Review Article

Comparison of Oral Lichen Planus and Systemic Lupus Erythematosus in Interleukins Level

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Abstract

Lichen planus (LP) is a chronic inflammatory mucocutaneous disorder with unknown etiology. Systemic lupus erythematosus (SLE) is known as a prototypic autoimmune disease. Cytokines play a key role in the pathogenesis of both diseases. Various cytokines, such as interleukin 6 (IL-6), interleukin 10 (IL-10), interferon alpha (INF-a), and Tumor Necrosis Factor-alpha (TNF-a) can serve as biomarkers to predict SLE severity and monitor disease activity. In this review, we compare interleukins in oral lichen planus and lupus erythematosus as an autoimmune disease prototype. So, this review may provide insight for researchers in completing the cytokine network in OLP.

Among the etiologic factors, the imbalance between Th-1 and Th-2 cytokine production plays an important role in the development of both diseases. By understanding cytokines and immunoregulatory networks of cytokines in these patients, appropriate treatment can be offered.

There are many limitations in cytokine studies, which we have described in this article.

Keywords: Interleukin, oral lichen planus, systemic lupus erythematosus

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Introduction

Lichen planus (LP) is a chronic inflammatory mucocutaneous disorder with unknown etiology.[1] Oral lichen planus (OLP) is more frequent than the cutaneous type and is prevalent in 0.5%–2% of the world population. Degeneration of basal cells, and infiltration of inflammatory cells into the subepithelial layer of connective tissue are the pathological characteristics of OLP. The majority of intraepithelial infiltrating lymphocytes are CD8+ T cells, whereas in lamina propria, they are mostly CD4+ T cells. Clinical and immunohistochemical studies strongly support the role of immune deregulation in the pathogenesis of oral lichen planus (OLP). Deregulation specifically involves the cellular immune system and a complex cytokine network.[2–7] Cytokines are low-weight soluble proteins produced by various cells in the innate and adaptive immune system. They activate or regulate the immune system by binding to cell surface receptors. They play a critical role in the activation, differentiation, and maturation of different immune cells.[8] OL P is type IV hypersensitivity reaction, and some authors have suggested that contact allergy may play a role in the pathogenesis and management of oral lichen planus.[9,10] Contact hypersensitivity responses require the participation of T cells, along with a variety of cytokines such as interleukin 3.[11]

Genetic variations which cause structural or expression alteration of a cytokine may lead to chronic diseases, increased risk of infection and changed outcome of acute disorders or surgery.[3] At this time, genetic factors causing imbalances in the level of Th2 and Th1 cause immune responses which lead to imbalances in pro- and anti-inflammatory cytokine production. While these genetic variations in OLP are not well understood, it is suggested that they increase susceptibility to OLP.[12]

Systemic lupus erythematosus (SLE) is known as a prototypic autoimmune disease,[13] and cytokines play a key role in its pathogenesis. Also, disease activity and organ damage are affected by the balance and regulation of cytokine production.[14] There is strong evidence that genetics play an important role in lupus, and more than one hundred possible genetic risk factors have been identified for lupus.[15] It is apparent that soluble mediators of immune reactions such as cytokines are the principal candidates for pathogenic factors responsible for this disease.[16]

Various cytokines, such as interleukin 6 (IL-6), interleukin 10 (IL-10), interferon alpha (INF-a), and Tumor Necrosis Factor-alpha (TNF-a) can serve as biomarkers to predict disease severity and monitor disease activity. Some defects in IL-8 may cause susceptibility to bacterial infections in SLE patients. A potential therapeutic strategy for the treatment of SLE may be manipulation of these cytokines.[8,17]

In this review, we compare interleukins in oral lichen planus with lupus erythematosus as an autoimmune disease prototype, to reveal the important but missed particles in pathogenesis of OLP. The most significant use of genetic data is to improve the accuracy of the diagnostic approach, and help the clinician with risk assessment and treatment assortment.[18] Lupus erythematosus, or lichen planus overlap syndrome, is a condition in which skin lesions present clinical, histologic, and/or immunopathologic features that may be classic for either or both diseases at the same time, and may strengthen the possibility of common biological pathways in these diseases.[19–21]

Additionally, this review may provide insight for researchers in completing the cytokine network in OLP.

