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REVIEW ARTICLE

The Immunopathogenesis of Oral Lichen Planus – is there a role for MAIT cells?

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Abstract

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Oral lichen planus (OLP) is a chronic, T cell mediated, immune condition of unknown cause. OLP may present with painful symptoms requiring treatment, as well as lesions outside the oral cavity. It is likely that what initiates the OLP disease process is a complex interaction of host susceptibility and environmental triggers. Whilst it is possible that OLP represents a true autoimmune condition against an epithelial autoantigen, the mechanisms that lead to this immune dysregulation are still poorly understood. In this review article, we discuss current concepts relating to the immunopathogenesis of OLP. Current theories on the possible contributors to the OLP disease process are discussed, as well as the role the oral microbiota and mucosal-associated invariant T (MAIT) lymphocytes may play in the pathogenesis of OLP.

Introduction

OLP is an immune mediated condition that affects the oral cavity in approximately 1-2% of the population ¹⁻³. It can affect any area of the oral mucosa including the buccal mucosa, tongue, alveolar ridge and gingival tissues ². OLP lesions are changeable with time and may take on multiple presentations. Different clinical forms of OLP have been described in the literature including reticular, papular, plaque-like, atrophic/erythematous, ulcerative and bullous presentations ². Of all the presentations, the reticular form is the most common ². Skin lesions on the flexor aspects of wrist, ankles, and genital lesions may also be present ⁴⁻⁶.

Management of OLP can pose a significant financial burden to the patient and the public health system. A recent cost assessment for managing OLP reviewed 100 patients with either mild OLP that was managed with topical corticosteroids, or severe OLP managed with both topical and systemic agents ⁷. On average, OLP patients would attend an appointment in the Oral Medicine unit 2.64 times per year with the average annual cost amounting to \$US579.53 (£385.58) per patient per year ⁷. The cost of managing patients with mild OLP was \$US438.01 (£301.04) per patient per year while those with severe OLP cost \$US964.67 (£663) to manage per patient per year ⁷. Assuming a prevalence of 1%, this

means that the cost of diagnosing and managing OLP ranges between 1.4 and 3.1 billion US\$ per year in the US only.

OLP develops as an immune-mediated disease defined by a cytotoxic T cell infiltration of the basal lamina zone resulting in basal keratinocyte apoptosis and basal lamina destruction⁸. The trigger that results in this persistent cytotoxic T-cell mediated destruction is currently unknown. This review explores current theories on the immunopathogenesis of OLP and sets forth a novel hypothesis for how the oral microbiota may act as an immunogenic trigger for OLP pathogenesis.

Immunopathogenesis of OLP

Much is still not known about the aetiology and pathogenesis of OLP. Histologically, OLP is characterised by vacuolar degeneration, T cell inflammatory infiltrate, hyperkeratosis or parakeratosis, and saw tooth rete ridges⁸⁻¹². Multiple theories exist on the immunopathogenesis of OLP and how immune dysregulation may initiate the chronic inflammatory process. The cells and inflammatory mediators that have been implicated in the aetiopathogenesis of OLP are outlined in Table 1 and discussed in detail below.

Cellular Immunity

Mast cells have been found in increased numbers in biopsy tissue samples from patients with OLP compared to normal controls and are also thought to play a role in OLP pathogenesis¹³. One hypothesis is that mast cells may initiate basement membrane disruption and facilitate the migration of cytotoxic T cells into the oral epithelium⁹. A study into the role of mast cells in OLP showed that 60% of mast cells were degranulated in OLP cases compared to 20% of control cases¹⁴. It was also shown that OLP lesional T cells produced and secreted the chemokine Regulated on Activation Normal T cell Expressed and Secreted (RANTES), a member of the CC chemokine family¹⁴. Secretion of RANTES was postulated to act as a trigger for mast cell degranulation that subsequently resulted in the release of tumour necrosis factor alpha (TNF- α) upregulating OLP lesional T cells to mediate keratinocyte apoptosis¹⁴.

