Clinics in Oncology

Review Article
Published: 11 Dec, 2023

Expression, Role and Mechanism of IL-6 in the Malignant Transformation of Oral Precancerous Lesions

Qu Y[1], Fu J[2], Liu Y[2], Qin L[1] and Han Z[1]**

[1]Department of Oral and Maxillofacial & Head and Neck Oncology, Beijing Stomatological Hospital, Capital Medical University, China

[2]Department of Periodontics and Laboratory of Tissue Regeneration and Immunology, Beijing Key Laboratory of Tooth Regeneration and Function Reconstruction, School of Stomatology, Capital Medical University, China

Abstract

Objective: Most clinical oral cancers develop from oral precancerous lesions. As an important proinflammatory cytokine, IL-6 has been suggested to be closely related to the occurrence and malignant transformation of oral precancerous lesions. This review will examine the expression and role of IL-6 in common oral precancerous lesions and the possible mechanisms of malignant transformation to identify new therapeutic targets and prevent cancer.

Methods: A literature review based on PubMed publications in the last two decades was performed to summarize progresses of IL-6 in several common oral precancerous lesions.

Results: Most studies have demonstrated that the level of IL-6 is increased in oral precancerous lesions compared with the control group, and there is a potential positive correlation between the level of IL-6 and the malignant transformation degree of lesions. In addition, IL-6 may promote the malignant transformation of oral precancerous lesions by regulating the methylation of tumor suppressor genes, affecting the status of fibroblasts and cancerous cells in the microenvironment, and inhibiting the infiltration and function of T cells.

Conclusion: This review provides new ideas for how IL-6 promotes the malignant transformation of oral precancerous lesions, which is helpful for the development of related research in the future.

Keywords: Oral precancerous lesions; Interleukin-6; Malignant transformation; Leukoplakia

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Correspondence:
Lizheng Qin, Department of Oral and Maxillofacial & Head and Neck Oncology, Beijing Stomatological Hospital, Capital Medical University, NO. 4 Tian Tan Xi Li, Dongcheng District, Beijing, 100050, China, Tel: +86-010-57099152; Fax: +86-010-57099151
Zhengxue Han, Department of Oral and Maxillofacial & Head and Neck Oncology, Beijing Stomatological Hospital, Capital Medical University, NO. 4 Tian Tan Xi Li, Dongcheng District, Beijing, 100050, China

Received Date: *16 Nov 2023*
Accepted Date: *01 Dec 2023*
Published Date: *11 Dec 2023*

Citation:
Qu Y, Fu J, Liu Y, Qin L, Han Z. Expression, Role and Mechanism of IL-6 in the Malignant Transformation of Oral Precancerous Lesions. Clin Oncol. 2023; 8: 2034.
ISSN: 2474-1663

Introduction

Oral cancer is among the most common malignancies worldwide, with nearly 355,000 patients newly diagnosed with oral cancer and 177,000 patients dying from oral cancer, according to the Global Cancer Statistics conducted in 2018. Oral cancer is still common in South and Central Asian countries [1]. More optimistically, oral cancer has decreased globally in recent years, but the 5-year survival rate for advanced oral cancer is only about 40.9%, regardless of the effect of ethnicity. Therefore, how to effectively prevent oral cancer has become the focus of most oral surgeons and oral mucosa doctors.

