However, despite of reprogramming, the recent studies also showed that the macrophages could be reverted their tumor supportive state at any given time [17, 26, 39, 48, 61, 65, 75-77].

Challenges on Durable effects in OSCC

The intense research on macrophage behaviour on OSCC TME resulted on developing a number of macrophage reprogramming strategies. Due to a strong influence of OSCC TME on the macrophages, by means of stromal, metabolic, and inflammatory constraints, a number of obstructing challenges are also existing for achieving full therapeutic success. The OSCC is a complex malignancy arising from the epithelial lining of the oral cavity and prevalent type of head and neck cancer. Even though a strategic therapeutic development is available, OSCC remains one of the cancers that have poor

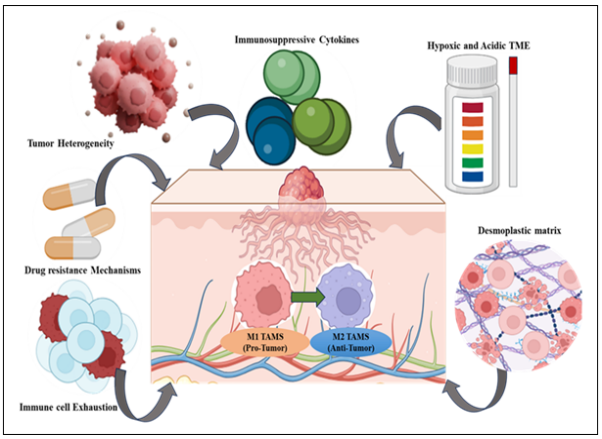

Figure 3. Schematic Diagram of Major Challenges Faced on Macrophage Reprogramming in TME of OSCC. The image highlights the different signalling factors that collectively, determine the fate of macrophages toward an immunosuppressive M2-like phenotype. These barriers limit durable M1 reprogramming, promote immune evasion, and contribute to therapy resistance in OSCC.

long- term survival. Higher incidence of recurrence and metastasis are the main factors for improving the patient's outcomes. Long- time control and sustainable tumor regression are the main goals of the durable therapeutic responses [78-80]. Meanwhile, OSCC showed a number of complications including the multiple sub clonal cells characterized with variance on epigenetic, phenol and genetical profiles. These are stabilized with different accumulated mutations and chromosomal instability [81, 82]. Hence, different subsets could exhibit irreverent responds to the same therapy. The occurrence of resistive sub-clones that survives after the therapeutic encounter, could severely contribute for the cancer relapse [83]. Further, they showed inter-patient heterogeneity that has diverse molecular aberrations and becomes a major obstacle for the one-size-fits-all therapeutic approach in OSCC [82, 84]. Epigenetic fixation of the M2 phenotype further undermines durable macrophage reprogramming. Chronic exposure to OCAF-derived cytokines induces stable epigenetic modifications in macrophages, including histone methylation and altered chromatin accessibility at M2-associated gene loci (Figure 3). These changes create an epigenetic "memory" that limits macrophage plasticity and reduces responsiveness to M1-polarizing stimuli. Consequently, therapeutic attempts at reprogramming often yield only partial or short-lived M1 activation, insufficient to sustain antitumor immunity [85, 86, 77].

Other important obstacles are cancer stem cells (CSCs) in OSCC. The CSCs are the specific sub clones of the cancer cells that have unique properties for differentiation, self- renewal and tumor initiation. These cells eventually escape for the conventional therapies (viz., chemotherapy and radiotherapy) that mainly target the actively dividing cells. These CSCs remain as dormant and repopulate again after certain periods, thus they serve as a major source of relapse and metastasis [87, 88]. Furthermore, CSCs exhibit intrinsic resistance mechanisms, such as overexpression of drug efflux transporters, enhanced DNA

repair pathways, and activation of survival signalling networks, which collectively contribute to their ability to withstand therapeutic interventions [88, 69]. These CSCs are surrounded by the immune suppressive macrophages and OCAFs; the OCAFs help for producing excessive cytokines, chemokines for maintain OSCC- derived paracrine signalling status and reinforce the stemness on OSCC [89, 18]. In other hand, OCAF- conditioned M2 macrophages could express TGF-β, VEGF and IL-10 for immune surveillance and promoting the tumor angiogenesis. Recent studies revealed that instability of the reprogrammed-M2 to M1, reintroduced on OSCC TME, has been restored M2 condition, mainly due to CSCs. These CSCs derived feedback- loop restored the immunosuppression, even after reprogramming in OSCC [90, 91].