Langerhans cells have been shown to be present in higher numbers in patients with OLP^{15,16}. The increase in Langerhans cells in OLP suggests a possible significant adaptive immune

system role in OLP pathogenesis ^{15,16}. In a study assessing biopsy samples from 18 OLP and 10 healthy controls by immunohistochemistry (IHC) for CD4, CD8, CD1a, Integrin Leukocyte Function Associated Antigen (LFA-1), Vascular Adhesion Molecule One (VCAM-1), and Ligand Intercellular Adhesion Molecule One (ICAM-1), it was found that there was an increase in CD4+, CD1a+ and CD8+ cells in OLP ¹⁷. Further, CD4+ and CD8+ cells expressed LFA-1, while both ICAM1 and VCAM-1 were significantly higher in OLP patients compared to control patients ¹⁷. The authors hypothesized that in OLP there may be an immune response to some unknown antigen within the basal keratinocytes and activated Langerhans cells present this unknown antigen to CD4+ cells that, through adhesion molecules, results in CD8+ cell induced epithelial destruction ¹⁷.

Macrophages have also been found in abundance in OLP disease affected areas suggesting a possible role in phagocytosis and antigen processing ¹⁸. The presence and distribution of macrophages was assessed in tissue specimens from 15 non-ulcerated OLP lesions ¹⁹. Macrophages were detected using the macrophage markers α_1 antitrypsin and lysozyme with all specimens showing accumulation of α_1 antitrypsin and lysozyme positive cells towards the basement membrane zone ¹⁹. It was shown that 60% of these cells were present within the 125 μ m epithelial/sub-epithelial junctional zone, supporting the hypothesis that macrophages play a significant role in the pathogenesis of OLP ¹⁹.

Regulatory T cells may also be important in the pathogenesis of OLP. Forkhead box protein 3 (FoxP3) expression plays a critical role in regulatory T cell development. In mice FoxP3 has been showed to be predominantly expressed in the CD25⁺CD4⁺ regulatory T cell population ²⁰. The role of FoxP3⁺ T cells have been assessed in OLP lesions. Tao et al., 2010 used IHC to assess the number of Foxp3⁺ T regulatory cells in OLP and control tissue lesions showing that FoxP3⁺ T regulatory cells were readily found in the lamina propria of OLP tissue ²¹. The reticular OLP group showed a significantly higher frequency of FoxP3⁺ T regulatory cells compared to the erythematous/erosive OLP group ($p=0.001$) ²¹.

More recently, Zhou et al., 2016 investigated the role that impaired CD4⁺CD25⁺ T regulatory cells play in OLP using venous blood from reticular and erythematous/erosive OLP patients and healthy controls. They further assessed the expression of T regulatory inflammatory mediators FoxP3, TGF- β and IL-10 as well as determined the proportion of IFN- γ /IL-17 amongst the CD4⁺FoxP3⁺ T cells ²². FoxP3 protein levels were significantly

elevated in T regulatory cells in both the reticular and erythematous/erosive OLP groups when compared to controls ²². Both OLP groups showed significantly higher percentages of CD4⁺Foxp3⁺IL-17⁺ cells when compared to normal controls with no significant differences noted between any of the groups with regards to the percentage of CD4⁺Foxp3⁺ IFN- γ ⁺ cells ²². Significantly impaired suppressive function of CD4⁺CD25⁺ was shown in the reticular OLP groups compared to the normal control groups supporting the hypotheses that functional impairment in the T regulatory cell population may be involved in the pathogenesis of OLP ²².

Separately, Javvadi et al., 2016 further assessed the role that T regulatory (FoxP3⁺) and Th17 (IL-17A⁺) cells play in regulation of the OLP immune response using 10 OLP and 9 non-specific inflammation tissue samples. Results of this study showed a significantly higher number of FoxP3⁺ cells in OLP when compared to non-specific inflammation whilst IL-17A⁺ cells were significantly more frequent in non-specific inflammatory tissue ²³. More FoxP3⁺ cells were present within the inflammatory infiltrate in the superficial connective tissue of OLP compared to IL-17A⁺ cells ²³. The FoxP3 gene was significantly up-regulated in the OLP group with the authors concluding that FoxP3⁺ cells may play a more prominent role in OLP pathogenesis than IL-17A⁺ cells ²³.

Moreover, an assessment of FoxP3⁺ cell subsets between different subtypes of OLP found that atrophic OLP showed the highest number of FoxP3⁺CD4⁺ T cells with the ulcerative form of OLP the lowest ²⁴. Interestingly, many of the observed FoxP3⁺CD4⁺ T cells expressed T-bet; an IFN- γ hallmark transcription factor, suggesting these cells have an inherent capacity to enhance rather than suppress inflammation, a factor that could explain the chronicity of OLP ²⁴.

