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Updates on immunological mechanistic insights and targeting of the oral lichen planus microenvironment

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Oral lichen planus (OLP) is a chronic immune inflammatory disease that is an oral potentially malignant disorder (OPMD), occurs in the oral mucosa and affects approximately 0.5% to 4% of the general population. There are usually five types of OLP: reticular/papular, plaque-like, atrophic/erythematous, erosive/ulcerative, and bullous. Furthermore, the chance of causing oral squamous cell carcinoma (OSCC) is 1.4%. Although the etiology of OLP is still unknown, accumulating evidence supports that immune dysregulation may play a vital role in the pathogenesis of OLP, especially the massive production of various inflammatory cells and inflammatory mediators. In this review, we focus on the relationship between OLP and its immune microenvironment. We summarize current developments in the immunology of OLP, summarizing functional cell types and crucial cytokines in the OLP immune microenvironment and the underlying mechanisms of key signaling pathways in the OLP immune microenvironment. We highlight the application potential of targeted immune microenvironment therapy for OLP.

KEYWORDS

oral lichen planus, immune microenvironment, immune cells, chemokine, immune therapy

1 Introduction

Oral lichen planus (OLP) is a chronic inflammatory condition that occurs in the oral mucosa and affects approximately 0.5% to 4% of the general population, and its malignant transformation rate is 1.4% (1, 2). Histopathologically, this lesion is characterized by lymphocyte band-like invasion of the lamina propria and basal keratinocyte destruction. The etiology of OLP may be primarily related to immune, genetic, infection, psychiatric, endocrine, microcirculation disorders and trace element deficiency. Mounting evidence

supports immunological processes playing critical roles in the pathogenesis of OLP, especially the massive production of various inflammatory cells and inflammatory mediators caused by immune dysregulation (3). It is currently suggested that persistent aggregation of T lymphocytes leads to a chronic inflammatory response to OLP. A range of cells and cytokines in the oral mucosa are involved in the development of OLP by affecting T lymphocyte-mediated basal cell liquefaction and epithelial keratinocyte apoptosis. Recently, there has been awareness of the association of chronic inflammation with various epithelial malignancies, such as chronic esophagitis-associated esophageal adenocarcinoma of esophagitis and chronic inflammatory enteritis-associated bowel cancer (4–7). Existing evidence suggests that the chronic inflammatory process per se is able to provide a cytokine-based microenvironment that is able to influence cell survival, growth, proliferation, differentiation and movement, hence the microenvironment contributes to cancer initiation, progression, invasion and metastasis (7, 8). The bases of OLP malignant transformation might be found in the OLP subepithelial inflammatory microenvironment, which presents activated inflammatory cells and cytokine networks that may act to promote squamous tumorigenesis. The production of tumor necrosis factor, macrophage inhibitory factor, matrix metalloproteinases (MMPs), chymase, interleukin 4 and 6 by macrophages, mast cells, fibroblasts and T-lymphocytes may lead to angiogenesis, degradation and remodeling of the extracellular matrix, thus ultimately influencing oral epithelial cell growth, survival, migration, apoptosis, and neoplastic transformation and ultimately promoting tumor initiation (9). The study of the OLP immune microenvironment greatly enriched our understanding of OLP and opened a broad field for the treatment of this disease. In this paper, we summarize current developments in the immunology of OLP.

2 OLP immune microenvironment

The immune microenvironment is a complex dynamic network system composed of many kinds of cells and immune molecules (10). Various injury factor stimulations can lead to inherent immune cell and immune cell type and function changes, resulting in local immune homeostasis and microenvironment changes and leading to chronic disease. The pathogenesis of OLP is currently controversial, but substantial evidence suggests that immune dysregulation plays a key role (3). Potential mechanisms related to immunopathogenesis may include antigen-specific cell-mediated immune responses, nonspecific mechanisms, autoimmune responses, and humoral immunity (11). Regardless of these immunopathologies, the immune microenvironment plays a crucial role. Alternatively, the immune microenvironment may influence the characteristics of the immune response, disease severity, and duration of OLP. The cellular and cytokine

networks activated in the immune microenvironment may underlie OLP carcinogenesis (9).

Since the immune microenvironment plays an important role in the pathogenesis of OLP, a thorough study of the immune microenvironment signaling pathway in OLP is critical for us to seek the correct therapeutic targets (Figure 1). Upon stimulation with viruses, bacterial infection, drugs or mechanical damage, MHC class II molecules and antigen binding on the surface of immature DCs in OLP lesion tissues are presented to CD4⁺ helper T cells. Their secreted interleukin-12 (IL-12) induces cytokine release from CD4⁺ T cells, including interferon gamma (IFN- γ) and IL-2, which recruit CD8⁺ T cells to subepithelial regions, activate CD8⁺ T cells, and activate proinflammatory type M1 macrophages, eventually leading to the onset of chronic inflammation (12). Then, CD8⁺ T lesion cells cause apoptosis when in contact with diseased keratinocytes with the corresponding antigens, which may be due to FAS-FAS ligand interactions between keratinocytes and cytotoxic T cells, cytotoxic T cells producing granzyme B into keratinocytes through perforin-induced membrane pores, and TNF- α secreted by cytotoxic T cells binding to the TNF- α receptor on the keratinocyte surface, leading to the occurrence of OLP (13). Th1 cells, which secrete the specific cytokines IFN- γ , IL-2 and TNF- α , recruit monocytes to lesions to differentiate into proinflammatory M1 macrophages, intensifying inflammation by secreting proinflammatory cytokines that upregulate cell adhesion molecules on the surface of endothelial cells and keratinocytes and induce T-cell chemokine expression (RANTES) to promote inflammatory cell recruitment (14, 15). Upregulation of MMP-9 indirectly affects T-cell polarization, and differentiated cytokine production, such as IL-12 \rightarrow Th1 or IL-4 and IL-5 \rightarrow Th2, increases the rate of basement membrane disruption (16). The interaction of T cells with mast cells activates and degranulates mast cells. Mast cell-derived TNF- α increases endothelial cell adhesion molecule expression and promotes lymphocyte adhesion and extravasation, and T cells secrete RANTES and MMP (17). RANTES results in sustained degranulation of mast cells, whereas MMP directly or indirectly disrupts the epithelial basement membrane (18). Thus, periodic interactions between T cells and mast cell secretion may be responsible for the long-term and chronic duration of the disease. IL-2, TNF- α and IFN- γ , representative cytokines of Th1 cells, may exacerbate disease severity and inhibit the differentiation of Th17 cells. At the same time, Th2 and Treg subsets may maintain the long-term chronicity of the disease by releasing IL-4 and TGF- β (19). Moreover, Th17 cells secreting IL-17, IL-21 and IL-22 may increase the inflammatory reaction. Furthermore, MMP derived from Th17 cells may damage the epithelial basement membrane, and Th9/IL-9 cells can exacerbate the occurrence of OLP disease by directly increasing Th17-cell levels or indirectly upregulating MMP9 levels in coordination with Th17 cells (20).

