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Review on Inflammatory Pathway on Oral Cancer Disease

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ABSTRACT

Oral cancer, characterized by malignant lesions in the oral cavity, poses significant health challenges globally. Inflammation has been increasingly recognized as a crucial factor in the pathogenesis and progression of oral cancer. This review synthesizes current knowledge on inflammatory pathways involved in oral cancer, emphasizing their role in tumor initiation, promotion, and progression. Key inflammatory mediators, including cytokines, chemokines, and prostaglandins, are examined for their contributions to the tumor microenvironment and their interactions with cancer cells. We explore the mechanisms by which chronic inflammation leads to genetic and epigenetic alterations, facilitating the transformation of normal epithelial cells into malignant ones. Additionally, the review discusses the impact of inflammatory signaling pathways, such as NF-κB, COX-2, and IL-6, on oral cancer progression and their potential as therapeutic targets. Insights into these inflammatory mechanisms offer valuable perspectives for developing novel diagnostic and therapeutic strategies to improve outcomes in oral cancer management.

Keywords: *Oral Cancer, Inflammatory Mediator, Diagnosis and Treatment, etc.*

1. INTRODUCTION

Oral squamous cell carcinoma accounts for the majority of oral cancer cases. Except for some regions of France, this illness is rare in the industrialized world but widespread in the developing world, especially in Southeast Asia and Brazil. Men over middle age are more likely to develop oral cancer (though it is becoming more common in younger people), as do smokers and those from lower socioeconomic backgrounds.[6] The most common symptom of oral cancer is a growth or persistent sore in your mouth. It is a type of cancer of the head and neck. It may also be referred to as oral cavity cancer or mouth cancer. Oropharyngeal cancer is a condition if it is located in the upper throat or back of the mouth. [7] Oral cancer develops through a multi-step process influenced by tobacco, alcohol, and genetic changes. Understanding this process is crucial for improving stagnant survival rates. Despite extensive research, new detection methods are not yet widely used clinically. Currently, cytological testing is the primary detection method. While light-based visual examinations have been explored, they have limitations. Biochemical and molecular assays of the oral mucosa offer the most promise for overcoming these diagnostic challenges.[3]

Chronic inflammation associated with cancer promotes unrestricted replication capacity, growth factor independence, resistance to growth inhibition, escape from programmed cell death, increased angiogenesis, tumor extravasation, and metastasis. Inflammation associated with cancer is the sixth indicator of cancer development. Inflammation can result from physical, chemical, or parasitic stressors and persistent microbial infections caused by bacteria, viruses, and parasites. In mice, bacterial infections that occur after primary tumors are surgically removed can encourage the establishment of metastases. Most likely, endotoxins modify the vital balance between angiogenesis and cell proliferation, which mediates this process. Furthermore, persistent inflammation brought on by non-infectious substances might promote the growth of tumors and aid in the development of cancer. In addition to toxins, growth factors, and oncoproteins can influence the host via activating pattern recognition receptors [4]

These receptors include members of the TLR family, C-type lectin receptors (CLR), triggering receptors on myeloid cells (TREM), nucleotide-binding oligomerization domain-like (NOD-like) receptors (NLR), and retinoic acid-inducible gene-I-like receptors. When PAMP binds to these receptors, inflammatory cells are activated, which starts the host immunological response. When PRR is activated, intracellular signaling pathways activate many transcription factors, including FOXO, STAT, and NF-κB. The expression of several genes involved in both innate and adaptive immunity is regulated by these factors. Chronic inflammation can be brought on by insufficient pathogen eradication, recurrent tissue damage, protracted inflammatory signaling, and malfunctioning anti-inflammatory mechanisms. Chronic inflammation subsequently promotes carcinogenesis.[4,8,9]

Major players in the pathogenesis of oral cancer include inflammatory mediators such as nuclear factor kappa B (NF-κB), vascular endothelial growth factor (VEGF), inflammatory cytokines, prostaglandins, p53, nitric oxide (NO), reactive oxygen species (ROS) and nitrogen species, and specific microRNAs (miRNAs).[3]