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Interleukin genes in lupus erythematosus

These interleukins are reviewed in Table 1.

Interleukin genes in lichen planus

These interleukins are reviewed in Table 2.

In Figure 1, the known cytokine genes in SLE are shown with their functional correlations (STRING (Search Tool for the Retrieval of Interacting Genes) database, Heidelberg, Germany),[30] and two cytokines (IL18, IL6) detected in OLP are circled. Using these tools has proven helpful in further analyzing the enormous data from microarray analysis and providing more understandable schema from bimolecular interactions.

Despite the fact that environmental factors such as ultraviolet (UV) light or infection are involved in disease pathogenesis, genetics are a strong component - 4% of patients are familial, with reports of concordance rates of 24%–65% in monozygotic twins.[31] Additionally, subjects who have a first-degree relative with SLE are over six times more likely to develop the disease than those without such relatives.[32]

Considerable study in genetic association with autoimmune diseases has focused on the detection of associations outside the HLA, mostly in the pathways of the immune system function.[33] One of the strongest associations with SLE outside of the MHC is Interferon regulatory factor 5 (IRF5). Variants within this locus increase the risk of developing the disease. IRF5 is a transcription factor which mediates type 1 interferon inflammatory and immune responses and by toll-like receptor signaling, ultimately results in the production of TNF-a, IL-12, and IL-6.[33]

Cytokines are pleiotropic and play their role in highly complicated cytokine networks to regulate immunity.[34] B and T lymphocytes, dendritic/macrophage cells, monocytes and thymus are key components of the immune system, and contribute to the underlying mechanisms of autoimmune diseases such as SLE. Among these factors, the imbalance between Th-1 and Th-2 cytokine production plays an important role in the development of the disease.[16] The cytokine profiles of Th1 and Th2 are different. Th1 cells are known to produce IL-2 and IFN-γ, and belong to cell-mediated immunity, but Th2 cells produce IL-4, IL-5, and IL-10 and are critical in humoral immunity.[35] In some studies, OLP was characterized by Th1 cytokine bias. In contrast, others have suggested the possibility of a Th2-dominated immune response occurring in a subgroup of OLP patients.[35]

Cytokine networks and epigenetic factors regulate the expression of chemokines and chemokine receptors. CCR5 is up-regulated by Th1 cytokines such as IL-2 and IFN-γ, and down-regulated by Th2 cytokines such as IL-4.[5]

Previous studies have indicated that concurrent expression of mRNAs for both pro- and anti-inflammatory cytokines occurs in OLP.[2] Other inflammatory and immune-mediated disorders, such as recurrent aphthous stomatitis, periodontal disease and graft-versus-host disease, are evidence of an association between genetic variations in cytokines and the disease.[2]

Understanding the role of cytokines in autoimmune diseases such as OLP may require accepting the concept of quantitative thresholds for immune-cell signaling, introduced in the past de-

Table 1. Interleukin genes in lupus erythematosus.

Interleukin	Author/ Year	Media	Genotype Assays	Locus	Function
IL-2	Hedrich CM et al, 2011[22]	Blood			Proliferation and activation of T lymphocytes. Functions as an auto- and paracrine growth factor
IL-4	Yu HH et al, 2010[23]				
IL-5	Sato EI et al, 2011[24]	Skin	PCR		
IL-6	Santos MJ et al, 2011[25] Chua K et al, 2009[26]	Blood Blood	PCR PCR	Chromosome 7p at location 21 to 15	Promotion of T cell proliferation Promotion of B cell differentiation
IL-10(IL10R1)	Hermann J et al, 2009[27]		PCR		Activates the JAK-STAT pathway. Plays a central role in regulation of growth and differentiation of B cells and auto-antibody production
IL-12B	Miteva LD. et al, 2012[28]	_	PCR		Pro-inflammatory cytokine as a key factor driving the differentiation of naive T cells toward the Th1 phenotype
IL -16	Xue H et al, 2009[29]	Blood	PCR	15q26.3	Contribution to the regulatory process of CD4+ cell recruitment Activation at the sites of inflammation in autoimmune diseases
IL-18	Sánchez E et al, 2009[13]	Blood	PCR	11q22.2–22.3	Mediate both Th1 and Th2 driven immune responses. In combination with IL-12, IL-18 induces IFN-g production in Th1 cells, B cells and natural killer cells, promoting Th1-type immune responses, but can also stimulate Th2 immune responses in the absence of IL-12
IL-21-R	Webb R. et al, 2009[15]	Blood and buccal cell swabs	Illumina Infinum II	16p11	Critically involved in B cell activation, differentiation, and immunoglobulin Production

Table 2. Interleukin genes in lichen planus.