Oral cancer usually develops from Potential Malignant Oral Epithelial Lesions (PMOELs). Common oral precancerous lesions include leukoplakia, oral submucosal fibrosis, lichen planus, discoid lupus erythematosus, erythema, chronic oral candidiasis and actinic cheilitis. However, only a small percentage of PMOELs develop cancer due to multiple local and systemic factors [2]. Tumorigenesis is a process that usually requires two major events to occur, acquiring at least 4 to 5 mutated genes in normal long-lived stem cells or instantaneously expanded cells, and epigenetic changes in cells. The modes include inactivation of the tumor suppressor pathway and activation of the carcinogenic pathway. PMOELs are usually in a chronic inflammatory microenvironment, and inflammatory factors in the microenvironment are thought to play a key role in the malignant transformation of oral precancerous lesions. The reasons include that inflammatory factors can lead to epigenetic changes conducive to tumorigenesis; cytokines produced by inflammatory cells can increase intracellular Reactive Oxygen Species (ROS) and Reactive Nitrogen Intermediate (RNI) in precancerous cells, which can cause mutations in neighboring epithelial cells due to DNA damage and genomic instability. In addition, inflammatory signals can shape the immunosuppressive Tumor Microenvironment (TME), thereby aiding the immune escape of cancerous cells [3].

Interleukin-6 (IL-6) is a major member of the pro-inflammatory cytokine family, and it was first named Interferon-β2 (IFN-β2) or B-cell Stimulator Factor-2 (BSF-2), which refers to the T cell product that has a differentiation stimulation effect on the B cell line. However, in 1986, J Van Damme confirmed that the protein is secreted by fibroblasts and showed its activity to stimulate b cell growth. In order to resolve prescribing nomenclature confusion, the protein was proposed to change the designation to IL-6 [4]. After stimulation, IL-6 is mainly produced by monocytes and macrophages with pattern-recognition receptors for pathogens or injury-associated molecular patterns. It can bind to the transmembrane IL-6 receptor (mIL-6R) or soluble IL-6R (sIL-6R) to mediate IL-6-related signaling by forming a complex with the signal transduction subunit molecule gp130. The three modes of IL-6 signaling are IL-6 binding to mIL-6R (classical), sIL-6R (trans-signaling), or binding to gp130 on nearby cells by IL-6R (trans-presentation). The existence of these signal transduction pathways and the fact that gp130 is generally expressed in most tissues and cells leads to the pleiotropy of IL-6 function [5]. This includes enhancing the immunological, blood, and acute phase response, helping the body eliminate infectious substances and repair damaged tissues. Moreover, IL-6 overproduction and signaling pathway malfunction cause long-term inflammation, autoimmune disorders, and cancer.

In oral cancer, IL-6 is usually highly expressed. As early as 1999, some scholars studied 57 patients with Oral Squamous Cell Carcinoma (OSCC) and found that the protein and mRNA levels of IL-6 in tumor tissues of these patients were significantly higher than those in normal tissues [6]. A recent meta-analysis of 15 kinds of literature concluded that the concentration of IL-6 in tumor patients' saliva was higher than in the control group and the group of patients with precancerous lesions [7]. Therefore, more and more scholars believe that IL-6 in patients' saliva can be used as an OSCC biomarker and a predictor of tumor recurrence [8]. IL-6 has been a key oral cancer prevention target in recent years. In a study of radiosensitive OSCC cell lines, it was found that increased IL-6 levels inhibited radiation-induced cell death, while Tocilizumab (TOC), a monoclonal antibody targeting IL-6R, made tumor cells more sensitive to radiotherapy by blocking IL-6 signaling pathway. Combining TOC with conventional radiotherapy may improve the therapeutic effect and overall survival rate of patients with radiotherapy tolerance to OSCC [9].

Histopathology shows variable degrees of inflammatory cell infiltration in oral precancerous lesions, and the lesions' malignant transformation process is dynamic. Thus, as an important pro-inflammatory cytokine, what role does IL-6 play in oral precancer and its carcinogenesis? This review summarizes the expression, role and potential mechanism of IL-6 in oral precancerous lesions and their malignant transformation process. It provides new therapeutic strategies and targets for the future treatment of oral precancerous lesions.