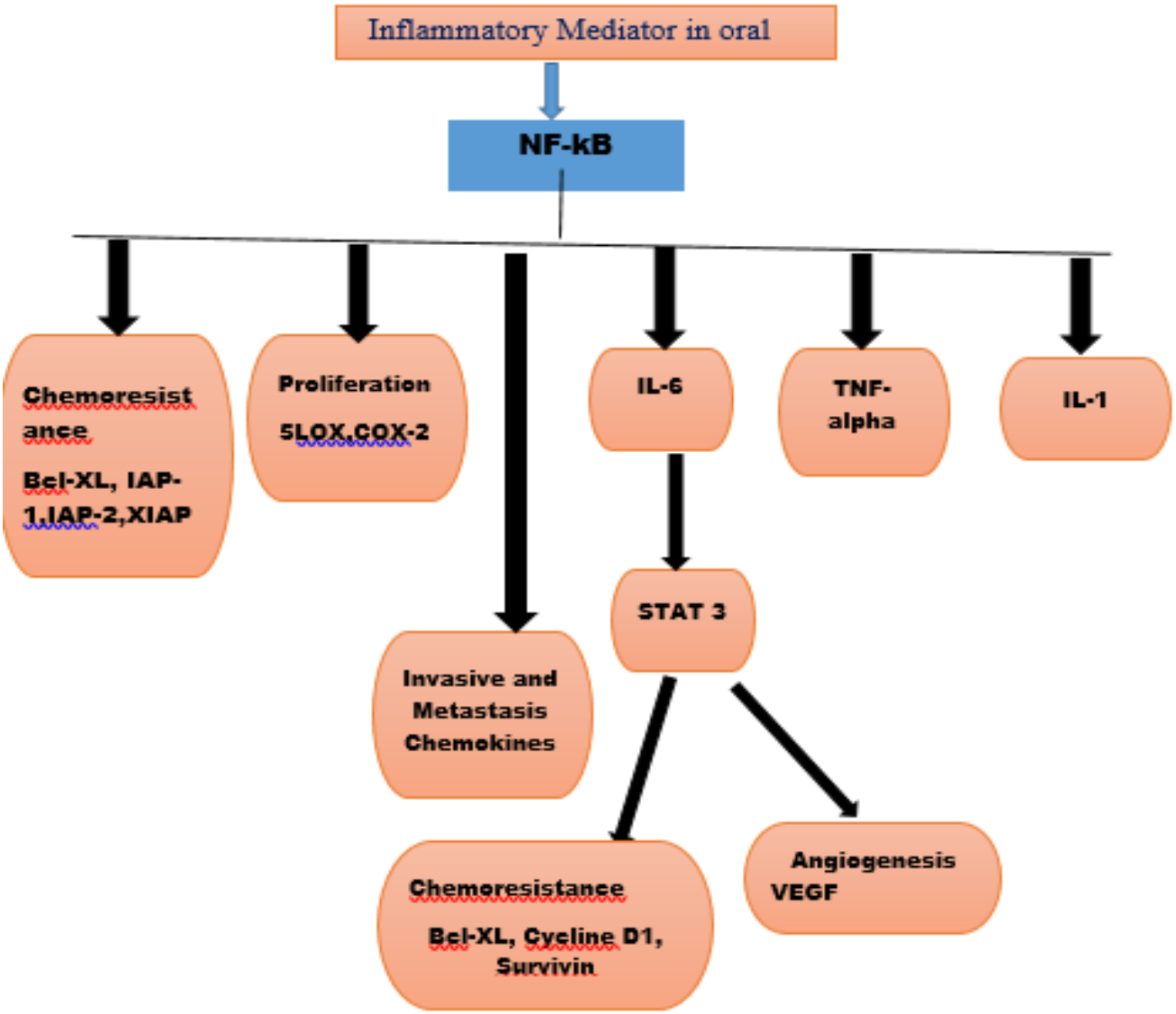

Fig 1: Inflammatory Mediators

2. INFLAMMATORY PATHWAYS

Both intrinsic and extrinsic pathways mediate the relationship between inflammation and carcinogenesis. Genetic changes trigger the intrinsic pathway, which results in inflammation and neoplasia. These changes include chromosomal rearrangement/amplification, inactivation of tumor suppressor genes, and mutation-driven proto-oncogene activation. An inflammatory microenvironment is created by transformed cells secreting inflammatory mediators.