Dysregulation of Inflammatory Mediators

Matrix metalloproteinases (MMP) have been strongly implicated as a key contributor in the destruction of the basal lamina zone in OLP ²⁵. Specifically, MMP-2, MMP-7, MMP-9, MMP-3, MMP-10 and tissue inhibitors of metalloproteinases (TIMPs) have all been implicated in the pathogenesis of OLP ^{25,26}. These proteins can cleave collagen type IV and laminin, the major constituent proteins of the basement membrane zone. Zhou et al., 2001

found the *in vitro* activation rate of MMP-9 was significantly higher ($p < 0.05$) in OLP lesional T cells compared to peripheral blood cells from OLP patients, concluding that the over-expression of MMP-9 may result in basement membrane disruption that in turn facilitates keratinocyte apoptosis and cytotoxic T cell migration²⁶. This migration into the epithelium may facilitate the keratinocyte apoptosis that subsequently contributes to basal membrane destruction²⁶.

The use of DNA microarray analysis to assess chemokine receptor and chemokine expression in the epithelial cell layers in OLP and normal gingival tissue has shown that high levels of Langerin⁺ Langerhans cells were noted within the OLP epithelium compared to healthy controls, with results suggesting infiltration of these cells is mediated through the C-C chemokine receptor 6 (CCR6) pathway²⁷. The epithelial cell layers of OLP tissue also showed significantly higher expression of Chemokine (C-X-C) motif ligand (CXCL)9, CXCL10, CXCL11 and Chemokine (C-C motif) ligand (CCL)5²⁷. CXCL9, CXCL10, CXCL11 are specific for the chemokine receptor CXCR3 and CCL5 is the ligand of CCR5²⁷. Both CXCR3 and CCR5 are selectively expressed on Th1 cells and results of this study suggest that the infiltration of T cells in OLP may be mediated through CXCR3 and CCR5 signalling pathways²⁷.

The Th1/Th2 cytokine profiles were assessed in tissue from 30 OLP and 30 healthy control patients with the OLP patients further classified as either reticular or erosive OLP²⁸. Serum levels of interleukin 2 (IL-2) were significantly decreased and interleukin 10 (IL-10) levels were significantly increased in all OLP patients when compared to controls²⁸. The decrease in IL-2 and increase in IL-10 suggests a Th1/Th2 imbalance towards the Th2 response²⁸. The authors suggest that the shift towards a Th2 profile could indicate that OLP is the result of a true delayed hypersensitivity²⁸.

An assessment of Toll Like Receptor (TLR) and inflammatory chemokine genes using real time PCR has been undertaken to assess the expression of genes involved in inflammation and innate immunity in 14 OLP/oral lichenoid reaction (OLR) patients and 23 healthy controls²⁹. Genes analysed included TLR genes such as TLR1 and inflammatory chemokine genes such as CXCL1, interleukin 8 (IL-8) and CD14²⁹. Compared to controls, OLP/OLR patients showed increased expression in the epithelium of the CXCL1, CD14, IL-8

and TLR1 genes confirming increased expression of genes associated with innate immunity in OLP/OLR patients and suggesting innate immunity dysregulation could be involved in the pathogenesis of OLP/OLR ²⁹.

Recently, it has been shown that both CD40 and CD86 are constitutively expressed at low levels in oral keratinocytes, specifically the H357 squamous cell carcinoma cell line and three strains of primary normal oral keratinocytes, and that expression was enhanced by IFN- γ stimulation ³⁰. IHC was used to further evaluate the involvement of CD40 in OLP with results showing strong intensity of CD40 staining in OLP tissues ³⁰. Overall, the results of this study strongly suggest that CD40 and CD86 may play an important pathophysiologic role in oral inflammatory diseases like OLP ³⁰.

Moreover, a recent study assessed the production of keratinocyte-derived CXCL9/10/11 under basal and inflammatory conditions as well as the role these chemokines may play in the pathogenesis of OLP ³¹. This study showed that tissues from OLP patients harboured significantly higher levels of CXCL9/10/11 compared to normal oral mucosa demonstrating that normal oral keratinocytes have the ability to produce chemotactic molecules and mediate T cell recruitment ³¹. This study further highlights how chemokine production in oral keratinocytes may play a key role in the pathophysiology and generation of the OLP inflammatory infiltrate ³¹. The antimicrobial activity of CXCL9 and CXCL10 on oral microflora and their expression profiles following exposure to inflammatory and infectious stimuli has been assessed in oral keratinocytes; both normal human oral keratinocytes and H357 oral squamous cell carcinoma cell line ³². It was shown that these chemokines derived from oral epithelium, particularly CXCL9, demonstrated antimicrobial properties ³². Thus, bacterial and inflammatory-stimulated up-regulation of CXCL9/10 could represent a key element in oral bacterial colonization homeostasis and host-defence mechanisms.