Oral Leukoplakia

Oral leukoplakia is mainly a white oral mucosa lesion that cannot be erased and diagnosed as other definable lesions by clinical histopathology. As a precancerous lesion, leukoplakia is among the most common oral potential malignant diseases in clinical practice, with high incidence and high possibility of cancer. Clinically, it is divided into homogeneous and heterogeneous types, the latter more likely to develop into oral cancer. Numerous clinical studies have shown that the level of IL-6 significantly increases in the serum and saliva of patients with oral leukoplakia. However, whether it can directly diagnose leukoplakia and predict its malignant transformation is still controversial. By comparing the concentration of IL-6 in the saliva of 30 patients with histopathologically confirmed leukoplakia with that of 34 healthy volunteers, Brailo et al. found that the level of IL-6 in the saliva of patients with leukoplakia was significantly increased. However, the level of IL-6 in saliva is not related to the size of leukoplakia (lesions), the site of malignant transformation risk (previous studies have suggested that leukoplakia at the bottom of the mouth and on the tongue has a higher risk of malignant transformation than leukoplakia in other parts of the mouth), and whether the patient smokes [10]. Sharma et al. found that leukoplastic periodontitis patients had higher saliva IL-6 levels than healthy controls. Moreover, in the leukoplakia group, IL-6 levels increased with the increasing severity of dysplasia, which indicates that the lesion is undergoing malignant transformation [11]. A study that measured IL-6 in the saliva of healthy volunteers, leukoplakia and oral cancer mentioned that the level of IL-6 in the saliva of patients with leukoplakia was higher than that of healthy volunteers but lower than that of patients with oral cancer. Patients with leukoplakia have higher saliva IL-6 levels may due to the localized lesion epithelium or diffuse, chronic inflammatory infiltrating lymphocytes in the tissues secreted. IL-6 levels are further elevated in patients with oral cancer, possibly due to local tumor cell secretion. Therefore, the level of IL-6 in the saliva of leukoplakia patients can predict the risk of malignant transformation [12]. The 2021 meta-analysis that included 28 studies published between 2004 and 2018 also confirmed the above conclusion, and compared to healthy controls, the level of IL-6 in the saliva of patients with leukoplakia was significantly increased but lower than in oral cancer patients [13]. Besides, one study suggested that although salivary IL-6 levels were significantly different in oral cancer, oral leukoplakia, and healthy volunteers, serum IL-6 levels were not statistically different among different groups [14]. However, other studies found that oral leukoplakia patients had considerably greater serum IL-6 levels than the control group [15].

NF-κB is activated in the early stage of oral cancer and is among the important transcription factors for malignant transformation. Unexpectedly, IL-6 expression did not correlate with NF-κB (p65) nuclear or cytoplasmic expression, suggesting that NF-κB is not involved in IL-6-mediated leukoplakia carcinogenesis [16]. Currently, the mechanism of IL-6 involvement in malignant transformation in leukoplakia is mainly focused on the mechanism related to IL-6 and iron death. Studies have demonstrated that the expression levels of IL-6 and cystine/glutamate antiporter (xCT) in the normal, leukoplakia and tumor groups are gradually increased. IL-6 can activate the transcription expression of xCT through the Janus Kinase 2/Signal Transduction and Transcriptional Activator 3 (JAK2/STAT3) pathway, and xCT is a key amino acid transporter to assist iron death resistance. Therefore, the authors concluded that IL-6 could induce the iron death resistance of tumor cells and promote the malignant transformation of leukoplakia [17].

Oral Submucous Fibrosis

Oral Submucous Fibrosis (OSF) is an inflammatory reaction caused by excessive Extracellular Matrix (ECM) deposition, which leads to atrophy of oral mucosal epithelium, collagen accumulation of oral submucosal lamina propria and decreased blood vessels. Late pathological symptoms include mild to moderate chronic inflammatory cell infiltration; some cases can see epithelial dysplasia. Chewing areca nut is the main cause of inducing Epithelial-to-