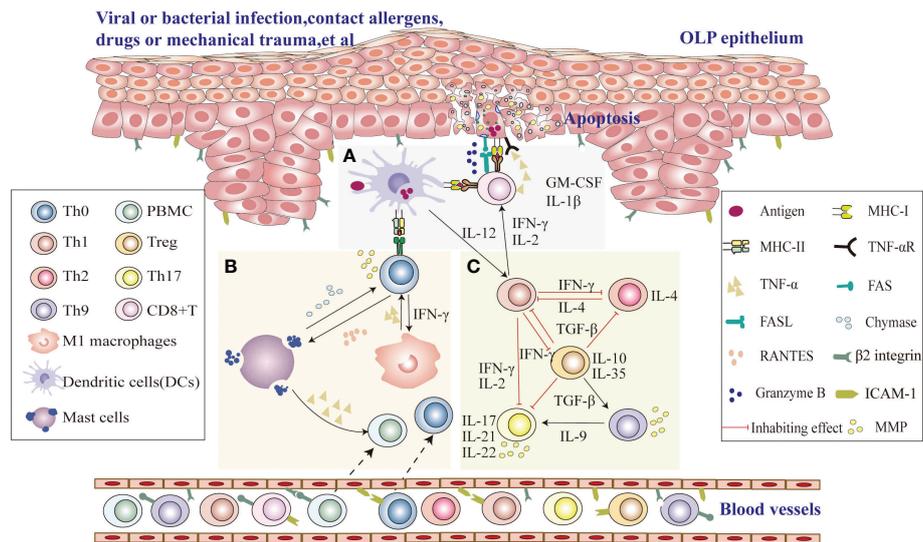


FIGURE 1

Possible role of the immune microenvironment in OLP pathogenesis (A) Upon stimulation with viruses, bacterial infection, drugs or mechanical damage, CD8⁺ T cells identify antigen-associated MHC class I molecules on target cells (damaged keratinocytes or DCs) that activate CD8⁺ cytotoxic T cells directly, and DCs in OLP lesion tissues process antigen-derived peptides and present them together with MHC class II molecules to CD4⁺ helper T cells, which recruit CD8⁺ T cells to subepithelial regions and activate CD8⁺ T cells via IL-2 and IFN-γ. Activated CD8⁺ T cells cause keratinocyte apoptosis, which may be due to FAS-FAS ligand interactions between keratinocytes and cytotoxic T cells, cytotoxic T cells producing granzyme B in keratinocytes through perforin-induced membrane pores, and TNF-α secreted by cytotoxic T cells binding to the TNF-α receptor on the keratinocyte surface, leading to the occurrence of OLP. (B) DCs in OLP lesion tissues process antigen-derived peptides and present them together with MHC class II to CD4⁺ helper T cells. Local production of IFN-γ secreted by Th1 cells activates proinflammatory type M1 macrophages. The production of TNF-α by type M1 macrophages can indirectly increase the disruption rate of the basement membrane by MMP-9 produced by T cells. RANTES secreted by T cells may attract mast cells into the developing OLP lesion and subsequently stimulate mast cell degranulation. Degranulating mast cells in OLP release TNF-α and chymase. TNF-α promotes inflammatory cell recruitment, and chymase directly or indirectly increases the disruption rate of the basement membrane by T-cell-secreted MMP-9. Thus, periodic interactions between T cells and mast cell secretion may be responsible for the long-term and chronic duration of the disease. (C) Th1 cytokines in local OLP lesions can aggravate the severity of the disease by the production of IFN-γ, IL-2 and TNF-α and thus negatively regulate Th17 differentiation and downregulate the immunosuppressive effect of TGF-β1. However, Th2 cells can maintain chronic disease by producing IL-4. The secretion of IL-17, IL-21, and IL-22 by Th17 cells may increase the inflammatory response. Furthermore, Th17 cells may also lead to an impaired epithelial basement membrane through the release of MMPs. Th9/IL-9 can exacerbate the occurrence of OLP by directly increasing Th17-cell levels or indirectly upregulating MMP9 levels.

3 Functional cells and key chemokines that regulate the OLP immune microenvironment

Currently, since the etiology of OLP remains unknown, substantial evidence supports that T lymphocytes in OLP may be activated by presenting antigens through major histocompatibility (MHC) molecules and triggering keratinocyte apoptosis, suggesting that immune dysregulation may be of great importance in OLP pathogenesis (21). MMP overexpression and mast cell degranulation in OLP lesions further aggravate T-cell accumulation, basement membrane destruction and keratinocyte apoptosis (12, 22). These immune inflammatory cells and their cytokines in the immune microenvironment may affect OLP immune response characteristics, disease severity, and duration.

3.1 Functional cells regulate the OLP immune microenvironment

In OLP, there is strong crosstalk among keratinocytes, fibroblasts, macrophages, dendritic cells (DCs), mast cells, CD8⁺ T cells and Th cells (23). These interactions appear to continuously amplify and maintain the chronicity of inflammation. In OLP early stages, the proportions of Th cells, macrophages and DCs were higher than those in advanced stages, suggesting that in early stages, there is a predominance of antigen-presenting cells and T lymphocytes responsible for the induction of inflammatory responses, but CD8⁺ T cells present high levels in OLP advanced stages (24).

3.1.1 Keratinocytes

Keratinocytes can produce the major constituent proteins that constitute the basement membrane to maintain their

integrity and act as nondedicated antigen-presenting cells to identify, phagocytose, and present self-antigens. OLP is an inflammatory disease that affects the oral mucosa with the involvement of immune cells. At the cellular level, OLP may be due to immunologically induced degeneration of the basal layer (25). The target cell is epithelial basal cells in OLP, and the initial step may be antigen recognition through mucosal Langerhans cells. Basal keratinocytes present antigens with MHC class I molecules to CD8⁺ cytotoxic T cells and then induce them to produce a variety of inflammatory mediators that promote the liquefaction and degeneration of keratinocytes (26). Keratinocytes are not only target cells for immune response damage, but also intermediate mediators of the immune response involved in the immune response by releasing a series of cytokines. Studies have reported that IL-1 β , tumor necrosis factor- α (TNF- α), GM-CSF, IL-8, RANTES, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1 are elevated in OLP keratinocyte culture supernatants compared with the control group (27, 28). These cytokines enhance the expression of β 2 integrin and ICAM-1, while upregulated adhesion molecules and cytokines may enhance monocyte migration (27–30). These results demonstrate that keratinocytes may be involved in the pathogenesis of OLP and that the inflammatory response at the lesion can be further exacerbated by the cytokines it produces.