Inflammation or infections that raise the chance of cancer developing in at-risk organs such as the prostate, pancreatic, colon, lung, and skin are the driving forces behind the extrinsic route. These pathways disrupt tumor cells and trigger the activation of multiple transcription factors, including NF-κB, STAT-3, and HIF-1. This leads to the production of pro-inflammatory factors, such as PGHS-2, cytokines, and chemokines. [2,13]

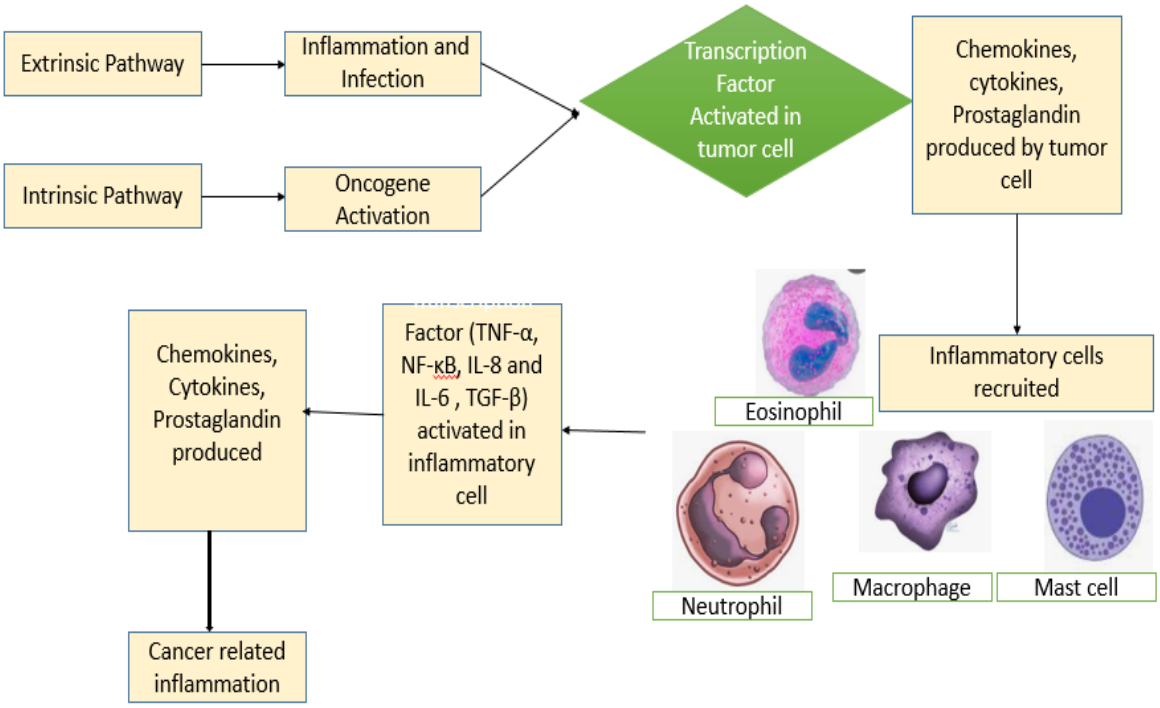

Fig 2: Inflammatory Pathway

2.1 (NF-κB)

A major inflammatory transcription factor that is widely expressed in tumors, nuclear factor kappa-beta (NF-κB) controls the expression of several genes involved in inflammation, proliferation, carcinogenesis, and cell survival [17-19]. Tumor necrosis factor alpha (TNFα), interleukin (IL)-1, and lipopolysaccharide (LPS) are the canonical stimuli that activate NF-κB [20]. This activation promotes the release of several cytokines, such as IL-1, IL-6, and IL-8. Its abnormal expression has been connected to EMT induction, Carcinogenesis, and Poorer Survival in Solid Cancers [21,22,23,24]. Owing to its constitutive activation, NF-κB is thought to be a prominent contributor to the inflammatory infiltration observed in the tumor microenvironment (TME) in OSCC. It is linked to the overexpression of several inflammatory genes, such as IL-6, IL-8, CCL5, and CXCL[10].In the malignant form of oral malignancies, NF-κB has a significant role in modulating bone invasion [20], enhancing angiogenesis, invasion, and metastasis as well as inducing EMT [26,27,28,30,29]. An essential step in the development of OSCC metastasis is the EMT process. It involves the expression of Slug, which is dependent on AKT-mediated NF-κB activation, suppressing E-cadherin, an essential epithelial adhesion molecule[28].EMT can be triggered by IL-8 and EGF through NF-κB activation, and EMT can be reversed by inhibiting AKT or NF-κB [32,33]. The significance of NF-κB during OSCC development is best illustrated by its inactivation, which reduces cell growth and survival; metastases, IL-1α, IL-6, and IL-8 expressions and cell survival.[27,34] NF-κB inhibition has thus been suggested as a potential treatment for the head and neck squamous cell cancer (HNSCC) microenvironment (TME)[31].