Mesenchymal cell Transformation (EMT) and activating Buccal Mucosal Fibrosis (BMFs), eventually leading to OSF. Epigenetic changes of Wnt Inhibitory Factor-1 (WIF1) and p16 gene were found in buccal cells of OSF patients, and their hypermethylation status also contributed to the potential malignant transformation of OSF [18,19]. After conducting RNA-seq analysis on OSF and normal mucosal tissue, Peng et al. [20] found that IL-6 mRNA levels significantly increased in OSF tissue. A clinical study on a Pakistani population found that OSF patients had greater saliva IL-6 levels than normal volunteers and lower than oral cancer patients [21]. Haque et al. [22] investigated the spontaneous and stimulated production of IL-6 by Peripheral Blood Mononuclear Cells (PBMCs) from OSF patients and compared them with genetically-related relatives, Indian and Caucasian control subjects, and demonstrated that increased serum levels of IL-6 and reduced anti-fibrotic IFN-gamma in patients with OSF, which may be central to the pathogenesis of OSF. Furthermore, some scholars used arecoline and arecoline alkaloids to stimulate human normal gingival, buccal and OSF buccal mucosal fibroblasts and observed that the level of IL-6 factor increased in normal gingival and OSF buccal mucosal fibroblasts. However, the normal buccal mucosa secreted less IL-6 [20].

IL-6 at the lesion site of OSF can accelerate the excessive deposition of ECM components by promoting α-Smooth Muscle Actin (α-SMA) -induced fibrosis and the transformation of fibroblasts into myofibroblast phenotypes, which is ultimately conducive to the occurrence and malignant transformation of OSF [20]. Therefore, targeting IL-6 is predicted to prevent the OSF malignant transformation effectively. Lee et al. [23] research team treated human Buccal Mucosa Fibroblasts (hBMFs) with immune regulatory protein GMI extracted from microspore Ganoderma lucidum and explored that the IL-6 production and secretion in hBMFs cells significantly decreased after exposure to GMI. Subsequently, the activity of myofibroblasts, including the ability of collagen gel contraction, migration, invasion and wound healing, is also inhibited, which plays an anti-oral mucosal fibrosis role.

Oral Lichen Planus

Oral Lichen Planus (OLP) is a chronic inflammatory disease that presents as streaky lesions of the oral mucosa that appear white or off-white. OLP is symmetrical, most common in buccal mucosa, and long-term erosive lesions may become malignant. The typical pathological features are liquefaction degeneration of basal cells and zonal infiltration of lamina propria lymphocytes. It was reported that 1.4% of oral lichen planus patients developed malignant transformation and the risk factors mainly include ulceration, tongue location and female [24]. Various clinical studies also found that the levels of IL-6 in saliva and serum were significantly increased in OLP patients. Rhodus and other researchers measured the concentration of IL-6 in total Unstimulated Saliva (WUS) of 13 OLP patients, 13 OSCC patients, and 13 age-gender-matched healthy volunteers. They found that in patients with moderate and severe dysplasia of OLP, IL-6 levels were significantly higher than in the control group and OLP patients without dysplasia and lower than in the OSCC group. This suggests the potential of IL-6 levels in saliva in monitoring the malignant transformation of OLP [25]. The Cheng et al. [26] research team analyzed and compared the concentration of IL-6 in the saliva of pre-treatment OSCC (n=18), disease activity OLP (n=21), non-diseased OLP (n=20) and healthy control group (n=21), and found that the level of IL-6 in the saliva of OLP patients was significantly higher than the control group but lower than OSCC patients. The level of IL-6 in the saliva of advanced OLP patients was higher than quiescent OLP patients [26]. A recent meta-analysis study examined serum IL-6 concentration in OLP patients during the past 20 years and shown that 299 studies involved 231 LP/OLP cases and 12 control subjects, and the serum IL-6 concentration in OLP patients was significantly higher than the control group [27]. Elevated levels of IL-6 in the saliva of OLP patients may be due to increased secretion of keratinocytes, locally infiltrated monocytes and diseased fibroblasts. The increase of IL-6 concentration in serum may be mainly caused by PBMCs and endothelial cells. Locally secreted IL-6 diffuses into capillaries or drains into lymphatic vessels and eventually enters the blood circulation. Local secretion of IL-6 and PBMC and systemic production of IL-6 by endothelial cells are possible causes of elevated serum IL-6 concentration in LP patients.