The oral cavity is colonised by a number of commensals, pathogenic and opportunistic microbes. *Candida albicans* is an opportunistic pathogen with the ability to invade the oral epithelium and found in the oral cavity at rates of approximately 48% ³³. Patients with OLP, in particular the erosive form, have been shown to harbour *Candida spp.* at significantly higher rates when compared to healthy controls ^{34,35}. Thus, it may well be that dysregulation of innate immunity could be involved in the pathogenesis of OLP and

defence against the oral microflora, in particular *Candida spp.*, could be critical to this dysregulation.

Mucosal Associated Invariant T cells

Mucosal associated invariant T (MAIT) cells are a subset of T cells thought to have an important role in immunity. MAIT cells are present in peripheral blood and comprise approximately 1-10% of the total of human peripheral blood cells^{36,37}. These T cells have an evolutionarily conserved invariant T cell receptor (TCR) α chain; V α 19-J α 33 in mice and V α 7.2-J α 33 in humans³⁶⁻³⁸. This is in contrast to conventional T cells that traditionally express highly variable and diverse TCR repertoires. TCRs consist of two different protein molecules, known as heterodimers. These heterodimers can be made of variable α , β , γ and δ protein chains. In humans, the vast majority of TCR consist of $\alpha\beta$ heterodimer combinations with a limited number of TCR comprising of $\gamma\delta$ heterodimer combinations. In tissues, MAIT cells are mostly found in the liver and gut mucosa^{36,38}. As the oral cavity forms part of the gastrointestinal system, MAIT cells may also be found in the oral mucosa.

MAIT cells are unique in that they are restricted by a non-polymorphic class Ib MHC molecule known as MHC class 1 related protein (MR-1)^{36,38}. The MR-1 protein is a highly conserved protein found in all mammals, including humans^{36,38}. In adult human blood, MAIT cells are mostly CD8⁺ T cells that express CD161, a C-type lectin receptor that is used as a marker of interleukin 17 (IL-17) producing T cells, including the Th17 subset of cells^{39,40}. The Th17 subset of cells are involved in mediating the host's defensive response to infections and play an important role in the pathogenesis of autoimmunity.

The pathogenic role of the Th17 T-helper cells (Th17 and Th17/Th1), Th0 and Th2 subsets has been studied in OLP using tissue samples from 14 OLP patients with either erosive or reticular OLP as well as normal mucosa as a control⁴¹. mRNA expression for cytokines associated with these subsets were assessed with results confirming an increase in Th17 and Th0 type mRNA molecules in erosive OLP tissue compared to normal tissue⁴¹. This was in contrast to the increase in Th2 type mRNA molecules observed in reticular OLP tissue⁴¹. The percentage of Th17 cells, confirmed by increased expression of CD161, was also shown to be significantly higher in erosive OLP tissue (35%) compared to normal tissue

(4%) ($p=0.001$)⁴¹. Results of this study support the conclusion that Th17, Th0 and Th2 may play an important role in the pathogenesis of OLP, however, further research is required to clarify how these different subsets of T cells participate in the OLP pathogenic process⁴¹.

MAIT cells can be activated by MR-1 bound intermediates derived from riboflavin, also known as vitamin B2. This is significant as riboflavin is not endogenously produced in humans, however it is produced by microbes including bacteria and *Candida*^{37,38,42}. Using an *in vitro* model Le Bourhis et al., 2010 cultured bone marrow-derived dendritic cells (BMDCs) from MR-1 sufficient and deficient mice. These cells were subsequently infected with *C. albicans*, *C. glabrata* and *Saccharomyces cerevisiae*⁴². The results of this *in vitro* experiment showed that *C. albicans*, *C. glabrata* and *S. cerevisiae* had the ability to induce a MAIT cell response in an MR-1 dependent manner⁴². Gold et al., 2014 obtained peripheral blood CD8+ cells from 4 donors and stimulated these by *ex vivo* exposure to A549 epithelial cells infected with *Mycobacterium semgmatis*, *Salmonella typhimurium* and *C. albicans*. It was found that MAIT cells had the ability to detect a diverse array of MR-1 restricted ligands, discriminate between the different pathogen-derived ligands and provide a basis for an adaptive immune response⁴³. However, this *in vitro* model also showed that the *C. albicans* MAIT TCR repertoire was less diverse than the MAIT TCR repertoire for the other two pathogens⁴³. To date the role of MAIT cells in commensal fungal colonization or pathogenic fungal infection in OLP has not been studied in human or animal cohorts.