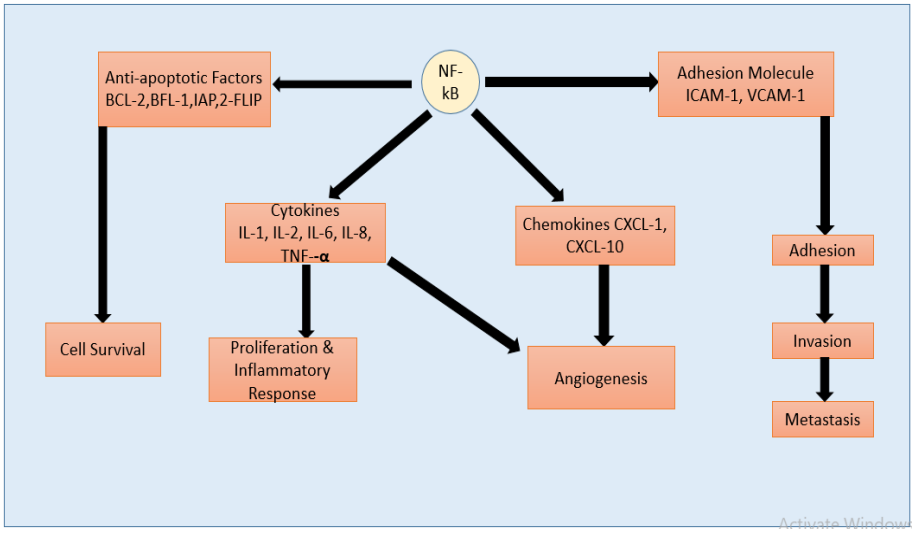

Fig 3- NF-kB target genes involved in inflammation development

2.2 AP-1Pathway

AP-1Pathway Activator protein1 (AP-1) is a transcription factor complex that controls the expression of several genes involved in inflammation, embryonic development, lymphoid proliferation, oncogenesis, and apoptosis [38,39].

It is made up of either homodimers of the Jun protein or heterodimers of the Jun and Fos proteins [40]. Given that high expression levels of AP-1 have been linked to treatment resistance, it appears that AP-1 activation has clinical significance in cancer [40]. Oral keratinocyte carcinogenesis induces AP-1 activation, and the growth of oral tumors enhances its expression [35,36]. Like NF-κB, it is also activated by IL-1, which causes the release of IL-8 and encourages the development and survival of HNSCC cells [37,41]. Targeting the AP-1 pathway may help overcome resistance to chemoradiation therapy in OSCC. A recent study found that AP-1 induces the expression of BCL-2, a proto-oncogene linked to apoptosis suppression implicated in resistance to chemoradiation therapy in OSCC and in recurrent chemo- and radioresistant oral tumors [36]. Targeting IL-1, which can activate AP-1, may help treat oral cancer since it can decrease the activation of NF-κB and AP-1 pathways, which in turn lowers bcl-2. However, this theory has to be verified.[13]