The TME itself act a strong shield having physiological layers of different cell types and contribute for tumor relapse. For instance, hypoxic regions within the tumor can impair the efficacy of radiotherapy, while the presence of regulatory T-cells and myeloid-derived suppressor cells can inhibit antitumor immune responses, reducing the potential durability of immunotherapies. The dense extracellular matrix and stromal barriers further impede drug penetration, preventing therapeutics from reaching all tumor regions effectively. Drug resistance majorly contributes for the failure of the durable therapeutic goals [2, 69, 92, 78].

Thus TME of OSCC challenges the therapies implementing by metabolic, spatial and immunological complications as persistent paracrine signals. It neutralizes the inflammatory signels on reprogrammed M2 to M1 driven macrophages and re-establish the M2, the tumor-supportive state. Thus, macrophage plasticity is not a reversible binary switch, but a context-dependent process tightly constrained by stromal dominance. Pre-genetic mutational alterations on cancer cells including EGFR, apoptotic regulators and TP53 render and confirm the ineffectiveness of cancer therapies [93, 94]. OCAFs enhance glycolytic flux and lactate production, leading to extracellular acidification and hypoxia. These conditions selectively favour M2 macrophage metabolism, which relies on oxidative phosphorylation and fatty acid oxidation, while suppressing glycolysis-dependent M1 effector functions. CSCs further exploit this metabolic environment by preferentially utilizing lactate and fatty acids, reinforcing a shared metabolic axis between OCAFs, TAMs, and stem-like tumor cells. As a result, even macrophages exposed to M1-polarizing stimuli are unable to sustain pro-inflammatory activity due to metabolic incompatibility, leading to rapid phenotypic regression [95, 96]. A second major barrier is metabolic reprogramming imposed by OCAFs. OCAFs remodel the metabolic landscape of the OSCC TME by promoting lactate accumulation, hypoxia, and nutrient competition. Macrophages exposed to this environment preferentially adopt oxidative phosphorylation and fatty acid oxidation, metabolic programs that support M2 identity. In contrast, stable M1 polarization requires a glycolytic shift, which is energetically unfavorable in the acidic and nutrient-depleted milieu shaped by OCAFs. As a result, even reprogrammed macrophages struggle to maintain M1 functionality, leading to rapid phenotypic relapse [2, 4, 30, 44, 65, 69, 72, 78, 79, 85, 90, 96].

Apart from this, OSCC have the acquired resistance that is characterized by reduced insensitivity towards the cytotoxic agents. This is developed due to therapeutic pressure, the cancer cells modify the DNA repair mechanisms, efflux pumps, enhanced epithelial mesenchyme transition (EMT) and up regulated survival pathways than normal cells. These dynamic and multiple factors urge us to develop a comprehensive therapeutic strategy for maintaining a long- term efficacy [2, 8, 32, 36, 60, 69, 78, 83]. Not only, have CSCs, also the dissipated cancer cells through the metastasis also undergone as dormant for a certain period at the newer sites, they reached during invasive time. Commonly, the OSCC cells dormant on distal organs such as the nodal lymph and lungs. Therefore, therapeutic strategies that fail to target both the primary tumor and dormant metastatic cells are unlikely to achieve sustained responses [69, 8, 44, 86, 50, 70, 56, 49, 88, 36].

The complex interaction between these CSCs and the TME vitally demine the molecular and biomarker profile of the heterogenetic OSCC tumors. Though the current therapeutic achievements contribute extensively, the absence of predictive markers hampers the ability to personalize therapy effectively, often resulting in suboptimal or short-lived responses [10, 61, 66, 96, 70, 78]. These complex mechanisms, on other side also provoke the toxicity and treatment tolerability that practically impose the severe constraints against the OSCC therapies. Particularly, the aggressive combination therapies and high- dose chemotherapy eventually contribute the unacceptable toxicity for the tumor surrounding normal tissues [1, 36, 60, 69, 83]. In OSCC, the oral cavity comprised mucosa, salivary glands, bucco-pharyngeal fascia, oter most skin ends. These alterations also severely reduce the swallowing ability and the quality of the life. Consequently, there is a delicate balance between administering a treatment potent enough to sustain tumor control and minimizing collateral damage to healthy tissues, often limiting the intensity or duration of therapy [9, 26, 44, 86].