Interleukin	Author / Year	Media	Genotype assay	Locus	Function
IL-1b(not significant)	Xavier GM, et al., 2007[2]	Oral mucosa swabs	PCR		
IL-6	Xavier GM, et al., 2007 [2]	Oral mucosa swabs	PCR	7p21–24	
IL-10(not significant)	Xavier GM, et al., 2007[2]	Oral mucosa swabs	PCR		
IL-8(not significant but associated with severity of OLP)	Dan H, et al., 2010 [3]	Blood		4q13–21	Able to attract neutrophils, induces migration of T lymphocytes, facilitates tumor growth and angiogenesis, inhibits collagen synthesis
IL18	Bai J, et al., 2007 [12]	Blood	PCR	11q22.2–22.3	Plays an important role in the regulation of IFN-g production and has multiple functions including (i) augmentation of T-cell- and natural killer-cell-mediated cytotoxicity through upregulation of FAS ligand, (ii) enhancing perforin-regulated killing,(iii) inducing proinflammatory cytokines and chemokines

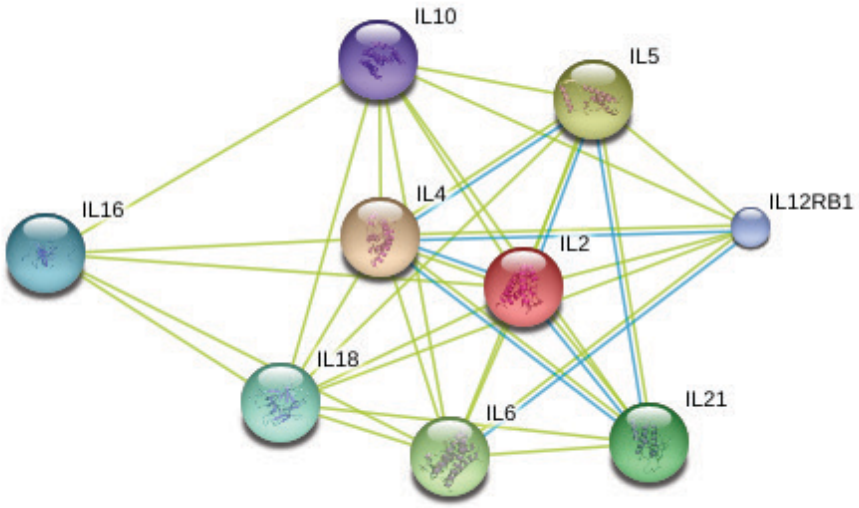

Figure 1. Cytokine genes in SLE and two cytokines (IL18, IL6) detected in OLP.

cade as a possible way of considering how susceptibility to autoimmune activation can be created by a combination of multiple genetic factors with relatively small effects.[18]

These genetic factors include the intracellular signaling that activates T and B cells, pathways which mediate innate immunity and microbial responses and signaling by cytokines and cytokine receptors.

As one of these genetic factors, cytokine signaling pathways are modulated through complex mechanisms. Also, polymorphisms occur frequently throughout the human genome, and may alter either the expression or the function of a gene product. Clearly, the goal is to understand the role of cytokines in signaling pathways, and the potential effects of their polymorphisms.

Overcoming these complexities can be achieved by focusing on specific genetic and phenotypic subgroups of a disease.[18] Therefore, an understanding of different genetic subgroups in autoimmune diseases can enhance both diagnostic and therapeutic approaches.