2.3TNF-α

TNF-α is a multifunctional cytokine that has been recognized as a key mediator of the formation of cancer as well as one that accelerates invasion, initiates EMT, and increases tumor angiogenesis [29,43,42,44]. TNF-α is expressed endogenously in oral carcinomas and certain oral potentially malignant disorders (OPMDs) such as OLP [45,46]. By upregulating genes linked to neutrophil recruitment, invasion, and invadopodia, TNF-α promotes a pro-invasive and pro-inflammatory phenotype in a paracrine manner in OSCC [58, 19]. Reductions in patients' overall survival as well as disease-free survival were linked to the over-expression of these genes. [58] The ability of TNF-α to stimulate the invasion of OSCC cells by enhancing matrix metalloproteinase (MMP)-2 and MMP-9 production which is regulated by the NF-κB, AKT and PI3K signaling pathways [58, 27, 29,47]. It has also been linked to elevated TNF-α receptor-1 (TNFR-1) signaling and OSCC metastasis. The ability of TNF-α to stimulate the invasion of OSCC cells by enhancing matrix metalloproteinase (MMP)-2 and MMP-9 production [27,29] which is regulated by the NF-κB, AKT and PI3K signaling pathways has also been linked to elevated TNF-α receptor-1 (TNFR-1) signaling and OSCC metastasis.[58, 27,29,47] As higher MMP expression is linked to greater OSCC invasion, metastasis, and a poor prognosis, it has been established that MMPs play crucial roles in OSCC [48–50]. Additionally, MMPs are said to play a significant part in the EMT process since MMP-2, MMP-9, and MMP-7 can improve EMT [51–54]. An essential MMP regulator is NF-κB and TNF-α can activate NF-κB through TNFR1, increasing MMP secretion [55,56]. Additionally, TNF-α can trigger EMT through p38 MAPK activation and the generation of cancer stem cells (CSCs) has been linked to TNF-α-induced EMT [43,57]. Significantly, CSCs are present in OSCC since they have been associated with treatment resistance and the worst prognosis. Through the activation of the PI3K/Akt/GSK3β and Raf-MEK ERK signaling networks, the expression of CD44, a well-known CSC marker, has been linked to increased cell invasion, cell migration, and therapy resistance in OSCC [59]. Additionally, it has been demonstrated that silencing CD47, a molecule involved in the generation of CSCs in OSCC, reduces EMT and the presence of CSCs. The formation of EMT, enhanced invasion, proliferation, and distant metastasis have all been linked to the activation of the PI3K/Akt/GSK3β signaling pathway [60-61]. Because TNF-α has so many positive effects on the development of cancer, treating OSCC may benefit from a method that targets TNF-α. Anti-TNF-α treatment has been demonstrated in vitro to decrease OSCC cell proliferation and metastasis yet Because TNF-α has so many positive effects on the development of cancer, treating OSCC may benefit from a method that targets TNF-α. Anti-TNF-α medication has been demonstrated in vitro to decrease OSCC cell proliferation and metastasis but more research is required before this can be applied in a clinical setting. [62]

2.4 IL-8 and IL-6

Because of the IL-8 and IL-6 ability to induce epithelial and endothelial cell migration and invasion [91], disrupt cell-cell communication, stimulate angiogenesis and tumor formation [89, 90], and block macrophage function, IL-6 and IL-8 are both referred to be "oncogenic cytokines." Patients with OPMDs and OSCCs have higher levels of IL-6 and IL-8 [6, 14,89,90, 92, 93]. This is likely due to abnormal activation of NF-κB. Malignant oral keratinocytes themselves as well as other TME cells such as tumor-associated macrophages (TAMs) can release IL-6 and IL-8. Given the significance of TAMs as a source for both of these cytokines, numerous efforts have been made to target TAMs to limit their secretion [94,95]. It has been suggested that IL-8 may serve as a mediator in the formation of OSCC and that it functions as an autocrine growth factor in HNSCC and other malignancies [15]. Malignant oral keratinocytes constitutively express it, and its inhibition increases the proliferation, angiogenesis, and survival rate of cancer cells while decreasing the viability, proliferation [6], and invasion of OSCC cells [6,16,96]. Similarly, overexpression of IL-6 in patients with HNSCC is linked to a bad prognosis, likely through increasing the number of myeloid-derived suppressor cells and PDL-1 expression, which in turn facilitates an immunosuppressive TME [97]. Furthermore, overexpression of IL-6 is thought to be a significant predictor of treatment outcome. Expressions of IL-6 and IL-8 in OSCC are linked to a more invasive growth mode. [11]

2.5 Family Members of IL-1

IL-1, which comprises IL-1α and IL-1β, is the model cytokine that promotes inflammation. Both IL-1α and IL-1β are identified in the saliva of OSCC patients [100, 101], are constitutively expressed in OSCC [9, 12, 98, 99], and have been linked to tumor growth and OSCC carcinogenesis [7, 10]. The OSCC-expressed IL-1α increases the expression of IL-8 [39] and IL-6 [98] and encourages the autocrine activation of NF-κB and AP-1. OSCC cells generate IL-1α [12], which stimulates cancer-associated fibroblasts (CAFs) to proliferate and secrete cytokines (IL-8, CCL7, and CXCL1), hence accelerating the growth of tumors [33]. Given that IL-1α is more abundant in metastatic HNSCC tumors than in non-metastatic HNSCC tumors, it appears to be crucial for the formation of distant metastases.