The presence of normal commensal oral flora, including bacteria and *Candida*, could act as a potential trigger for T cell activation and initiation of the OLP disease process. The ongoing presence of *Candida* as a normal oral commensal could also account for the longevity of the OLP disease process.

In response to a microbial infection, MAIT cells will rapidly release IL-17, IFN- γ , TNF- α and IL-22 to help coordinate an appropriate immune response^{39,42,44}. IFN- γ and TNF- α are important mediators required for the activation and coordination of the innate and adaptive immune responses to microbial and viral infection. Gibbs et al., 2017 showed MAIT cells in the female genital tract exhibited a bias towards expression of IL-17 and IL-22 when stimulated with *Escherichia coli* (*E. coli*). This is in contrast to blood MAIT cells that primarily produced IFN- γ , TNF and granzyme B under the same conditions⁴⁴. Results of this study suggest that due to the preferential expression of IL-17 and IL-22, mucosal MAIT cells may

have an important role to play in mucosal homeostasis and maintenance of mucosal barrier integrity ⁴⁴. Diseases, such as OLP that induce inflammation and keratinocyte apoptosis have the potential to disrupt the production of IL-22 and this may in turn influence the maintenance of mucosal barrier integrity. Concomitant fungal colonisation in OLP patients also has the potential to activate regional MAIT cells in oral mucosal epithelium. Presence of common oral commensals such as *C. albicans* may result in a bias towards oral IL-17 and IL-22 expression, in a way similar to how MAIT cells in the female genital tract exhibit a bias towards IL-17 and IL-22 production when stimulated with *E. Coli* ⁴⁴.

IL-22 and IL-23 expression was assessed in 80 patients with lichen planus, 42 OLP and 38 cutaneous lichen planus patients, as well as 20 normal control samples including 10 samples from oral mucosa and 10 from skin ⁴⁵. Cellular expression of IL-22 and IL-23 was significantly higher in the epithelial and subepithelial regions in lichen planus tissue compared to normal control tissue ($p < 0.001$) ⁴⁵. Expression of IL-22 in the subepithelial layer and expression of IL-23 in both the epithelial and subepithelial layers was significantly higher in OLP compared to cutaneous lichen planus ($p = 0.036$, $p = 0.003$ and $p = 0.006$) respectively ⁴⁵. Higher expression in OLP suggests the IL-22 cells form an important part of the oral mucosal defence system against pathogenic microbes ⁴⁵.

The IL-17/IL-23 axis, thought to be involved in the pathogenesis of chronic immune mediated and inflammatory disorders has also been studied in OLP ⁴⁶. Lu et al., 2014 collected tissue samples from 13 erosive OLP patients, 14 reticular OLP patients and 10 normal mucosa controls, as well as collected blood from 10/14 reticular OLP patients to assess the IL-17/IL-23 axis. The marker IL-23 p19, a sub-unit of IL-23 and IL-17, was used with IHC to assess IL-17/IL-23 expression, demonstrating an overexpression of IL-17/23 in OLP lesions compared to controls ⁴⁶. These results provide evidence that the IL-17/IL-23 axis plays a regulatory role in OLP ⁴⁶. It is possible that activation of MAIT cells may result in overproduction of IL-22 and IL-17 in response to normal oral microbes and contribute to the OLP disease process.

MAIT cells can be detected in tissue by co-staining with an anti-TCRV α antibody and CD161 ⁴⁷. Other markers that can be used to detect MAIT cells in tissue sections interleukin 18 receptor alpha (IL-18R α) and CD3 ^{39,48}. IL-18R is a receptor with alpha and beta subunits that has a high affinity for the IL-18. Both IL-18 and IL-12 work together to generate a cell

mediated immune response following a microbial infection and exposure to microbial products such as lipopolysaccharide (LPS) ⁴⁹. The role of IL-18 has been explored in OLP. Serum and salivary IL-18 levels were significantly higher in patients with OLP compared to controls, and interestingly significantly higher in erosive OLP compared to non-erosive OLP ⁵⁰. IL-18 may play a role in OLP and it is possible that serum and salivary production of IL-18 may be linked with a MAIT cell in response to normal oral microbes.