3.1.2 Fibroblasts

Fibroblasts are the main cellular components of connective tissue and have unique spindle structures (31). They not only function in the construction and remodeling of the extracellular matrix but are also key immune sentinel cells (32). Fibroblasts can detect damage-associated molecular patterns and pathogen-associated molecular patterns and activate proinflammatory signaling pathways to aid in leukocyte recruitment and regulate their activity; thus, these cells are now considered “nonclassical” branches of the innate immune system (33–36). In diseases such as chronic inflammatory diseases and cancer, inappropriate fibroblast activation promotes disease persistence by inducing proinflammatory and immunosuppressive properties, respectively (37). However, few studies have investigated the effects of OLP fibroblasts. Zhang Y et al. showed that the immune activation of OLP fibroblasts promotes CD4⁺ T-cell proliferation and migration and inhibits CD4⁺ T-cell apoptosis (38). Xu X et al. showed that fibroblasts located at OLP lesions upregulate IL-6, thus enhancing OLP angiogenesis and that anti-IL-6 receptor antibodies inhibit the OLP-interstitial IL-6 signaling pathway and inhibit OLP angiogenesis. This suggests that this may be a potential target for developing OLP therapies (39).

3.1.3 Dendritic cells

Of note, DCs are dedicated antigen-presenting cells and are important components that induce the immunological response (40). CD4⁺ T helper and CD8⁺ cytotoxic T cells are activated when antigens are presented by MHC class I and class II molecules on dendritic cells, thereby inducing initial T-cell proliferation and initiating the immune response (41). Previous studies have shown increased aggregation of DC subsets in OLP lesion tissues, such as CD1a+/Langerin+ (Langerhans cells), DC-SIGN+ DCs, and CD123+/BDCA2+ plasmacyte-like DCs (PDCs) (26) (42). DCs in OLP can present antigens to CD4⁺ T cells, and their secreted interleukin-12 (IL-12) induces cytokine release from CD4⁺ T cells, including interferon gamma (IFN- γ) and IL-2, recruits CD8⁺ T cells to subepithelial regions and activates CD8⁺ T cells, eventually leading to the onset of chronic inflammation (43–45).

3.1.4 Macrophages

Macrophages are differentiated from blood monocytes and are recruited to inflammatory sites by chemokines (46). Macrophages play a significant role in inflammation and cytotoxicity, chemokines (46). Macrophages play a significant role in pro-inflammation and cytotoxicity, phagocytosis of pathogens, immune surveillance, and immune regulation. Thus, they are the first line of defense in immune defense. Depending on their effector function, they can be classified as classically activated (M1) and alternatively activated (M2) macrophages (47). Infiltrating monocytes recruited to lesions differentiate into proinflammatory M1 macrophages at high levels of TNF- α , GM-CSF and IFN- γ , intensifying inflammation by the secretion of proinflammatory cytokines, including IL-1 β and TNF- α , which upregulate cell adhesion molecules on the surface of endothelial cells and keratinocytes and induce T-cell chemokine expression (RANTES) to promote inflammatory cell recruitment (14–16, 23). Upregulation of matrix metalloproteinase 9 (MMP-9) indirectly affects the polarization of T cells and promotes basement membrane disruption by producing differentiated cytokines, such as IFN- γ and IL-12 \rightarrow Th1 or IL-4 and IL-2 \rightarrow Th2 (3, 48).

3.1.5 Mast cells

Mast cells are derived from hematopoietic stem-fine, granular, mobile leukocytes with a wide range of functions, including inflammation, tissue repair, remodeling, and immune modulation (49). Compared with normal mucosal tissue, mast cells accumulated significantly more in OLP lesioned tissue and were mostly common in deeper connective tissue (50). The interaction of T cells with mast cells allows them to activate and degranulate mast cells, which secrete a series of cytokines and chemokines, such as chymase, trypsin, TNF- α

and a range of interleukins, including IL-8 and IL-16 (51). Zhao et al. found that mast cell-derived TNF- α increases lymphocyte adhesion and extravasation by increasing the expression of endothelial cell adhesion molecules and promotes T-cell secretion of RANTES and MMP (17). RANTES results in sustained degranulation of mast cells, whereas MMP directly or indirectly disrupts the epithelial basement membrane (18). Thus, periodic interactions between T cells and mast cell secretion may be responsible for the long-term and chronic duration of the disease.

3.1.6 T lymphocytes

The present study demonstrates that T lymphocyte-mediated liquefaction degeneration of basal keratinocytes leads to the occurrence of OLP, primarily in CD4⁺ T and CD8⁺ T cells. CD4⁺ T cells predominantly infiltrate connective tissue below the affected epithelium, namely, the subepithelial epithelium, whereas CD8⁺ T cells are usually located at the interface of epithelial and connective tissues, namely, the intraepithelial epithelium, sometimes adjacent to apoptotic keratinocytes (3, 52).

3.1.7 CD4⁺ T

Currently, CD4⁺ T helper cells can be classified into Th1, Th2, Th17, Treg, Th9 and Tfh subsets based on the secretion of cytokines. IL-2, TNF- α and IFN- γ are representative cytokines of Th1 cells that activate macrophages and cytotoxic T lymphocytes, promote the production of cytokines, and participate in cellular immunity. Th2 cells promote B lymphocyte antibody production mainly through the secretion of cytokines such as IL-4 (53). The characteristic cytokine of Th1 cells is IFN- γ , which plays a key role in maintaining Th1 differentiation and proliferation, while IL-2 acts as a specific factor for Th2 cells and primarily promotes the clonal expansion of Th2 cells. The current measure of the Th1/Th2 balance is the ratio of IFN- γ /IL-4. IFN- γ and IL-4 were found to be significantly increased in OLP-diseased tissue, saliva and serum, suggesting that Th1 cells may be closely related to the development of OLP (54, 55). In addition, it has been reported that the levels of characteristic Th1 cytokines are lower in OLP patient serum than in normal control serum (56–58). Cytokines derived from Th1 cells inhibit the differentiation of Th17 cells (19). Our previous study showed that the reduced proportion of IFN- γ /IL-4 in OLP saliva suggests a possible dominance of Th2 cells in OLP saliva. Thus, increasing evidence suggests that Th1/Th2 imbalance may play a leading role in the occurrence of OLP (59). Th17 cells primarily secrete proinflammatory cytokines, including IL-17, IL-21 and IL-22 (60). Studies have shown that the level of IL-17 in serum as well as the proportion of Th17 cells in OLP lesion tissue and peripheral blood increased compared with healthy controls, suggesting that Th17 cells may be involved in the pathogenesis of OLP, especially in erosive OLP, whereas

Th2 cells may be predominant in reticular OLP (20, 61). IL-23 was recently found to be a cytokine of the IL-12 family that maintains the differentiation and proliferation of Th17 cells (62–64). Lu et al. showed that both the IL-23p19 subunit and IL-17 are significantly elevated in OLP, demonstrating the selective regulatory role of the IL-23/IL-17 axis in OLP (65, 66).

The cell markers of Tregs are primarily CD25 and Foxp3, which maintain the body's immune tolerance and homeostasis during the immune response by regulating the Th1/Th2 balance (67). Tao et al. found an increased proportion of CD4⁺CD25⁺Treg⁺ cells in OLP lesion tissues and peripheral blood compared to normal controls (68). Treg cells mainly secrete specific cytokines, such as TGF- β , IL-10 and IL-35, of which TGF- β is the signature cytokine and can regulate the Th1/Th2 balance (69, 70). Furthermore, IL-10 secreted by Treg cells suppresses Th1 and Th2 cell proliferation (67). In addition, IL-35 can inhibit Th17 cells and Th1 cells through the proliferation of strong Tregs and IL-10 expression (71).