This is most likely made possible by IL-1α's capacity to promote the production of genes involved in metastasis, including MMP-9, PGE2, VEGF, and IL-8, as well as to cause tumor cells to transmigrate across the endothelium [10]. Furthermore, because intranuclear IL-1α has been demonstrated to cause malignant transformation, it has been suggested that IL-1α can function as an oncoprotein on its own.[102]

Through initiating EMT, IL-1β raises the amounts of IL-6 and IL-8 expressed by OD and OSCC cells, promoting the invasiveness of OSCC [9]. Additionally, it has been determined that IL-1β is a critical node gene in the OSCC TME in vivo [7]. Precursor IL-1β mRNA expression has been linked to malignant alterations (from moderate dysplasia to OSCC) [9], and increased expression of IL-1β has been linked to lymph node metastases in OSCC [103]. The HNSCC's IL-1 can also encourage CAFs to release other cytokines. along with typical fibroblasts such CCL-5, CXCL1, IL-8, and CCL-7 [33, 104].

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Along with IL-1β, the IL-1 agonist receptor, IL-1R1, has also been demonstrated to stimulate cancer and is also overexpressed in OSCCs. development and spread by the overexpression of CXCR4, which may be reversed by overexpressing the interleukin and blocking IL-1R1. An inhibitor of IL-1 receptor (IL-1RA) [13]. Remarkably, IL-1RA has been documented as being downregulated in OSCC and OD [20] and is said to control the release of IL-6 and IL-8 triggered by IL-1 by NF-κB, and p38 MAPK pathways are inhibited. [50, 105]

2.6 COX-2

Arachidonic acid is converted by the enzyme cyclooxygenase-2 (COX-2) into prostaglandins, including prostaglandin E2 (PGE2). Oral squamous cell carcinoma (OSCC) is one of the many cancer types that commonly express COX-2. It is linked to a number of cancer-promoting factors, such as the induction of CSC-like activity, angiogenesis, proliferation, apoptotic resistance, inflammation, invasion, and metastasis of cancer cells [68].

Many substances, such as interleukin-1 (IL-1), epithelial growth factor (EGF), transforming growth factor-beta (TGF-β), and tumor necrosis factor-alpha (TNF-α), can promote the production of COX-2. Early in the course of oral carcinogenesis, COX-2 is expressed and the degree of dysplasia is correlated with COX-2 expression levels [67,75,69,70,71]. It correlates with advanced tumor stages, a higher likelihood of distant metastasis and a worse prognosis for patients with OSCC. It is markedly overexpressed in OSCC [72,73,74,76].

PGE2 increases the expression of intercellular adhesion molecule-1 (ICAM-1) which has an impact on cell migration. In order to maintain a persistent inflammatory state in oral cancer, COX-2 is crucial [78,79]. Moreover, COX-2 regulates the process of lymphangiogenesis by controlling the synthesis of vascular endothelial growth factor (VEGF) [77,80,81]. Higher TNM stages, lymphangiogenesis, and lymph node metastases are associated with co-expression of COX-2 and VEGF-C. In OSCC, VEGF is often overexpressed. This co-expression is reportedly a different predictor of survival for OSCC patients [77]. VEGF expression rises in oral cancer as a result of tumor-associated hypoxia. Hypoxia-inducible factor-1α (HIF-1α) binds to hypoxia response elements in response to low oxygen levels, upregulating VEGF and promoting angiogenesis.[82-83] In ovarian cancer (OSCC), HIF-1α and HIF-2α positively correlate with clinical-pathological features such as tumor size and microvessel density. In vivo studies have demonstrated that downregulating HIF-1α and HIF-2α reduces tumor angiogenesis and proliferation [86]. Furthermore, VEGF can stimulate COX-2 expression, which increases PGE2 synthesis and triggers NF-κB (nucleus kappa B) [85]. This is another way that hypoxia exacerbates an inflammatory state.