Kurioka et al., 2015 showed that resting MAIT cells have a lack of cytotoxic activity with low levels of granzyme B and perforin expression. On bacterial activation with *E. coli* the MAIT cells were able to rapidly induce granzyme B and perforin ⁵¹. Thus, resting state MAIT cell cytotoxicity is suppressed, however on continued exposure to bacteria the MAIT cells acquire a cytotoxic phenotype that enables them to kill infected cell ⁵¹. This entire process is dependent on MAIT cells binding MR-1.

Furthermore, MAIT cells have been shown to be activated by epithelial cells, specifically HeLa cells, infected with the invasive bacteria *Shingella flexneri* and that MAIT cells were able to kill infected epithelial cells expressing MR-1 ⁵². Interestingly, epithelial cells infected with the invasive bacteria *Salmonella enterica Typhimurium* did not activate a MAIT cell response ⁵². The fact that MAIT cells possess an inherent capacity to kill epithelial cells infected with invasive bacteria is significant. *Candida spp.* can invade the superficial epithelium and have the potential to act as a trigger for MR-1 production. This in turn could induce a MAIT cell death response to kill infected keratinocytes and this may act as a trigger for the initiation of the OLP disease process.

Thus, it can be hypothesised that interaction between the oral flora and the immune system, and specifically interaction between oral microbes that metabolise riboflavin and MAIT cells, may be a key initiating event in OLP. A diagrammatical representation of the hypothetical role of MAIT cells in the aetiopathogenesis of OLP is outlined in Figure 1. Antigen presenting cells, most likely Langerhans cells, would be critical to this interaction, and result in basal membrane destruction, the infiltration of cytotoxic T cells, and ultimately the chronic inflammatory state with keratinocyte apoptosis that is central to the pathogenesis of OLP. This process may be only likely, and potentially worsened, in patients who have specific predisposition, an inherited tendency or diathesis, such as a diminished T cell repertoire, specific genetic polymorphisms, or other yet unknown predisposing factors.

Conclusion

To date the exact trigger that initiates the chronicity of the OLP disease process is unknown. OLP may in fact be a localised, organ specific, autoimmune condition that is initiated by a complex mix of microbial, environmental and genetic factors. The role that MAIT cells may play in the initiation and chronicity of OLP is a novel hypothesis for the pathogenesis of OLP and central to this hypothesis is the role that the commensal oral flora plays in activating these cells. Further research is required to assess whether MAIT cells are indeed upregulated in OLP and if MAIT cells actually respond to common commensal oral microbes.

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Conflicts of Interest

None declared

Author Contribution

L. M. DeAngelis led the review team. L.M. DeAngelis, N. Cirillo and M. J. McCullough reviewed the literature and wrote sections of the manuscript. All authors revised, edited and approved the submitted version of the manuscript.

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Figure 1: Diagrammatical representation of the hypothetical role of MAIT cells in the aetiopathogenesis of OLP.

Legend: OK = Oral keratinocyte, AK = *Candida* affected keratinocyte, LC = Langerhans cell, MC = MAIT cell, AM = Activated MAIT cell, TC = T cell

Table 1: The cells and inflammatory mediators that have been implicated in the aetiopathogenesis of OLP

Cell	Function	Potential Role in OLP	References
Mast cells	Allergy and anaphylaxis due to release of histamine	<ul style="list-style-type: none"> Found in increased numbers in OLP May contribute to basement membrane disruption and facilitation of cytotoxic T cell infiltration Production of RANTES in OLP may facilitate mast cell degranulation and release of TNF-α which in turn mediates T-cell mediated apoptosis 	9,13,14
Macrophages	White blood cell and phagocytic cell that phagocytoses microbes and foreign substances	<ul style="list-style-type: none"> Found in abundance in OLP tissue close to the area of basement membrane destruction May play a potential role in phagocytosis and antigen processing 	19
Langerhans cells	Dendritic cell and professional APC found in the skin and mucosa	<ul style="list-style-type: none"> Found to be present in higher numbers in OLP tissue May play a possible significant role in the adaptive immune response in OLP, specifically with relation to antigen presentation It has been suggested that Langerhans cells may present an unknown antigen to CD4+ cells and this promotes CD8+ epithelial destruction 	15,17,18
Helper T cell	T lymphocyte that recognises MHC class II and work to release cell	<ul style="list-style-type: none"> In OLP presentation of MHC class II molecule from keratinocytes or Langerhans cell can activate CD4+ cells and in turn result CD8+ keratinocyte apoptosis 	8,17