The Th22, Th9, and Tfh subsets are recently described subsets of CD4⁺ T cells. The former mainly secretes IL-22. Some studies have shown that IL-22 can promote OLP epithelial remodeling by inducing keratinocyte proliferation and epithelial cell proliferation and that TNF- α and IL-6 play crucial roles in the differentiation and proliferation of Th22 cells (72, 73). IL-9 is mainly produced by Th9 cells, and Wang et al. showed that Th9/IL-9 cells could exacerbate the occurrence of OLP by directly increasing Th17 cell levels or indirectly upregulating MMP9 levels in coordination with Th17 cells (20). The characteristic cytokine of the Tfh subset is IL-21, which promotes B-cell proliferation and autoantibody production and disrupts plasma cell differentiation (74). Tan et al. speculated that the Th1/Th2 imbalance might be partially attributed to the increase in Tfh-like cells (75).

3.1.8 CD8⁺ T

CD8⁺ T cells play a vital role in the pathogenesis of OLP, especially in advanced OLP.

CD8⁺ T cells may migrate into the OLP epithelium through the basement membrane (BM) break region (21). It is mainly believed that CD8⁺ T lesion cells identify antigen-associated MHC class I on diseased keratinocytes and are activated by cytokines secreted by Th1 cells, which then cause keratinocyte apoptosis, leading to the occurrence of OLP (3). Possible mechanisms underlying apoptosis include (a) FAS-FAS ligand interactions between keratinocytes and cytotoxic T cells. (b) Cytotoxic T cells produce granzyme B in keratinocytes through perforin-induced membrane pores. (c) TNF- α secreted by cytotoxic T cells binds to the TNF- α receptor on the keratinocyte surface. Lage et al. confirmed the increased expression of granzyme B and perforin seen in OLP compared with cutaneous lichen planus and suggested that this increase is associated with the clinical behavior of the disease (13). These

mechanisms activate a cysteine-containing aspartate protease (CaSpase)-mediated cascade, leading to apoptosis in keratinocytes.

3.2 Key secreted proteins regulate the OLP immune microenvironment

Cytokines are bioactive small peptide proteins that can be synthesized and secreted by various immune and nonimmune cells to regulate cell growth, function and differentiation and promote intercellular communication (76). They can induce each other to mediate local and systemic inflammation in an autocrine, paracrine, and endocrine manner (77). They generally initiate complex intercellular molecular interactions by binding the corresponding receptors, altering gene regulation, and resulting in altered phenotypic and functional changes in the target cells (78). Cytokine network imbalance may be related to immune-mediated OLP pathogenesis. In fact, overexpression of various proinflammatory factors, including interleukin (IL), IFN- γ and TNF- α , has been found in OLP lesions, peripheral blood, and saliva.

3.2.1 Chemokines

Chemokines are proinflammatory cytokines that move cells direction toward high concentration stimuli and can induce directional chemotaxis in nearby response cells (79), which can be divided into four categories, CC, CXC, C and CX3C, according to their structure. RANTES, also known as CCL5, belongs to the CC chemokine family and could recruit lymphocytes, mast cells, monocytes, and natural killer cells in OLP (3). Shan et al. showed that CCL5 and CCR5 are upregulated in OLP, and the CCL5-CCR5 axis promotes CD4⁺ T lymphocyte aggregation in OLP tissues after inhibiting CCR5 expression while promoting T-cell apoptosis (80). This study also found that the pathological features of the oral mucosa in OLP patients can be formed by chemokines through regulating the migration of T lymphocytes, contributing to the emergence of T lymphocyte-infiltrating bands. Ichimura et al. showed that CXCL9, CXCL10, CXCL11, and CCL5 expression was higher in OLP than in normal tissues, which can recruit T lymphocytes, and the ligands of CXCR3 are CXCL9, CXCL10 and CXCL11, while the ligand of CCR5 is CCL5 (81). In addition, CXCR3 and CCR5 of Th1 cells are strongly expressed in OLP. This finding indicates that T-cell infiltration in OLP may be signaling through CXCR3 and CCR5.

3.2.2 Interleukin

IL can be secreted by many kinds of cells and acts by transmitting information and immune regulation, and IL also

plays a pivotal role in inflammatory processes in the human response. The major ILs currently are upregulated in OLP, such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17 and IL-18 (82). IL-2 and its receptor IL-2R are highly expressed in OLP (65, 83). The IL-2/IL-2R signaling axis may regulate T-cell expansion and activation in foci (84). It was found that the B7-H1/PD-1 pathway negatively regulates IL-2, indicating that the IL-2/IL-2R signaling pathway may be a therapeutic target (85, 86). In addition to IL-2, IL-4 appears to be important in the pathogenesis of OLP because it can not only control Th2 cell differentiation but also negatively regulate Th1- and Th17-mediated inflammatory responses by inhibiting IL-17, IFN- γ and TNF- α production. Liu et al. found higher IL-4 levels in OLP saliva than in healthy controls (59), but studies also reported that there was no difference between OLP patients and normal controls (87). IL-6 is upregulated in OLP lesion tissues, saliva, and peripheral blood, especially in the eroded form, and may affect the infiltration of immunoinflammatory cells, leading to increased proinflammatory cytokine production in OLP lesions and exacerbating OLP inflammation (82, 88–90). All the above studies suggest an association between IL and the onset of OLP and that the proinflammatory effect of IL may aggravate the pathological injury of OLP. The detection of IL concentrations in OLP lesion tissue facilitates the clinical assessment of OLP patients.

3.2.3 Tumor necrosis factor- α

TNF- α is an endotoxin-induced glycoprotein and is currently the most widely studied cytokine. Previous studies agreed that the expression of TNF- α was significantly elevated in both lesions and peripheral blood in OLP patients compared with healthy controls (3, 91, 92). Moreover, TNF- α was found to be overproduced in degranulated mast cells with OLP lesions (52). Topical steroids can inhibit elevated TNF- α in OLP lesions, indicating that TNF- α overexpression may play an essential role in OLP (93).

The study showed that TNF- α stimulation could induce RANTES, MMP-9 and TNF- α production and promote the expression of endothelial cell adhesion molecules in OLP, recruiting lymphocytes from blood vessels to extravascular regions (94–96). TNF- α can also contribute to epithelial basement membrane breakage by stimulating T-cell secretion and MMP activation (97). TNF- α also induces keratinocyte apoptosis by binding to TNF- α receptors on the surface of keratinocytes (91). In addition, it can cause secretion of RANTES in T cells to attract mast cells. TNF- α and thrombin released after degranulation can further stimulate more RANTES secretion, leading to chronic chemistry of OLP (52).