Therapeutic approaches and impact on clinical medicine

In recent years, new treatment approaches have emerged using antibodies or molecule inhibitors specifically targeting cytokines, signaling mechanisms or cellular receptors. Compared to "traditional" treatments administered to SLE patients, these new treatments have yielded several adverse effects. It is useful to keep in mind that no single treatment is effective and completely safe, and physicians should seriously consider that every patient exhibits a unique cellular and molecular profile.[36]

The response to each specific drug and severity of the disease may also be influenced by genetic profiles. The best therapeutic

approach would include a combination of immunosuppressant and anti-inflammatory drugs, which should be administered with consideration to the cellular and molecular profile specific to each SLE patient.[36]

It is therefore important to understand the pathological roles of these abnormally induced cytokines and immunoregulatory networks of cytokines in these patients, so that appropriate treatment can be offered.[34]

Tocilizumab is a mouse-human chimeric anti-human anti-IL-6R mAb. Although preliminary results suggest that it can control SLE disease activity, its ultimate clinical utility may be limited due to increased risk of infections.[37]

Compared with 'conventional' therapies such as glucocorticoids or cytotoxics drugs, cytokine-targeted therapy may prove valuable in the treatment of SLE, and offer a less toxic alternative. There are many more cytokines besides the four cytokines reviewed above, including IFNγ, IL-1, and IL-17, that are involved in SLE. As mentioned before, cytokine biology is very complex, and this complexity increases in a disease such as SLE. Investigations of cytokine pathways in animal models, in human SLE tissues, and in the genetics of SLE will help researchers to find additional cytokines in disease pathogenesis, and could suggest further novel targets for treatment.[37]

The WHO classifies OLP and other diseases such as discoid lupus erythematosus as precancerous conditions. Despite considerable attempts in oropharyngeal cancer therapies, the five year survival rate, even in developed countries, is not satisfactory.[38] Therefore, new therapies are needed to target the underlying mechanism in these diseases. Cytokine-targeted therapy such as basiliximab (IL2 receptor blocking antibody) has been effective in treatment of erosive OLP, which strengthens the dominance of Th1 bias in OLP. Therefore, other Th1 blocking agents may be efficient in OLP treatment.[39]

Gene expression profiling in SLE may solve one part of the puzzle in pathogenic mechanisms, and as a model can offer parts of pathogenesis in OLP, and new therapies for them.

Limitation in genetic studies

In summary, SLE as an autoimmune prototype disease, may be a clue and provide guidance for future studies in OLP. However, looking at Figure 1, and taking IL10 as an example, we can see that it plays a role in the pathogenesis of SLE, but no significant correlation was found with respect to OLP in one study. Such findings highlight three major limitations of genetic studies. Firstly, there are different SNPs for each IL, so this result may not be the same with other SNPs of IL10 or IL8. The second limitation is related to population heterogeneity. The third limitation is the impact of different disease stages on gene expressions. Cell destruction and erosive OLP indicate higher gene expression of inflammatory cytokines.

So, in this review we considered cytokines level in SLE compared to OLP, in order to gain additional information about theses autoimmune disorders.

Interleukins in serum

Interleukins in serum or saliva of OLP patients are reviewed in Table 3 and Interleukins in serum of SLE patients are reviewed in Table 4.

We have tried to show controversies in results if they exist, so one original article was chosen in a group of articles with the same result and methods about a certain cytokine. We searched the database PubMed. Details of these studies are summarized in Table 4.

In Figure 2, the known cytokines in serum of SLE patients are shown with their functional correlations (STRING database).[30] Eight cytokines (IL2, IL4, IL5, IL6, IL8, IL10, IL17, IL18) detected in OLP are circled.

The predominance of the Th1 effect is established for rheumatoid arthritis, but the condition is much more complex in SLE.[75] A deficiency in Th1 cytokines and a relative excess in Th2 cytokines have been reported.[76] Based on these results, this relationship does not exist.

IFN-α has a key role in the pathogenesis of SLE and has been determined as a new treatment for SLE.[58] Recently, it has been shown that IL-10 increases in the serum of SLE patients more frequently than IFN-α, and has been suggested as a marker of SLE.[58,75] Interleukin-10 (IL-10) plays an important immunoregulatory role, and is secreted by various immune cell groups. Two types of disease can be identified according to IL-10 changes. Diseases with an increased IL-10 level include systemic lupus erythematosus, melanoma, lymphomas, systemic sclerosis; diseases with decreased IL-10 include chronic inflammatory bowel diseases (includes Crohn's disease, ulcerative colitis), rheumatoid arthritis, and psoriasis.[76]

Table 3. Interleukins in serum or saliva in OLP patients.