	cytokines that mediate a T cell response		
Cytotoxic T cell	T lymphocyte that recognises and binds MHC class I and kills the cell displaying MHC class I	<ul style="list-style-type: none"> The OLP disease process is defined by CD8+ infiltration and destruction of the basal lamina zone Possibly CD8+ cells may recognise MHC class I on keratinocytes to initiate keratinocyte apoptosis 	8,10
Regulatory T cell	T lymphocyte that plays a regulatory role in preventing autoimmune disease and limiting chronic inflammation	<ul style="list-style-type: none"> Regulatory T cells are high in Foxp3, CD4 and CD25 Increased numbers of regulatory T cells higher numbers in OLP tissue compared to control, especially erosive/ulcerative subtypes of OLP This suggests that regulatory T cells may play an important role in the pathogenesis of OLP 	21-24

Inflammatory Mediator	Function	Potential Role in OLP	References
Matrixmetalloproteinases	Endopeptidases that can degrade extracellular matrix including collagen and laminin	<ul style="list-style-type: none"> The activation rate of MMP-9 has been shown to be significantly higher in OLP lesional T-cells MMP2 and 3 have been shown to be present in OLP epithelium Overexpression of MMP-9 may result in basement membrane disruption and cytotoxic T cell infiltration 	25,26
Chemokine dysregulation	Cytokines produced by immune cells that can act	<ul style="list-style-type: none"> OLP has shown significantly higher levels of CXCL9/10/11 Oral keratinocytes can produce these chemokines CXCL9/10/11 	27,30,32

	as signalling molecules and induce chemotaxis	<ul style="list-style-type: none"> • CXCL9/10/11 are specific for CXCR3 and CCL5, the ligand for CCR5 • CCR5 and CXCR3 are selectively expressed on TH1 T cells • CXCL9 and 10 production, in particular CXCL9 production, by oral keratinocytes can be upregulated following inflammatory and infectious exposure • Production of these molecules by oral keratinocytes may mediate a T cell inflammatory response 	
Interleukins	Cytokines with the primary function of modulating cellular behaviour	<ul style="list-style-type: none"> • Significantly decreased tendency for IL-2 has been shown in erosive and reticular OLP while a significantly increased tendency for IL-10 has been shown in erosive and reticular OLP when compared to healthy controls. • This cytokine profile suggests a Th1/Th2 imbalance towards the Th2 response in OLP • Overexpression of IL-22, IL-23, IL-18 and IL-17 in OLP patients could suggest a role for these cytokines in the pathogenesis of OLP 	28,45,50,53

Cell	Function	Potential Role in OLP	References
Mast cells	Allergy and anaphylaxis due to release of histamine	<ul style="list-style-type: none"> Found in increased numbers in OLP May contribute to basement membrane disruption and facilitation of cytotoxic T cell infiltration Production of RANTES in OLP may facilitate mast cell degranulation and release of TNF-α which in turn mediates T-cell mediated apoptosis 	(Zhao, Savage et al. 1997), (Zhao, Sugerman et al. 2001), (Zhou, Sugerman et al. 2002)
Macrophages	White blood cell and phagocytic cell that phagocytoses microbes and foreign substances	<ul style="list-style-type: none"> Found in abundance in OLP tissue close to the area of basement membrane destruction May play a potential role in phagocytosis and antigen processing 	(Matthews, Basu et al. 1985)
Langerhans cells	Dendritic cell and professional antigen presenting cell found in the skin and mucosa	<ul style="list-style-type: none"> Found to be present in higher numbers in OLP tissue May play a possible significant role in the adaptive immune response in OLP, specifically with relations to antigen presentation It has been suggested that Langerhans cells may present an unknown antigen to CD4+ cells and this promotes CD8+ epithelial destruction 	(Gueiros, Gondak et al. 2012), (Regezi, Stewart et al. 1985), (Villarroel Dorrego, Correnti et al. 2002)
Helper T cell	T lymphocyte that recognises MHC class II and work to release cell cytokines that mediate a	<ul style="list-style-type: none"> In OLP presentation of MHC class II molecule from keratinocytes or Langerhans cell can activate CD4+ cells and in turn result CD8+ keratinocyte apoptosis 	(Sugerman, Savage et al. 2002), (Villarroel Dorrego, Correnti et al. 2002)