3.3 Other routes regulate the OLP immune microenvironment

Exosomes are extracellular vesicles with a diameter of 30-150 nm that can be secreted by T cells, B cells, hematopoietic cells, reticulocytes, dendritic cells, and tumor cells (98). Exosomes secreted by immune cells regulate the immune response and are associated with the pathogenesis of autoimmune diseases (99). Exosomes are newly recognized natural nanocarriers and intercellular messengers that have become important mediators of signal transmission. It has been suggested that aberrant expression of exosomal miRNAs may participate in the development of OLP (100, 101). Peng Q et al. found that circulating exosomal miR-34a-5p and miR-130b-3p were upregulated, while miR-301b-3p was downregulated in patients with OLP. Exosomal miR-34a-5p was positively correlated with the severity of OLP (102). In addition, they also found that in OLP, especially in erosive OLP, circulating exosomes significantly enhanced T-cell proliferation and migration, increased the proportion of IFN- γ /IL-4, and decreased apoptosis, which may accelerate the progression of OLP by regulating the T-cell-mediated inflammatory response (103). J-S Byun et al. reported that exosomal miR-4484 saliva was increased in OLP patients (104).

There are few articles investigating neutrophil extracellular traps (NETs) in OLP. They found that neutrophils isolated from the peripheral blood of OLP patients exhibit a potent ability to produce NETs, and the presence of excessive NETs may lead to many adverse consequences associated with OLP pathogenesis and the potential transition to OSCC (103). The inhibitory effect of flavonoids (epicatechin, catechin hydrate and rutin trihydrate, quercetin and luteolin) on NET formation in OLP patients (105, 106). Flavonoids can be considered a therapeutic strategy for NET-mediated diseases (such as OLP). However, the application of routes such as exosomes and NETs in the diagnosis and treatment of OLP still needs further study to design a correct therapeutic strategy for the disease.

4 Application potential of targeted immune microenvironment therapy for OLP

Since OLP is thought to be a T-cell-mediated disease associated with a Th1/Th2 imbalance in cytokine production, most therapeutic interventions are aimed at targeting the inflammatory pathway of OLP (44, 87, 107). Although steroids are the first-line medication for treating OLP, favorable evidence for their effectiveness is lacking. To date, multiple treatments have been used to treat symptomatic OLP, but it is difficult to completely cure due to its stubbornness. Thus, there is a

tremendous challenge in treating symptomatic OLP, and there is now an urgent need to look for new therapies for symptomatic OLP.

4.1 Current immune-based therapies in OLP

Pharmacotherapy with corticosteroids, calcineurin inhibitors, thalidomide, mycophenolate mofetil (MMF), retinoids, BCG-PSN and traditional Chinese medicine (TCM) has been tried in clinical trials and has achieved varying degrees of success. The mode of action and effects of common drugs and drug categories of OLP are shown in Table 1, and the specific screening strategies were performed as described previously (126, 127). They can control the symptoms, but they are difficult to cure completely.

Topical corticosteroids can serve as first-line medicine to treat OLP, and medications for topical treatment include triamcinolone acetonide, clobetasol propionate, fluocinonide, fluocinolone acetonide, fluticasone propionate, and betamethasone pentate/sodium phosphate. Systemic corticosteroids are suitable for severe, extensive, or erosive OLP or drug-resistant/refractory OLP (113–116). It primarily inhibits the CD4⁺ Th subpopulation of OLP patients. For instance, 0.1% fluocinolone acetonide has an immunomodulatory effect on the reduction of IFN- γ (128).

Calcineurin inhibitors mainly include tacrolimus, pimecrolimus, and cyclosporine, second-line medicines to treat OLP. Calcineurin inhibitors primarily inhibit IL-2 transcription, reducing T-cell activation (111, 129, 130). Tacrolimus inhibits cytokine production and T-cell activation, reduces Treg proliferation, and downregulates NF- κ B signaling (112). In addition, tacrolimus suppresses mast cell activation and affects Langerhans cell function (68, 108, 110, 118, 131). However, due to symptoms such as burning sensation occurring for a short time and relapses of OLP after cessation, it is advocated for short-term use (132, 133). Pimecrolimus first reduces cytokine synthesis and release to inhibit T-cell activation and then reduces CD95 (Fas) expression on keratinocytes in OLP (117, 134). Cyclosporine can induce T-cell apoptosis by inhibiting NF- κ B signaling, inhibiting the immortalized proliferation of keratinocytes, and inhibiting Treg proliferation and activation (119, 120, 135, 136). Tacrolimus and pimecrolimus have a higher safety profile than cyclosporine (116). Thalidomide has antiangiogenic, anti-inflammatory, and anti-immune properties that suppress Th-cell activity, inhibit the production of TNF- α by promoting TNF- α mRNA degradation and inhibiting NF- κ B activity and reduce IFN- γ , VEGF, and IL-6 production (122, 137). Mycophenolate mofetil (MMF) is an immunosuppressor that suppresses DC maturation and antibody formation and inhibits activated T-cell proliferation in a reversible and specific way. However, it is not recommended

TABLE 1 Main mechanisms of action and efficacies of common drugs and drug categories used for treating oral lichen planus.

Drugs/drug class	Mechanism of action	Author, Year	Treatment scheme	Efficacy
Corticosteroids				
Triamcinolone	Reduces the exudation of leukocytes	Siponen et al, 2017 (108)	Group 1 (n = 11): tacrolimus 0.1% ointment, 3× daily for 3 weeks Group 2 (n = 7): triamcinolone acetonide 0.1%, 3× daily for 3 weeks Group 3 (n = 9): placebo (Orabase® paste), 3× daily for 3 weeks	Groups 1 and 2 showed a greater reduction in clinical score (p = 0.012 and 0.031, respectively) and VAS (44–77%) than placebo in the 3rd week, but with no significant difference between them. Groups 1 and 2 showed a 50% decrease in VAS after 6 months of treatment
		Singh et al, 2017 (109)	Group 1 (n = 10): 0.1% triamcinolone acetonide 0.1%, 2× daily for 3 months Group 2 (n = 10): oral dapsone 100 mg + iron and folic acid tablet, 2× daily for 3 months Group 3 (n = 10): tacrolimus 0.1%, 2× daily for 3 months Group 4 (n = 10): retinoid, 2× daily for 3 months	The four treatment groups showed significant clinical improvement in signs and symptoms after 3 months (p < 0.05), with no difference between them. Among nonsteroidal drugs, oral dapsone showed a better response than topical retinoid (p < 0.05).
		Sivaraman et al, 2016 (110)	Group 1 (n = 10): triamcinolone acetonide 0.1%, 3× daily for 6 weeks Group 2 (n = 10): clobetasol propionate 0.05%, 3× daily for 6 weeks Group 3 (n = 10): tacrolimus 0.03%, 3× daily for 6 weeks	At the end of treatment, there was a significant difference between the 3 groups (p = 0.004), with group 2 being better than group 3 (p = 0.007). There was no recurrence after 3 months of follow-up.
		Vohra, Singal, Sharma, 2016 (111)	Group 1 (n = 20): tacrolimus 0.1% ointment, 2× daily for 8 weeks Group 2 (n = 20): pimecrolimus 1%, 2× daily for 8 weeks	Both groups showed a statistically significant reduction in clinical score and mean serum levels of IL-6 and IL-8 at the end of treatment and follow-up compared to baseline (p < 0.05), but without significant differences between them.
Clobetasol	Inhibits the lysozyme release and phagocytosis	Hettiarachchi et al, 2017 (112)	Group 1 (n = 34): clobetasol propionate 0.05% cream, 2× daily + nystatin mouthwash, 2× daily for 3 weeks Group 2 (n = 34): tacrolimus (0.1%), 2× daily + nystatin mouthwash, 2× daily for 3 weeks	Statistically significant reduction in mean VAS and clinical score between end of treatment (3 weeks) and after 5 weeks compared to baseline in groups 1 and 2 (p < 0.05).
		Sivaraman et al, 2016 (110)	Group 1 (n = 10): triamcinolone acetonide 0.1%, 3× daily for 6 weeks Group 2 (n = 10): clobetasol propionate 0.05%, 3× daily for 6 weeks Group 3 (n = 10): tacrolimus 0.03%, 3× daily for 6 weeks	At the end of treatment, there was a significant difference between the 3 groups (p = 0.004), with group 2 being better than group 3 (p = 0.007). There was no recurrence after 3 months of follow-up.
Betamethasone	Inhibits the proliferation of fibroblasts	Samimi et al, 2020 (113)	Group 1 (n = 36): betamethasone dipropionate ointment 0.05% + oral placebo solution (excipient of solution, Phosal), 2× daily for 3 months Group 2 (n = 39): rapamycin oral solution 1 mg/ml + placebo (Vaseline ointment), 2× daily for 3 months	There was no difference between groups when compared to clinical remission. However, betamethasone showed a significantly greater reduction in VAS compared to rapamycin at the end of 3 months. At the end of the follow-up, there was no difference between the groups.