Discoid Lupus Erythematosus

Discoid Lupus Erythematosus (DLE) is an autoimmune disease of the skin-mucosa-connective tissue characterized by inflammatory plaques. About 30% of patients have oral mucosa lesions. The lesion is characterized by persistent erythema with a disk-shaped central atrophic depression. Its pathogenesis involved abnormal immune response, apoptotic cell clearance, and environmental factors. Prolonged DLE lesions are at risk of becoming cancerous under prolonged exposure to light, smoking and chronic irritation, especially DLE in the lower lip. Of DLE patients, 5% develop Systemic Lupus Erythematosus (SLE), and 25% develop oral mucosal lesions [28].

The expression of IL-6 in DLE is not well defined. So far, only one study has suggested that IL-6 expression is only mildly positive in DLE lesions, either in the sun-exposed lesion area (lip) or in the non-irradiated lesion area (inner mouth) [29]. There is no consensus on the level of IL-6 and the severity of clinical symptoms in SLE. Some studies have shown that elevated IL-6 levels reflect the active phase of the disease, and that patients are susceptible to a variety of symptoms, including fatigue, joint pain, proteinuria, fever, rash, renal disease, and oral lesions [30]. Meanwhile, other researchers have failed to find any significant correlation between IL-6 and SLE [31]. Nevertheless, IL-6 expression levels are significantly increased in many parts of the body of SLE patients. The mucosa and lip tissues of healthy people express a certain degree of IL-6, but the expression of IL-6 in the same part of SLE patients is significantly increased [29]. The concentration of IL-6 in the saliva of SLE patients was significantly higher than the control group. Meanwhile, increased IL-6 expression can be observed in serum and peripheral blood cells of SLE patients regardless of whether they are in the active stage of the disease [31,32]. In addition, interestingly, a clinical study targeting SLE patients with low disease activity who were given additional Hydroxychloroquine (HCQ), a well-established immunosuppressive drug in the treatment of SLE, found that, the expression of IL-6 in serum was significantly decreased after oral HCQ treatment [33].

Potential Mechanism of IL-6 Involvement in Malignant Transformation of Oral Precancerous Lesions

Inflammation and carcinogenesis are closely linked processes because inflammation promotes DNA instability, and both processes are driven by pathways like NF-κB, STAT3, mTOR, and MAPK. These signaling pathways regulate the release of multiple pro-inflammatory