Interleukin	Author / Year	Media	Results
IL-2	Pekiner FN, et al., 2012[35]	Serum	Decreased in OLP group
IL-4	Liu WZ, et al., 2013[35,40]	Serum & saliva	Increased in OLP group
IL-5(Not significant)	Pekiner FN, et al., 2012[35]	Serum	
IL-6	Sun A, et al., 2005[41]	Serum	Increased in OLP group
IL-8	Sun A, et al., 2005[41]	Serum	Increased in OLP group
IL-10	Pekiner FN, et al., 2012[35] Kalogerakou F, et al., 2008[42]	Serum Serum	Increased in OLP group Decreased in OLP group
IL-17	Pouralibaba F, et al., 2013 [43,44]	Serum	Increased in OLP group
IL-18	Zhang Y, et al., 2012[45]	Serum & saliva	Increased in OLP group

Table 4. Interleukins in serum of SLE patients.

Interleukin	Authors / year	Media/Sample Size	Study result	Function
IL-1ra (receptor antagonist)	Capper Er, et al., 2004[31]	Serum ELAISA SLE:	Increased in SLE but not significant	IL-1RA is a member of the interleukin 1 cytokine family. IL1Ra is secreted by various types of cells including immune cells, epithelial cells, and adipocytes, and is a natural inhibitor of the pro-inflammatory effect of IL1β and IL1α [46]
IL-2 receptor α	El-Shafey Eid, et al., 2008[47]		Increased in SLE group, indicator of early renal involvement	IL-2 binds to this receptor to promote T cell proliferation [48]
IL-3	Fishman P, et al., 1993[49]		Increased in SLE group	IL-3 is a pleotrophic growth factor affecting the proliferation and differentiation of stem cells to committed progenitors of several hematopoietic lineages including megakaryocytes and lymphocytes.
IL-4	Wong Chun Kwok, et al., 2000[50]		Increased in SLE group	
IL-5	Anzai M, et al., 2008[51]		Increased in SLE group	
IL-6	Linker-Israeli M, et al., 1991[52] Ripley BJM, et al,, 2005[53]		Increased in SLE group	IL6 produced in response to inflammatory stimuli; including IL1 and tumour necrosis factor a, it has pivotal roles in regulating the host immune response to infection. It is a potent stimulator of the differentiation and activation of lymphoid and myeloid cells and a key regulator of various other cellular processes, including erythropoiesis, neuronal cell differentiation, and bone metabolism
IL-7	Badot V, 2013[54]	Serum, urine, kidney tissue ELAISA, PCR SLE:87 Control: 119	Increased in sera of SLE group and correlated with SLE Disease Activity Index (SLEDAI) scores especially nephritis	sIL-7R is produced by fibroblasts after stimulation with proinflammatory cytokines
IL-8 (Receptor)	Hsieh S, et al., 2008[17]	polymorphonuclear neutrophils, flow cytometry SLE:	There is SLE-PMN hyporesponsiveness to IL-8 stimulation in vitro.	IL-8 is a potent autocrine chemokine specific for PMN chemoattraction and activation
IL-8	Hrycek E, 2013 [55]	Serum EAISA SLE(under medical therapy): 48 Control:29	Decreased in SLE group	
IL-9	Ouyang H, et al., 2013[56]	mRNA and serum IL-9 levels PCR, ELAISA	Both increased in SLE group	IL-9 is a T cell-derived factor preferentially expressed by CD4+ T cells
IL-10	Gröndal G et al, 1999[57]	Serum ELAISA SLE: 52 Control:29	Increased in SLE group	IL-10 has both immunosuppressive and immunostimulatory properties. IL-10 has been shown to significantly affect the differentiation, maturation and function of dendritic cells derived from monocytes [58]
	Capper ER, et al., 2004[31]	Serum ELAISA	Increased in SLE group	