(Continued)

TABLE 1 Continued

Drugs/drug class	Mechanism of action	Author, Year	Treatment scheme	Efficacy
		Ezzatt, Helmy, 2018 (114)	Group 1 (n = 15): pimecrolimus 1% cream, 0.5 ml 4× daily for 4 weeks Group 2 (n = 15): betamethasone 17-valerate 0.1%, 0.5 ml 4× daily for 4 weeks	Groups 1 and 2 showed a reduction in clinical score (p < 0.001), VAS (p < 0.001), and expression of CD133 after 4 weeks of treatment compared to baseline (p < 0.002), and this reduction was significantly smaller in group 1.
Fluocinonide – 0.1%, 0.05%	Inhibits the pro-inflammatory cytokines IL-1, IL-2, IL-3, IL-6, TNF-α, GM-CSF, IFN-γ	Carbone et al, 1999 (115)	Group 1 (n = 25): 0.05% clobetasol propionate ointment, 2× daily for 4 months, 1× daily for 2 months Group 2 (n = 24): 0.05% fluocinonide ointment, 3× daily for 2 months, 2× daily for 2 months, 1× daily for 2 months Group 3 (n = 11): hydroxyethyl cellulose gel and antimycotic, 2× daily for 6 months	All patients treated with clobetasol and 90% of the patients treated with fluocinonide witnessed some improvement, whereas in the placebo group only 20% of patients improved (P < 0.0001 and P = 0.00029, respectively)
Calcineurin inhibitors				
tacrolimus	inhibit cytokine production and T-cell activation, reduce Treg proliferation and downregulate NF-κB signaling, suppresses mast cell activation and affects Langerhans cell function	Singh et al, 2017 (109)	Group 1 (n = 10): 0.1% triamcinolone acetonide 0.1%, 2× daily for 3 months Group 2 (n = 10): oral dapsone 100 mg + iron and folic acid tablet, 2× daily for 3 months Group 3 (n = 10): tacrolimus 0.1%, 2× daily for 3 months Group 4 (n = 10): topical retinoid, 2× daily for 3 months	The four treatment groups showed significant clinical improvement in signs and symptoms after 3 months (p < 0.05), with no difference between them. Among nonsteroidal drugs, oral dapsone had a lower score of signs and symptoms than topical retinoid (p < 0.05).
		Hettiarachchi et al, 2017 (112)	Group 1 (n = 34): clobetasol propionate 0.05% cream, 2× daily + nystatin mouthwash, 2× daily for 3 weeks Group 2 (n = 34): tacrolimus (0.1%), 2× daily + nystatin mouthwash, 2× daily for 3 weeks	Statistically significant reduction in mean VAS and clinical score between end of treatment (3 weeks) and after 5 weeks compared to baseline in groups 1 and 2 (p < 0.05).
		Siponen et al, 2017 (108)	Group 1 (n = 11): tacrolimus 0.1% ointment, 3× daily for 3 weeks Group 2 (n = 7): triamcinolone acetonide 0.1%, 3× daily for 3 weeks Group 3 (n = 9): placebo (Orabase® paste), 3× daily for 3 weeks	Groups 1 and 2 showed a greater reduction in clinical score (p = 0.012 and 0.031, respectively) and VAS (44–77%) than placebo in the 3rd week, but with no significant difference between them. Groups 1 and 2 showed a 50% decrease in VAS after 6 months of treatment
		Sivaraman et al, 2016 (110)	Group 1 (n = 10): triamcinolone acetonide 0.1%, 3× daily for 6 weeks Group 2 (n = 10): clobetasol propionate 0.05%, 3× daily for 6 weeks Group 3 (n = 10): tacrolimus 0.03%, 3× daily for 6 weeks	At the end of treatment, there was a significant difference between the 3 groups (p = 0.004), with group 2 being better than group 3 (p = 0.007). There was no recurrence after 3 months of follow-up.
		Vohra, Singal, Sharma, 2016 (111)	Group 1 (n = 20): tacrolimus 0.1% ointment, 2× daily for 8 weeks Group 2 (n = 20): pimecrolimus 1%, 2× daily for 8 weeks	Both groups showed a statistically significant reduction in clinical score and mean serum levels of IL-6 and IL-8 at the end of treatment and follow-up compared to baseline (p < 0.05), but without significant differences between them.