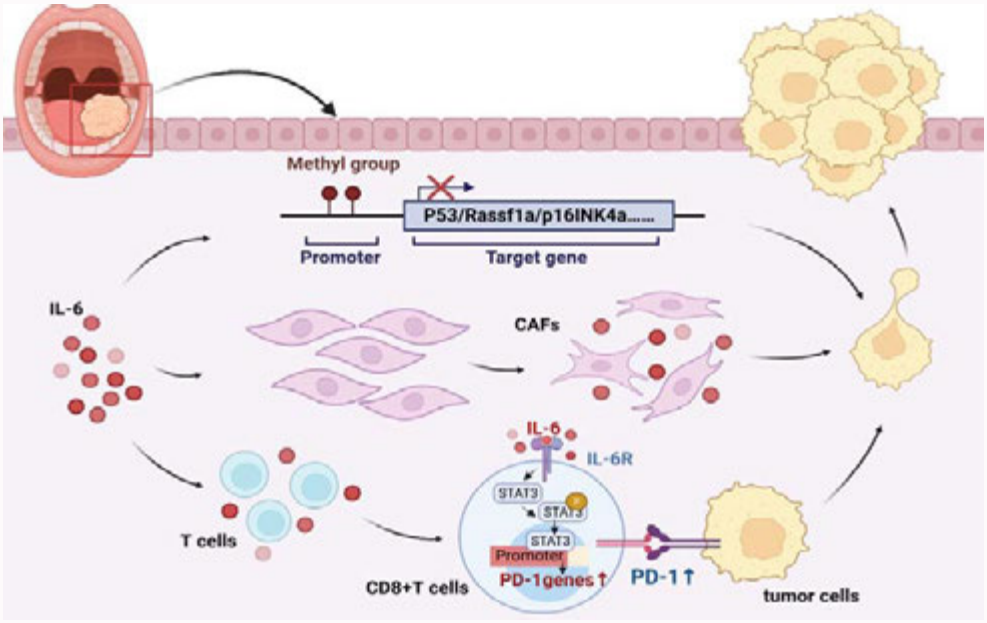

Figure 1: Possible mechanism of IL-6 promoting malignant transformation of oral precancerous lesions. IL-6 expression is increased in saliva of patients with oral precancerous lesions. Furthermore, IL-6 may play a role in promoting the malignant transformation of oral precancerous lesions by regulating the methylation of tumor suppressor genes and growth cycle regulation genes, affecting the activation and transformation of fibroblasts in the microenvironment, and inducing the expression of PD-1 of CD8+ T cells in the early tumor microenvironment.

cytokines, including IL-6, which control their activation and play a key role in shaping the immune response [34]. IL-6, as an important pro-inflammatory cytokine, plays a key role in the growth and survival of different types of tumors. Still, the mechanism by which this pleiotropic cytokine promotes the malignant transformation of oral precancerous lesions remains unclear. We hypothesize that IL-6 may promote the malignant transformation of oral precancerous lesions through gene DNA methylation, fibroblast state, and T cell immunity, based on existing research on its role in various tissue and organ carcinogenesis (Figure 1).

IL-6 promotes malignant transformation of oral precancerous lesions by influencing gene DNA methylation

DNA methylation is a form of chemical modification of DNA that can alter genetic expression without altering the DNA sequence. The so-called DNA methylation refers to the covalent binding of a methyl group to cytosine 5 carbon of CpG dinucleotide under the action of DNA methylation transferase [35]. Growing evidence shows that abnormal DNA methylation may contribute to OSCC tumorigenesis. Tumor cells can specifically repress or lower the expression of many tumor suppressor and cell cycle regulatory genes due to this common epigenetic change. Oral precancerous tissues have abnormal DNA methylation. And existing studies suggest that DNA methylation patterns have potential utility as a diagnostic biomarker of oral precancerous progression [36]. At the same time, some scholars have suggested that the new assay based on quantitative NGS analysis of bisulfite may be a highly sensitive and specific method. It is a non-invasive, easy-to-perform method to detect methylation changes occurring in early oral squamous cell carcinoma using only brushing sampling methods [37].

Numerous studies have confirmed that IL-6 can maintain the hypermethylation state of multiple tumor suppressor genes and CpG island, the promoter region of cell cycle regulation genes, in cancerous tissues. This leads to a long-term inactivation state and smooth carcinogenesis of the diseased tissues. Hodge's team found that in the human multiple myeloma cell line KAS 6/1, sensitive to IL-6, the p53 promoter region is epigenetically modified by methyltransferase, resulting in decreased expression levels. Moreover, IL-6-treated cells showed increased expression of DNMT-1, a DNA-maintaining methylase. DNA methyltransferase inhibitor zebularine can reverse the p53 promoter methylation and restore its expression, leading to the tumor cells' death [38]. Zhou et al. [39] found that in liver cancer pre-lesions, continuous secretion of IL-6 inhibits the expression of DNA damage checkpoint protein RAD51B through methylation, activates DNA damage response and genomic instability, and promotes carcinogenesis.