These complex factors also reflect on the immune evasion of the OSCC tumors. Since, the OSCC could extensively exploit the various immune check points such as PD-1/ PD- L1 for inhibiting the T- cell mediated cytotoxicity and related anti tumor immunity. Again, TME contributes micro environmental-derived immune suppression that enhancing the immune escape mechanisms [8, 10, 11, 45, 52, 53, 56, 72, 90, 96]. Hence, another critical aspect of OCAF-driven macrophage dysfunction is the disruption of immune network coordination. OCAF-conditioned macrophages exhibit impaired antigen presentation, reduced expression of co-stimulatory molecules, and increased expression of immune checkpoint ligands such as PD-L1. These alterations weaken macrophage–T cell interactions, suppress cytotoxic T-cell activation, and promote the recruitment

Table. 4. Major Challenges on Reprogramming the Tumor Associated Macrophages in OSCC

Biological Axis	Key Players	OCAF-Driven Mechanisms	Impact on Macrophage Function	Effect on CSCs, Dormancy & Dissemination	Why M2 → M1 Reprogramming Is Unstable	Therapeutic Implications	References
Stromal dominance	OCAFs, TAMs	Persistent secretion of TGF-β, IL-6, IL-10, PGE2, CXCL12, CSF-1	Suppresses NF-κB/STAT1 signaling; reinforces M2 polarization	Supports CSC niche maintenance and immune evasion	Continuous stromal cues override transient M1-inducing therapies	Need OCAF-targeted or stromal-neutralizing strategies	[97, 98]
Macrophage polarization plasticity	TAMs (M2-biased)	Chronic paracrine re-education by OCAFs	Partial and t ransient M1 activation	Fails to clear CSCs and residual tumor cells	Macrophage phenotype rapidly reverts after therapy withdrawal	Combination stromal–immune modulation required	[99, 100, 88]
Metabolic reprogramming	OCAFs, TAMs, CSCs	Lactate accumulation, hypoxia, nutrient depletion	Promotes FAO and OXPHOS favoring M2 phenotype	CSCs exploit lactate-rich niches	Glycolysis-dependent M1 state cannot be sustained	Metabolic inhibitors + immune reprogramming	[101, 102]
Epigenetic fixation	TAMs	OCAF-induced histone modifications and chromatin remodeling	Locks macrophages i nto M2 transcriptional programs	CSC-derived signals reinforce immune tolerance	Epigenetic "memory" resists durable phenotype switching	Epigenetic modulators needed for stability	[69, 75]
CSC niche formation	CSCs, OCAFs, M2 TAMs	Activation of Wnt, Notch, Hedgehog, TGF-β pathways	Macrophages secrete stemness-sup portive cytokines	Maintains CSC self-renewal and therapy resistance	CSC-macrophage feedback loops restore M2 dominance	Target CSC–stromal signaling axes	[76, 103]
Dormant CSCs	Quiescent CSCs, TAMs	Survival signals and immune tolerance enforcement	Reduced immune surveillance	Dormant CSCs evade M1-mediated clearance	Low antigenicity limits macrophage cytotoxicity	Dormancy-targeted and immune awakening strategies	[104-107]
Disseminated cancer cells	Circulating tumor cells, fibroblast-like stromal cells	M2 macrophages facilitate EMT and immune evasion	Macrophages promote metastatic seeding	Supports secondary niche establishment	Local macrophage reprogramming lacks systemic durability	Systemic stromal-immune interventions needed	[108, 109, 88]
Extracellular matrix remodeling	OCAFs	Dense ECM deposition and stiffness	Physical barrier to immune infiltration	Protects CSCs and residual cells	Limits M1 macrophage access to tumor cells	ECM-targeted therapies to enhance immune penetration	[18, 110]
Immune checkpoint remodeling	TAMs, CSCs	Upregulation of PD-L1, TIM-3, CD47	Suppressed a ntigen presentation and phagocytosis	CSCs evade immune recognition	Checkpoint signaling counteracts M1 activation	Combine macrophage reprogramming with ICI	[4, 11, 2, 78, 34, 13, 88, 23, 41]
Impaired macrophage–T cell crosstalk	TAMs, T cells	Reduced co-stimulatory molecules	Weak T-cell priming	Adaptive immunity remains suppressed	M1 macrophages fail to sustain immune networks	Multi-cell immune restoration required	[98, 38, 60, 1, 50, 66, 20, 22, 101, 49, 65]
OCAF heterogeneity	Distinct OCAF subsets	Variable immunosuppressive capacity	Incomplete macrophage re-education	Residual niches preserve CSCs	Partial stromal targeting allows phenotype relapse	Precision targeting of OCAF subsets	[94, 72, 69, 8, 44, 15, 86, 97, 104, 11, 16, 34, 110]
Therapy-induced adaptive resistance	Tumor cells, TAMs, OCAFs	Feedback activation of suppressive pathways	Macrophages re-enter M2 state	CSC enrichment post-therapy	Adaptive re-education undermines durability	Adaptive combination regimens	[45, 9, 30, 90, 52, 97, 22, 101, 49]
Systemic immune tolerance	Bone marrow, lymph nodes	OCAF-like stromal education of macrophages	Peripheral immune suppression	Enables metastatic outgrowth	Local M1 reprogramming insufficient	Whole-system immune modulation	[94, 26, 69, 30, 107]
Clinical translation barriers	Patients, tumor heterogeneity	Inadequate modeling of stromal–immune interactions	Overestimation of macrophage plasticity	CSC persistence overlooked	Preclinical success not durable clinically	Advanced co-culture and organoid models	[45, 69, 30, 10, 96, 19, 20, 56, 51, 49, 88]