	T cell response		
Cytotoxic T cell	T lymphocyte that recognises and binds MHC class I and kills the cell displaying MHC class I	<ul style="list-style-type: none"> The OLP disease process is defined by CD8+ infiltration and destruction of the basal lamina zone Possibly CD8+ cells may recognise MHC class I on keratinocytes to initiate keratinocyte apoptosis 	(Sugerman, Satterwhite et al. 2000, Sugerman, Savage et al. 2002)
Regulatory T cell	T lymphocyte that plays a regulatory role in preventing autoimmune disease and limiting chronic inflammation	<ul style="list-style-type: none"> Regulatory T cells are high in Foxp3, CD4 and CD25 Increased numbers of regulatory T cells higher numbers in OLP tissue compared to control, especially erosive/ulcerative subtypes of OLP This suggests that regulatory T cells may play an important role in the pathogenesis of OLP 	(Tao, Xia et al. 2010), (Pereira, Monteiro et al. 2012), (Zhou, Cao et al. 2016), (Javvadi, Parachuru et al. 2016), (Schreurs, Karatsaidis et al. 2016)

Inflammatory Mediator	Function	Potential Role in OLP	References
Matrixmetalloprotinases	Endopeptidases that can degrade extracellular matrix including collagen and laminin	<ul style="list-style-type: none"> The activation rate of MMP-9 has been shown to be significantly higher in OLP lesional T-cells MMP2 and 3 have been shown to be present in OLP epithelium Overexpression of MMP-9 may result in basement membrane disruption and cytotoxic T cell infiltration 	(Zhou, Sugerman et al. 2001)
Chemokine dysregulation	Cytokines produced by immune cells that can act	<ul style="list-style-type: none"> OLP has shown significantly higher levels of CXCL9/10/11 Oral keratinocytes can produce these chemokines CXCL9/10/11 	(Marshall, Celentano et al. 2016), (Marshall,

	as signalling molecules and induce chemotaxis	<ul style="list-style-type: none"> • CXCL9/10/11 are specific for CXCR3 and CCL5, the ligand for CCR5 • CCR5 and CXCR3 are selectively expressed on TH1 T cells • CXCL9 and 10 production, in particular CXCL9 production, by oral keratinocytes can be upregulated following inflammatory and infectious exposure • Production of these molecules by oral keratinocytes may mediate a T cell inflammatory response. 	Celentano et al. 2017), (Ichimura, Hiratsuka et al. 2006)
Interleukins	Cytokines with the primary function of modulating cellular behaviour	<ul style="list-style-type: none"> • Significantly decreased tendency for IL-2 has been shown in erosive and reticular OLP while a significantly increased tendency for IL-10 has been shown in erosive and reticular OLP when compared to healthy controls. • This cytokine profile suggests a Th1/Th2 imbalance towards the Th2 response in OLP • The Th2 response is critical for humoral mediated immunity, in OLP. 	(Pekiner, Demirel et al. 2012)
Cluster of differentiation	Cell surface molecules used for cell immunophenotyping. Some of these molecules may also be receptors or	<ul style="list-style-type: none"> • CD40 and CD86 have been shown to be expressed constitutively in oral keratinocytes • CD40 is a receptor found mainly on antigen presenting cells with CD86 being a costimulatory molecule • IFN-γ can enhance the expression of CD40 and CD86 	(Marshall, Celentano et al. 2017)

	ligands	<ul style="list-style-type: none"> Strong staining of CD40 detected with IHC has been shown in OLP tissue suggesting a possible important pathophysiologic role in OLP 	
Genes associated with inflammation and innate immunity	Genes that regulate inflammation and innate immunity	<ul style="list-style-type: none"> TLR genes including TLR1 which play a role in pattern recognition of microbial ligands has shown increased expression in OLP/OLR patients Inflammatory chemokines genes including CXCL1, CD14 and IL-8 have also been shown to have increased expression in OLP/OLR Increased expression of these genes may suggest a role of innate immunity dysregulation in the pathogenesis of OLP 	(Adami, Yeung et al. 2014)

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