2.7 TGF-β

TGF-β is a multifunctional pro-inflammatory cytokine that can either stimulate angiogenesis, irritation, EMT, and immune suppression, or it can induce apoptosis and growth arrest, inhibit proliferation, and promote tumor formation and progression of many cancers [86]. TGF-β's ability to prevent or stimulate tumor growth is dependent on the cellular and regional environment [87]. It has been found that TGF-β promotes carcinogenesis in OSCC [88]. The expression of greater TGF-β levels in OPMDs [18] and OSCC [90, 91] than in healthy controls, as well as the correlation between high TGF-β levels and poor prognosis in OSCC patients [90], all provide credence to this. Different pathways could be involved in TGF-β's ability to induce tumors in oral cancer. The differentiation of CAFs is primarily influenced by TGF-β and the accumulation of CAFs has been identified as an independent prognostic factor in OSCC. The TME can be modulated by CAFs, which speeds up the development of cancer [128]. TGF-β1 was transgenically produced in an in vivo mouse model, and the results showed that TGF-β1 induced hyperproliferation of epithelia, severe inflammation, and angiogenesis at levels comparable to those found in HNSCCs, indicating that TGF-β1 offers a milieu that promotes Tumor [88]. Through the protein phosphatase 1 (PP-1) signaling pathway, TGF-β increases cell motility in OPMDs, promoting a more malignant phenotype [93]. Given that TGF-β may cause EMT in endothelial cells and that these cells can cause EMT in OSCC cells when grown with TGF-β, TGF-β appears to be crucial for the development of EMT [94]. Moreover, TGF-β can cause EMT by promoting the production of ADAM12, a metalloprotease, and disintegrin linked to cancer [95].

2.8 Suppressive Immune Cytokines

Additionally involved in the development of oral carcinogenesis are anti-inflammatory cytokines. They have two different functions: they can decrease the immune system's ability to fight tumors by lowering its anti-tumor response, and they can counteract the pro-inflammatory counterpart's ability to cause tumors [96]. Table 1 lists the various functions that several immunosuppressive cytokines have been reported to play in the development of OSCC, with IL-1RA, IL-4, IL-10, and IL-13 being the most frequently studied. The IL-1RA gene, IL1RN, is downregulated in HNSCC [97,98], and IL-1RA itself declines during the oral carcinogenesis process. Theoretically, this would permit increased IL-1 activity and the previously indicated effects. However, progressed and poorly differentiated OSCCs have been found to have significant IL1-RA expression [20, 24], indicating that IL-1RA expression may accelerate tumor growth.

Additionally involved in the development of oral carcinogenesis are anti-inflammatory cytokines. They have the ability to operate as a double-edged sword and reduce the tumorigenic potential of this, but more research is necessary to fully understand this. In comparison to healthy controls, OSCC patients have also been shown to have higher levels of IL-4, IL-10, and IL-and a more

aggressive OSCC phenotype has been linked to increased IL-10 expression [13,24, 25, 111,114]. Tumor rejection is prevented by IL-4, which causes an immunological divergence from TH1 to TH2 responses, IL-10, which reduces anti-tumor immunity and aids in tumor immune escape and IL-13, which impairs the anti-tumor response by preventing IFN-γ release and CD8+ T cell activation [71, 72].

3. DIAGNOSIS

To diagnose oral cancers, various techniques are used:

3.1 Physical Examination:

Your doctor or dentist will inspect your lips and mouth for abnormalities, such as sores or white patches (leukoplakia), which might indicate cancerous changes.

3.2 Biopsy:

If an abnormal area is found, a biopsy may be performed to collect a tissue sample for laboratory analysis. This can be done using a cutting instrument or a needle to extract cells. The lab will examine these cells for cancer or precancerous changes that could suggest future cancer risk.

3.3 Staging Tests: Once oral cancer is diagnosed, additional tests help determine its stage or extent. These tests may include:

- **Endoscopy**: A small, flexible camera is inserted through the throat to check for signs of cancer spread.
- **Imaging Tests**: Various imaging techniques, such as X-rays, CT scans, MRIs, and PET scans, may be used to assess whether the cancer has spread beyond the mouth. The choice of tests depends on your specific situation, and not all tests may be necessary. [25,26, 27]