Additionally, the level of IL-6 in the lesion was positively correlated with the expression of UBE2D1, a member of the E2 ubiquitin-binding enzyme family, which mediates the ubiquitination and degradation of tumor suppressor protein p53 [39]. In Cholangioma, IL-6 regulates miR-148a and miR-152, upregulates the activity of DNMT-1, and promotes the methylation of tumor suppressor genes Rassf1a and p16INK4a [40]. The studies of the association of abnormal methylation with cancer development suggest that genome-wide hypomethylation and promoter hypermethylation induce chromosome instability and transcriptional silencing of growth-regulating genes, respectively. By establishing an *in vitro* model of IL-6-mediated chronic inflammation of OSCC cells, Gasche et al. [41] proposed that IL-6 induces the hypomethylation of the inherent hypermethylated repeating element LINE-1 sequence, resulting in increased chromosome instability and, thus, mitosis disorder. Contrarily, IL-6 induces several important tumor suppressor genes. Methylation changes of CpG promoters, including CHFR, GATA5 and PAX6, promote the occurrence of cancer through the combined effect of these two aspects.

Furthermore, the up-regulation of IL-6 expression may also reduce the sensitivity of tumor cells to methylation inhibitor therapy

[42]. These findings imply that IL-6 levels associated with the malignant transformation of oral precancerous lesions continue to rise. This may lead to cancer by influencing gene methylation and losing cell carcinogenesis' regulatory role.

IL-6 promotes the carcinogenesis of oral precancerous lesions by influencing cell status

The continuous local malignant transformation of oral precancerous lesions gradually forms a TME that promotes tumor growth. Cancer Associated Fibroblast (CAF) is an important component of TME, which promotes tumorigenesis by secreting growth factors, modifying the extracellular matrix, supporting angiogenesis and inhibiting anti-tumor immune response. Previous studies have found that long-term chronic inflammation in the precancerous state will induce the formation of CAFs and promote the secretion of IL-6, which can further promote the activation of fibroblasts to mediate the interaction between tumor cells and CAFs and ultimately lead to the smooth progress of the carcinogenesis.

Karakasheva's team proposed that chronic inflammation in the microenvironment during carcinogenesis would activate normal fibroblasts and convert them into CAFs. CAFs acquire a new secretion profile and produce pro-tumor cytokines, including IL-6. CAFs also interact directly with tumor cells and alter their gene expression profile, causing tumor cells to secrete high IL-6 levels. This cytokine activates the receptor (IL-6R) on tumor cells and CAFs in an autocrine paracrine manner, thereby activating STAT3 and MEK/ERK signaling pathways to varying degrees, ultimately promoting tumors' occurrence and development [43]. Peterfi et al. [44] found that IL-6 was expressed in interstitial fibroblasts in the microenvironment in kidney precancerous lesions, and the intensity of its expression was significantly correlated with the remodeling of the microenvironment. Normal renal fibroblasts can maintain normal tissue structure and prevent cancer through direct cell-cell interaction. However, a long-term chronic inflammatory state in diseased tissues causes normal interstitial fibroblasts to transform into activated fibroblasts, similar to CAFs. CAFs that produce IL-6 are largely responsible for changes in the extracellular matrix, which supports carcinogenesis in this state. In addition, CAFs can induce EMT. Some researchers have significantly reversed the IL-6-induced EMT phenotype by inhibiting CAF-secreted IL-6 with neutralizing antibodies [45]. Wu et al. [46] found that IL-6 secreted by CAFs enhances the migration and EMT of gastric cancer cells by activating the JAK2/STAT3 pathway in gastric cancer cells. In conclusion, it can be hypothesized that CAFs induced by long-term inflammation in the oral cavity secrete a large amount of IL-6, which in turn can act on CAFs to interact with tumor cells and promote the carcinogenic effect of oral precancerous lesions.