of regulatory immune cells. As a result, macrophage reprogramming alone fails to restore effective adaptive immune responses, limiting its impact on long-term tumor control and reducing synergy with immunotherapies such as immune checkpoint inhibitors [12, 19, 25, 27, 28, 32, 46, 49, 53, 55, 88].

Addressing these challenges requires a multifaceted approach that includes combination therapies targeting both bulk tumor cells and CSCs, modulation of the tumor microenvironment, use of predictive biomarkers for personalized treatment, strategies to overcome immune evasion, and careful management of therapy-related toxicity [66, 70, 49]. The heterogeneity of OCAFs adds another layer of complexity. Emerging evidence indicates that OCAFs are not a uniform population but consist of distinct subtypes with varying immunomodulatory functions. Some subsets are strongly immunosuppressive, while others may play structural or homeostatic roles. The lack of specific markers to selectively target pro-tumorigenic OCAF subsets poses a significant challenge, as indiscriminate stromal targeting risks tissue damage and may paradoxically worsen immune dysfunction [19, 22, 41, 52, 78, 87]. This heterogeneity complicates therapeutic design and contributes to inconsistent and non-durable immune outcomes.

Advances in molecular profiling, nano-medicine, immunotherapy, and precision medicine hold promise for overcoming these barriers and achieving more durable therapeutic outcomes in OSCC (Table 4). Ultimately, improving long-term survival in OSCC will depend on integrating a deep understanding of tumor biology with innovative therapeutic strategies designed to target the complex mechanisms that drive recurrence and resistance [27, 33, 34, 37, 43, 48].

Future Perspectives

Future therapeutic strategies aimed at restoring durable antitumor immunity in oral squamous cell carcinoma (OSCC) must move beyond macrophage-cantered interventions and adopt a tumor microenvironment–integrated approach, with particular emphasis on oral cancer–associated fibroblasts (OCAFs) as master regulators of immune dysfunction. Given the demonstrated role of OCAFs in enforcing macrophage plasticity toward an unstable M2-dominant state, targeting the bidirectional crosstalk between OCAFs and tumor-associated macrophages (TAMs) represents a promising yet underexplored avenue for long-term therapeutic benefit [1, 2, 22, 23, 26, 38, 44, 52, 60, 69, 87, 94, 101, 104, 108].

One key future direction lies in selective targeting or functional reprogramming of OCAFs rather than complete stromal depletion, which may cause tissue damage and adverse effects. Advances in single-cell transcriptomics and spatial proteomics are expected to enable the identification of distinct OCAF subpopulations with immunosuppressive versus homeostatic functions. This stratification will allow the development of therapies that specifically neutralize pro-tumorigenic OCAF subsets or block their immunosuppressive secretome, including TGF-β, IL-6, CXCL12, and PGE2 [44, 61, 66, 79, 83, 93, 105]. Such precision targeting could relieve stromal pressure on macrophages and permit stable M1 polarization. Another promising area is the integration of metabolic intervention strategies. Since OCAFs impose a metabolic framework that favors M2 macrophage maintenance, future therapies may combine macrophage reprogramming agents with inhibitors of lactate transporters, fatty acid oxidation, or key metabolic enzymes within the TME [2, 13, 22, 78, 85]. Modulating local nutrient availability and pH could help sustain glycolysis-dependent M1 macrophage activity and improve antitumor immune persistence. Importantly, nanoparticle-based drug delivery systems may enhance the spatial precision of such metabolic interventions, limiting off-target effects [12, 76, 16, 101, 99, 65, 87].