(Continued)

TABLE 1 Continued

Drugs/drug class	Mechanism of action	Author, Year	Treatment scheme	Efficacy
pimecrolimus	reduces cytokine and CD95 (Fas) expression, inhibit T-cell activation	Ezzatt, Helmy, 2018 (116)	Group 1 (n = 15): pimecrolimus 1% cream, 0.5 ml 4× daily for 4 weeks Group 2 (n = 15): betamethasone 17-valerate 0.1%, 0.5 ml 4× daily for 4 weeks	Groups 1 and 2 showed a reduction in clinical score ($p < 0.001$), VAS ($p < 0.001$), and expression of CD133 after 4 weeks of treatment compared to baseline ($p < 0.002$), and this reduction was significantly smaller in group 1.
		Riaz et al, 2017 (117)	Group 1 (n = 18): pimecrolimus 1% cream, 4× daily for 8 weeks Group 2 (n = 18): Triamcinolone acetonide 0.1% paste 3× daily for 8 weeks	There was a significantly greater reduction in VAS in group 1 at 4 and 8 weeks, as well as at follow-up.
		Vohra, Singal, Sharma, 2016 (111)	Group 1 (n = 20): tacrolimus 0.1% ointment, 2× daily for 8 weeks Group 2 (n = 20): pimecrolimus 1%, 2× daily for 8 weeks	Groups 1 and 2 showed a statistically significant reduction in clinical score and mean serum levels of IL-6 and IL-8 at the end of treatment and follow-up compared to baseline ($p < 0.05$), but without significant differences between groups.
cyclosporine	inhibit NF- κ B signaling, the immortalized proliferation of keratinocytes, and Treg proliferation and activation	Thongprasom et al, 2007 (118)	Group 1 (n = 7): triamcinolone acetonide 0.1%, orabase, 3× daily for 8 weeks Group 2 (n = 6): cyclosporine 100 mg/ml solution, mouthwash 3× daily for 8 weeks	There was no significant difference between the groups regarding the clinical response and the burning sensation ($p > 0.01$). At week 8, 50% of group participants had a complete clinical response and 50% partial response. In group 2, 33.33% had a partial clinical response and 66.66% had no response.
		Yoke et al, 2006 (119)	Group 1 (n = 71): triamcinolone acetonide 0.1%, orabase, 3× daily for 8 weeks Group 2 (n = 68): cyclosporine 100 mg/ml solution, mouthwash 3× daily for 8 weeks	There were no significant differences between groups at 4 and 8 weeks.
		Conrotto et al, 2006 (120)	Group 1 (n = 19): clobetasol propionate gel 0.025%, 2× daily for 8 weeks + miconazole gel 1× daily + chlorhexidine 0.12% mouthwash, 3× daily Group 2 (n = 20): cyclosporine gel 1.5%; 2× daily for 8 weeks + miconazole gel 1× daily + chlorhexidine 0.12% mouthwash, 3× daily	After 4 weeks, group 1 had a greater number of patients (94.73%) with complete or partial response, when compared to group 2 (65%) ($p = 0.04$). There was no difference between groups regarding reduction of symptoms. In group 2, there was greater stability of the lesions after 2 months of follow-up ($p = 0.04$).
Monoclonal antibodies				
Efalizumab	block T-cell activation and migration	Heffernan et al. 2007 (121)	Group 1 (n=4): 0.7 mg/kg subcutaneously at week 0 followed by 1.0 mg/kg weekly from week 1 to week 11	The mean reduction in the affected mucosal surface area was 71.1% (range 57.3% to 96.8%). The mean improvement in the 100-mm VAS for pain was 82%.
Others				
Shalidomide	suppress Th-cell activity and NF- κ B signaling, reduce the production of cytokines such as TNF- α , IFN- γ , VEGF, and IL-6	Wu et al, 2010 (122)	Group 1 (n = 37): thalidomide 1% paste, 3× daily for 1 week Group 2 (n = 32): dexamethasone 0.043% paste, 3× daily for 1 week Patients who did not obtain a complete response, continued treatment 3× daily per week for an additional 3 weeks	After 1 week of application, both groups showed significant reductions in erosive areas and VAS scores ($p < 0.001$), but with no difference between them. Regarding the recurrence of injuries, there was also no statistically significant difference between the groups.
Mycophenolate mofetil (MMF)	suppresses dendritic cell (DC) maturation and	Samiee et al, 2020 (123)	Group A (n = 10): bilateral oral lichen planus. Mycophenolate	There was no difference between the size of the lesions that received the immunomodulator in relation to the

(Continued)

TABLE 1 Continued

Drugs/drug class	Mechanism of action	Author, Year	Treatment scheme	Efficacy
	antibody formation, and inhibit the proliferation of activated T cells		mofetil 2% mucoadhesive on the lesion on one side, 2× daily for 4 weeks. Placebo applied on the lesion on the other side, 2× a day, for 4 weeks Group B (n = 17): unilateral oral lichen planus. Mycophenolate mofetil 2%, 2× for 4 weeks	placebo. At the end of 4 weeks of treatment, the group that received mycophenolate mofetil reduced the size of the lesion compared to baseline. While the placebo reduced pain and burning after 4 weeks when compared to its baseline.
BCG-PSN	modulates T-cell subsets, elevates the secretion of IFN- γ and regulates the imbalanced state of the IFN- γ /IL-4 cytokine ratio	Mohamad et al. 2017 (124)	n=11: 0.5 ml BCG-PSN twice weekly for three weeks	9 of 11 BCG-PSN-treated patients showed complete response
Retinoids	regulation function on T cells and macrophages	Xiong et al, 2009 (125)	Group 1 (n = 31): 0.5 ml BCG-PSN every other day for 2 weeks Group 2 (n = 25): 10 mg triamcinolone acetonide, every week for 2 weeks	27 of 31 BCG-PSN-treated patients (87.1%) and 22 of 25 TA-treated patients (88.0%) healed. There were no significant differences between the two groups in erosive areas (27.86 +/- 27.97 vs. 25.68 +/- 34.65, P = 0.801) and VAS scores (2.45 +/- 1.64 vs. 2.40 +/- 1.38, P = 0.946).
Visual analog scale/score: VAS				

because there is not sufficient evidence to support OLP treatment (123, 138, 139). Retinoids also have a regulatory function on T cells and macrophages (109, 124, 140, 141).

Efalizumab is a recombinant humanized monoclonal IgG1 antibody against CD11a, which is a subunit of LFA-1 (lymphocyte function-associated antigen 1) (142). Efalizumab can reduce T lymphocyte infiltration and activation by binding to CD11a, thereby blocking the interactions between LFA-1, which is expressed on the surface of endothelial cells and T lymphocytes, and ICAM-1, which is expressed on antigen-presenting cells (143). It has been shown that Efalizumab may be useful in the treatment of erosive oral lichen planus (121).