IL-6 promotes the carcinogenesis of oral precancerous lesions by influencing the immune microenvironment

Under normal physiological conditions, the cancerous cells produced in the malignant transformation of diseased tissue will be recognized and killed by human immune cells as specific antigens, hindering cancerous transformation. Among them, CD8+ T cells, as the main executor, have the effect of directly killing cancerous cells. Previous studies have suggested that IL-6 secreted by various cells can promote carcinogenesis by regulating the differentiation and function of T cells.

Programmed Death Ligand 1 (PD-L1), as a ligand of immune checkpoint PD-1, is usually upregulated in cancerous cells and inhibits the killing function of effector CD8+ T cells by binding to PD-1 on the surface of T cells infiltrated into the microenvironment [45]. Chans et al. found that IL-6 activates the JAK1 phosphorylation to PD-L1 at Tyr112, thereby raising endoplasmic reticulum-related n-glycosyltransferase STT3A to catalyze PD-L1 glycosylation and maintain the stability of PD-L1 in cancerous cells to help it escape immune. Blocking the IL-6/JAK1 pathway leads to PD-L1 stability loss and makes cancerous cells sensitive to Tim-3 immune checkpoint therapy [47]. By building mouse models of colitis and colon cancer, Hailemichael and other researchers found that the continuous accumulation of IL-6 in the pathological tissues may limit CD4+/CD8+ effector T cell infiltration, which promotes tumorigenesis. However, blockade of IL-6 was associated with increased infiltration of CD4+/CD8+ effector T cells and decreased infiltration of Th17, macrophages and bone marrow cells [48]. Moreover, other studies have shown that the signal transduction of IL-6/JAK/STAT3 pathway can induce the PD-1 expression in CD8+ T cells in pathological tissues, and conversely, inhibition of IL-6/JAK/STAT3 signaling down-regulates the PD-1 expression [49]. It is concluded that IL-6 in oral precancerous lesions can maintain the stability of immune checkpoint of CD8+ T cells, thus promoting the immune escape of cells that undergo early malignant transformation in the pathological tissue.

Summary and Prospect

In summary, long-term chronic inflammation is closely related to the malignant transformation of oral precancerous lesions. As an essential multi-effect pro-inflammatory cytokine, IL-6 is highly raised in local lesion tissue, saliva, and serum of most oral precancerous lesions patients and positively connected with dysplasia severity. The elevated level of IL-6 secretion in saliva is a possible diagnostic indicator of oral precancerous lesions and even has certain predictive value for malignant transformation of lesions [13,49]. Due to the lack of uniformity in relevant study design, large-scale, multi-center clinical prospective investigations based on existing research are still needed to corroborate this result.

Only a few studies have been reported on the role and mechanism of IL-6 in promoting malignant transformation in oral precancerous lesions. By reviewing the IL-6 role in the carcinogenesis of other tissues and organs and its molecular mechanism, we speculated that IL-6 may promote the malignant transformation of oral precancerous lesions by regulating the methylation of tumor suppressor genes and growth cycle regulation genes, affecting the fibroblasts' activation and transformation, and inhibiting CD8+ T cell infiltration and function in the microenvironment. Future studies can be combined with new technologies, like single-cell sequencing and spatial transcriptomics, that have emerged in recent years to reveal the specific mechanism of IL-6 in the malignant transformation process from the above aspects. Only one study used IL-6 as a therapeutic target for oral precancerous lesions. This study found that local injection of TOC in a mouse oral leucoplakia model inhibited the progression of the lesions, suggesting it could delay HNSCC tumors [50]. However, the current research on the target of IL-6 in oral precancerous lesions is still limited, and there is a lack of large animals and clinical studies. Based on its important role in oral cancer, the expansion of basic research fields can be further strengthened, and clinical studies can be conducted to achieve transformation.

Acknowledgement

This research was funded by the Beijing Stomatological Hospital,

Capital Medical University Young Scientist Program, grant number YSP202107 and the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support, grant number ZYLX202121 to Y.L.

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