Epigenetic reconditioning of macrophages represents an additional frontier. The instability of M2 → M1 reprogramming in OSCC is partly driven by epigenetic memory induced by prolonged OCAF exposure. Future research should focus on identifying epigenetic checkpoints that lock macrophages into an immunosuppressive phenotype. Combining epigenetic modulators such as histone deacetylase or DNA methyltransferase inhibitors with macrophage-polarizing agents may enable more durable reprogramming and prevent phenotypic relapse [2, 9, 11, 15, 19, 30, 34, 45, 52, 53, 75, 87, 107]. From an immunotherapeutic standpoint, rational combination strategies will be essential. OCAF-targeted approaches may synergize with immune checkpoint inhibitors, cancer vaccines, or adoptive cell therapies by restoring effective antigen presentation and T-cell activation. Clinical trials designed with adaptive biomarkers such as macrophage polarization signatures or OCAF-derived cytokine profiles will be crucial to identify responders and optimize treatment sequencing. Finally, future perspectives must also emphasize clinically relevant model systems. Advanced 3D organoids, co-culture platforms, and patient-derived xenografts incorporating fibroblasts and immune cells will be instrumental in faithfully recapitulating OCAF–macrophage interactions. These models will accelerate translational validation and improve the predictive power of preclinical findings [1, 4, 18, 63, 69, 97, 71, 76, 79, 91, 104]. In summary, durable reprogramming of macrophages in OSCC will likely depend on simultaneously dismantling OCAF-mediated immune suppression, correcting metabolic and epigenetic constraints, and integrating macrophage modulation with broader immunotherapeutic strategies. Such multidimensional approaches hold promise for overcoming stromal-driven immune resistance and achieving sustained clinical responses in OSCC. This examination highlights the pivotal role of oral cancer–associated fibroblasts (OCAFs) in enforcing macrophage dysfunction within the oral squamous cell carcinoma (OSCC) tumor microenvironment and underscores why M2 → M1 macrophage reprogramming remains inherently unstable in this disease. OCAFs emerge as central regulators of immune suppression, actively shaping macrophage phenotype, metabolism, and function in ways that favour tumor progression and therapeutic resistance [53-58].

OCAFs sustain M2-like macrophage polarization through the persistent secretion of immunosuppressive cytokines and growth factors, including TGF-β, IL-6, IL-10, PGE2, CSF-1, and CXCL12, which collectively suppress pro-inflammatory signalling and inhibit classical M1 activation pathways such as NF-κB and STAT1. Even when therapeutic interventions transiently induce M1-like features, the continuous paracrine influence of OCAFs rapidly drives macrophages back toward an M2-dominant, tumor-supportive state. This highlights that macrophage reprogramming in OSCC is not a cell-autonomous process but is tightly constrained by stromal cues. A key factor contributing to the instability of M2 → M1 reprogramming is metabolic conditioning imposed by OCAFs. OCAFs promote oxidative phosphorylation, fatty acid oxidation, and lactate utilization in tumor-associated macrophages, metabolic states that are incompatible with sustained M1 polarization, which requires glycolytic reprogramming. The OCAF-driven accumulation of lactate and extracellular acidity further suppresses M1-associated cytokine production while reinforcing M2-associated gene expression, creating a metabolically hostile environment for durable pro-inflammatory macrophage function [60-73].

Epigenetic reinforcement also plays a crucial role. Chronic exposure to OCAF-derived signals induces stable epigenetic modifications in macrophages, including histone methylation and acetylation patterns that lock in M2-associated transcriptional programs. As a result, even when M1-polarizing stimuli are applied, macrophages exhibit only partial or transient activation, rapidly reverting to an immunosuppressive phenotype once external pressure is removed [66-69]. This epigenetic "memory" represents a major barrier to durable macrophage reprogramming in OSCC. Additionally, OCAFs contribute to immune dysfunction by impairing macrophage–T cell crosstalk. OCAF-conditioned macrophages display reduced antigen presentation capacity, increased expression of immune checkpoint ligands, and enhanced recruitment of regulatory T cells, collectively dampening adaptive immune responses. This not only limits the effectiveness of macrophage-centered therapies but also undermines immunotherapeutic strategies such as immune checkpoint blockade, further explaining the lack of sustained clinical benefit [79-87].

In conclusion, the instability of M2 → M1 macrophage reprogramming in OSCC is driven by persistent OCAF-mediated cytokine signaling, metabolic reprogramming, epigenetic fixation, and suppression of immune crosstalk. These findings suggest that strategies targeting macrophages alone are unlikely to achieve durable antitumor immunity in OSCC. Instead, co-targeting OCAFs alongside macrophage reprogramming approaches, potentially in combination with metabolic and epigenetic modulators, may be essential to overcome stromal-imposed immune dysfunction and achieve sustained therapeutic responses.

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Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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