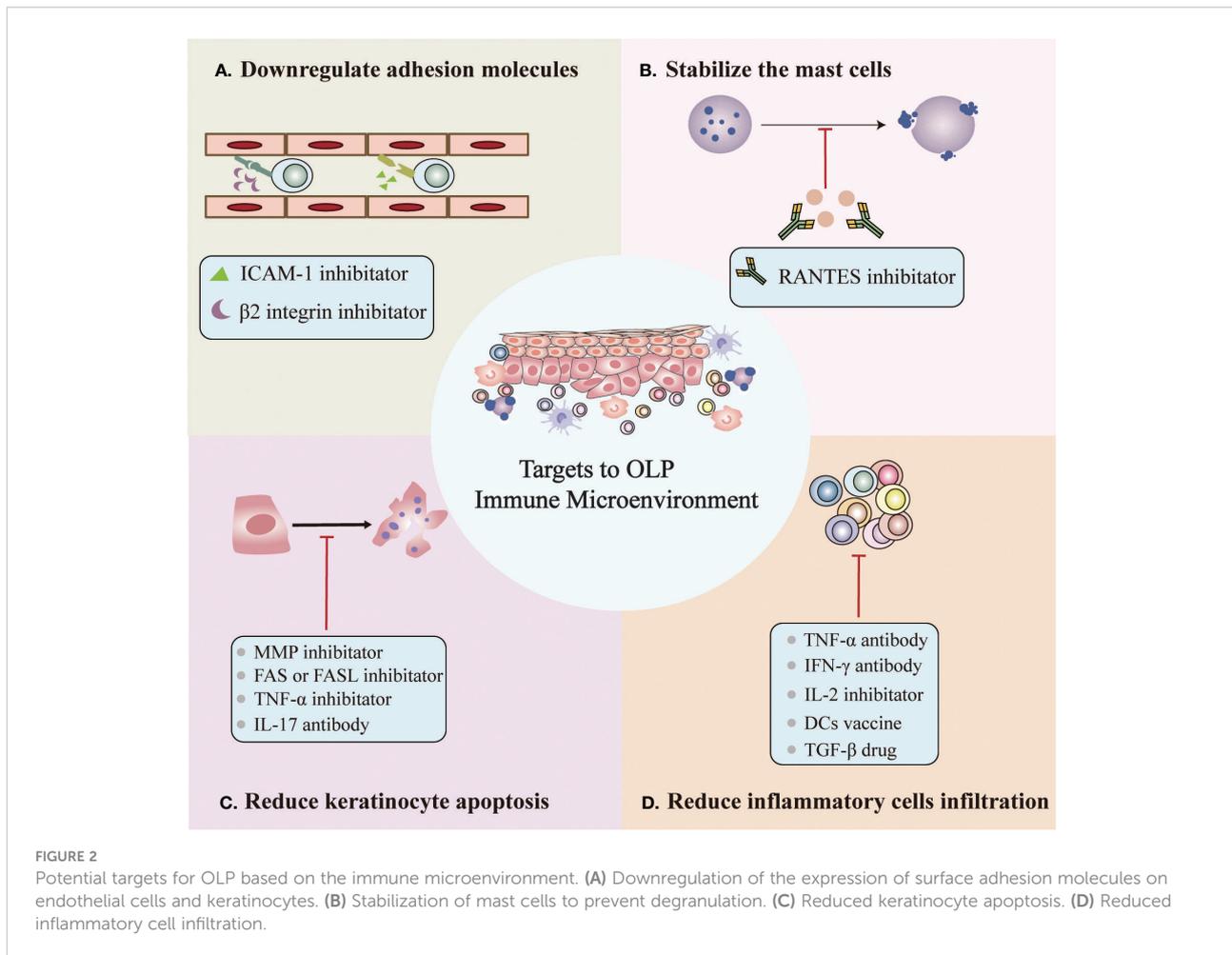
BCG-PSN, a novel potent bioimmunomodulator, modulates T-cell subsets and maintains the proportion of CD4⁺ T/CD8⁺ T cells at normal levels; furthermore, it also elevates the secretion of IFN- γ and regulates the imbalanced state of the IFN- γ /IL-4 cytokine ratio (144, 145). In addition, a previous *in vitro* study found that BCG-PSN could upregulate IFN- γ secretion from the PBMCs of OLP patients, increase the ratio of IFN- γ /IL-4 cytokines, and regulate Th1/Th2 disequilibrium in OLP (146). Additionally, BCG-PSN can serve as an alternative treatment for erosive OLP (125, 145).

Traditional Chinese medicine (TCM) regulates the function of internal organs based on the overall concept and syndrome differentiation. The treatment of OLP in TCM can better avoid the adverse reactions caused by the long-term use of Western medicine and the problems that easily relapse after drug withdrawal (147). The first two types of TCM to treat oral

lichen planus are heat-clearing and tonifying deficiency tonic drugs, followed by wet medicine, promoting blood circulation and removing blood stasis drugs (148). T lymphocyte function is diminished, and T-cell subsets are unbalanced in OLP patients (149). TCM treatment has a two-way regulatory effect on patients' immunity, which can restore the immune balance and achieve good clinical results (150).

4.2 Therapeutic prospects for OLP based on the immune microenvironment

In addition to known therapeutic targets, we propose potential therapeutic targets based on the OLP immune microenvironment, which can be roughly divided into four categories (Figure 2) (1): Downregulation of the expression of surface adhesion molecules on endothelial cells and keratinocytes, such as β 2 integrin and ICAM-1 inhibitors (27, 30) (2). Stabilize mast cells to prevent degranulation, such as the RANTES inhibitor mast (3, 17, 18, 51) (3). Reduced keratinocyte apoptosis, e.g., MMP inhibitor, FAS or FASL inhibitor, TNF- α or TNF- α R inhibitor and IL-17 antibody (13, 91) (4). Reduced inflammatory cell infiltration, such as TNF- α antibody, IFN- γ antibody, IL-2 antibody, DC vaccine, and TGF- β drug (27, 44, 45, 52). However, potential therapeutic targets based on the OLP immune microenvironment require additional research before they can be clinically applied.



5 Conclusions and further perspectives

In recent years, although significant progress has been made in the research of the OLP immune microenvironment, there are still many aspects worth our deep investigation, especially the intrinsic mechanisms by which the immune components in the immune microenvironment led to the chronic inflammatory environment of OLP, highlighting the need for further innovation in the field. Moreover, the antigenic nature of the initial events that induce OLP pathogenesis remains elusive. However, it is becoming increasingly clear that immune components in the immune microenvironment play an extremely key role in the pathogenesis of OLP, with numerous factors working in concert to form unique immune modulatory modes in the OLP immune microenvironment. Furthermore, studies of the OLP immune microenvironment will facilitate further exploration of therapeutic strategies against OLP, indicating new directions for

developing safer and more effective therapeutic targets. Although there are several targeted immune microenvironment therapies or treatments, new alternative therapies are highly appreciated due to the lack of any strong evidence for OLP treatment. As we mentioned above, blocking either IL-2, IL-17, TNF- α , IFN- γ , MMP-9 or RANTES activity or upregulating TGF- β activity in OLP may have therapeutic value. To date, our study of OLP remains at the cellular level, and there is no appropriate animal model for clinical patients with OLP. Therefore, more studies are needed to obtain accurate animal models of OLP, so the efficacy observed by blocking or upregulating one factor or multiple factors can be verified at the animal level. In the future, we can adopt emerging technologies such as mass spectrometry flow cytometry and single-cell RNA sequencing to explore the immune cell subtypes and discover new cell subtypes in the OLP immune microenvironment and through a multiplex immunohistochemistry approach to explore the exact role of immune cells and cytokines and their differential changes in the

process of treatment to further explore the interaction relationship among immune inflammatory cells, keratinocytes and cytokines and how they can synergize or antagonize each other to affect ongoing inflammation in the OLP immune microenvironment.

Author contributions

JL and LJ contributed to designing the manuscript. XD, YW and QC drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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