4. TREATMENT

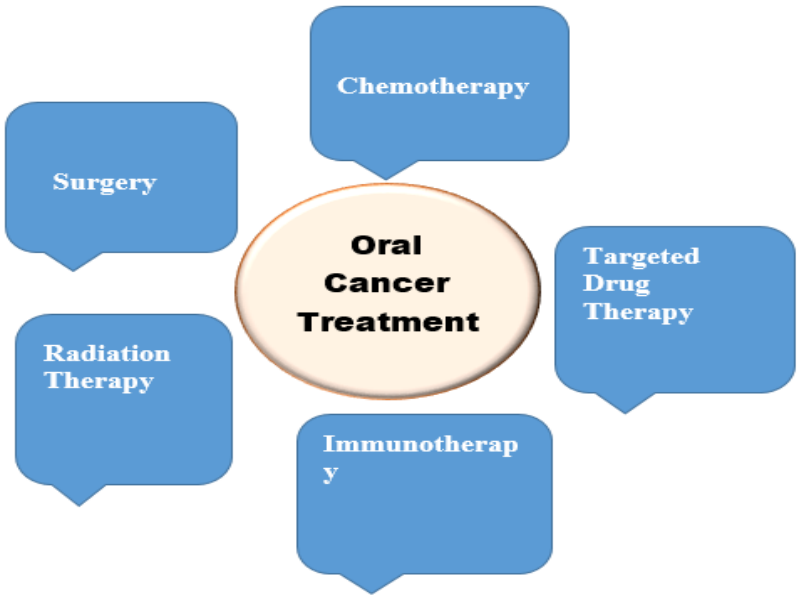

Fig 4 Oral Cancer Treatment

Treatment for mouth cancer is tailored based on the cancer's location, stage, your overall health, and your preferences. Options may include surgery, radiation therapy, chemotherapy, targeted drug therapy, and immunotherapy. Discussing these options with your doctor is essential to determine the best approach for you.

4.1 Surgery

Surgery aims to remove cancerous tissue and may involve:

- ***Tumor Removal***: The surgeon will excise the tumor along with a margin of healthy tissue to ensure all cancer cells are eliminated. Smaller tumors might be removed with minor surgery, while larger tumors could require more extensive procedures, such as removing part of the jawbone or tongue.
- ***Neck Dissection***: If cancer has spread to the lymph nodes in your neck, the surgeon may remove affected lymph nodes and surrounding tissues. This helps eliminate cancer cells and can provide information on whether additional treatments are needed.
- ***Reconstructive Surgery***: Post-surgery, reconstructive procedures may be necessary to rebuild the mouth. This can involve grafts of skin, muscle, or bone from other body parts and possibly dental implants to replace lost teeth.[115]

Surgical risks include bleeding, infection, and potential impacts on appearance, speech, eating, and swallowing. You might require a feeding tube temporarily or long-term, either through the nose or directly into the stomach. Specialists may assist with adjustments to these changes.

4.2 Radiation Therapy

Radiation therapy uses high-energy beams, such as X-rays or protons, to kill cancer cells. It can be delivered externally or through radioactive seeds placed near the cancer (brachytherapy). It is often used after surgery but can also be used alone for early-stage

cancers or combined with chemotherapy for enhanced effectiveness. In advanced cases, it may alleviate symptoms like pain.Possible side effects include dry mouth, tooth decay, and jawbone damage. Consulting a dentist before starting radiation therapy can help ensure your teeth are in good condition and reduce the risk of complications.[115,116]

Fig 5 : Radiation Therapy

4.3 Chemotherapy

Chemotherapy involves drugs that target and kill cancer cells. It can be used alone, with other chemotherapy drugs, or combined with other treatments like radiation. The combination often improves effectiveness but can also increase side effects. Common side effects include nausea, vomiting, and hair loss. Your doctor will inform you about the potential side effects based on the specific drugs you receive. [115,116]

4.4 Targeted Drug Therapy

Targeted drugs focus on specific aspects of cancer cells to hinder their growth. They can be used alone or with other treatments. For instance, cetuximab (Erbitux) targets a protein more prevalent in cancer cells. Side effects may include skin rash, itching, headache, diarrhea, and infections. [115,116]

4.5 Immunotherapy

Immunotherapy leverages your immune system to combat cancer. It works by enhancing the immune system's ability to recognize and attack cancer cells. This approach is generally used for advanced mouth cancers that do not respond to standard treatments.Each treatment type has its considerations and potential side effects, so it’s crucial to have a thorough discussion with your healthcare team to choose the most suitable options for your condition.[26,27]

5. CONCLUSION

The review of inflammatory pathways in oral cancer underscores the significant impact of chronic inflammation on the disease's initiation and progression. Inflammatory mediators, including cytokines and immune cells, not only promote tumor growth and survival but also enhance metastasis and resistance to therapy. The interplay between inflammation and genetic alterations further complicates the disease landscape, highlighting the need for a multifaceted approach to treatment.

Targeting specific inflammatory pathways offers promising therapeutic avenues, potentially leading to better clinical outcomes. Continued research into the molecular mechanisms involved in inflammation-related oral carcinogenesis will be essential for developing novel strategies for prevention, diagnosis, and treatment. Ultimately, a deeper understanding of these pathways can contribute to more effective interventions and improved patient quality of life in oral cancer care.

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