IL-11 (its correlation with proteinuria)	Chien JW, et al., 2006[59]	Urinary ELAISA SLE:40	The correlation was significant	IL11 has hematopoietic and anti-inflammatory effects. It has ability to reduce macrophage activation and divert the immune response from a Th1 response to a Th2 response.
IL-12	Liu T, et al., 1998[60]	Peripheral blood mononuclear cells SLE:49 Control:18	Production of IL-12 in SLE PMBCs were decreased, It was NOT due to diminished number of monocytes	
	Tokano Y, et al., 1999[61]	Serum EAISA SLE: 39 Control: 12	IL-12 in active lupus patients was Increased.	
	Horwitz D, et al., 1998[62]	Peripheral blood mononuclear cells SLE:10 Control:10	Production of IL-12 in SLE PMBCs were decreased	
IL-13				
IL-14	Ambrus J, et al., 1995[63]	Peripheral blood mononuclear cells	Increased in SLE group	(IL-14) is implicated in the generation and maintenance of normal memory B cells. It cause synthesis and upregulation of IL-14 receptors, are dependent on the formation of prostaglandin E
IL-15	Baranda L, et al., 2005[64]	Peripheral blood mononuclear cells Serum SLE:18(10 inactive, 8 active diease) Control:14	monocytes from active SLE patients expressed higher levels of membrane-bound IL-15 compared with both inactive patients and healthy controls	IL-2 and IL-15 share several effects, such as the activation of NK cells, the induction of CD8þ T cell proliferation and the costimulation of B-cell proliferation and differentiation.IL-15 has additional effects, including the induction of T-cell polarization, differentiation of dendritic cells, inhibition of apoptosis of lymphoid cells, and activation of polymorphonuclear leucocytes [64]
	Aringer M, et al., 2001[65]	Serum ELAISA SLE: 65 Healthy control:20 Rheumatoid arthritis: 10	Increased in serum of SLE group(no difference between active and inactive SLE) IL-15 increased in SLE group compare to control, but this increase was not seen in RA.	
IL-16	Lee S et al, 1998[66]	Serum ELAISA SLE:49 Control:49	IL-15 increased in SLE group and there was a correlation between IL-16 level and disease activity indicated by SLEDAI score.	
IL-17	Vincent FB, et al., 2013[67]	Serum ELAISA SLE: 98(57.3% of patients were receiving prednisone) control:	IL-17 increased in SLE group	IL-17 is the prototypic T helper 17 (Th17) cell pro-inflammatory cytokine.
	Zhao XF, et al., 2010[68]	serum ELAISA SLE: 57 Control:30	IL-17 increased in SLE group	

IL-18	Park MC, et al., 2004[69]	Serum ELAISA SLE: 35 Control:35	IL-18 increased in SLE group and these increase levels correlated with SLE disease activity indicated by SLEDAI score.	IL-18 is a member of the IL-1 family and promotes the proliferation and IFN-γ production of Th1, CD8+ cells and natural killer cells
IL-20	Li H et al., 2008[70]	Serum Immunohistochemical staining SLE:25	IL- 20 detected in both mesangial cells and inflammatory cells in kidney biopsies lupus nephritis and it's expression in the inflammatory cells was correlated with the lupus nephritis WHO class	IL-20 is one member of IL-10 family, which includes IL-10, -19, -20, -22, -24, and -26
IL-21	Lan Y, et al., 2014[32]	Serum ELAISA SLE:175 Control: 190	IL-21 increased in SLE group	IL-21 has an important role in B cell responsiveness, proliferation, plasma cell differentiation, and immunoglobulin production
IL-22	Pan HF, et al., 2009[71]		IL-21 decreased in SLE group	
IL-23	Wong CK, et al., 2008[72]	Serum and culture ELAISA or flow cytometry	IL-23 increased in SLE group	
IL-27	Duarte A, et al., 2013[73]	Serum ELAISA SLE: 70 Control: 30	IL-27 decreased in SLE group and there was no association of serum IL-27 levels with disease activity evaluated by SLEDAI score	IL-27 is a member of IL-12 cytokine family and could promote naïve CD4 T cells to differentiate into Th1 cells trough an increase of IFNγ production
IL-33	Yang Z, et al., 2011[74]	Serum ELAISA SLE: 70 Healthy control:40 RA: 28	IL-33 increased in patients with SLE than in healthy controls, but lower than in RA ones	IL-33 is a member of the IL-1 family and exerts both proinflammatory and protective effects

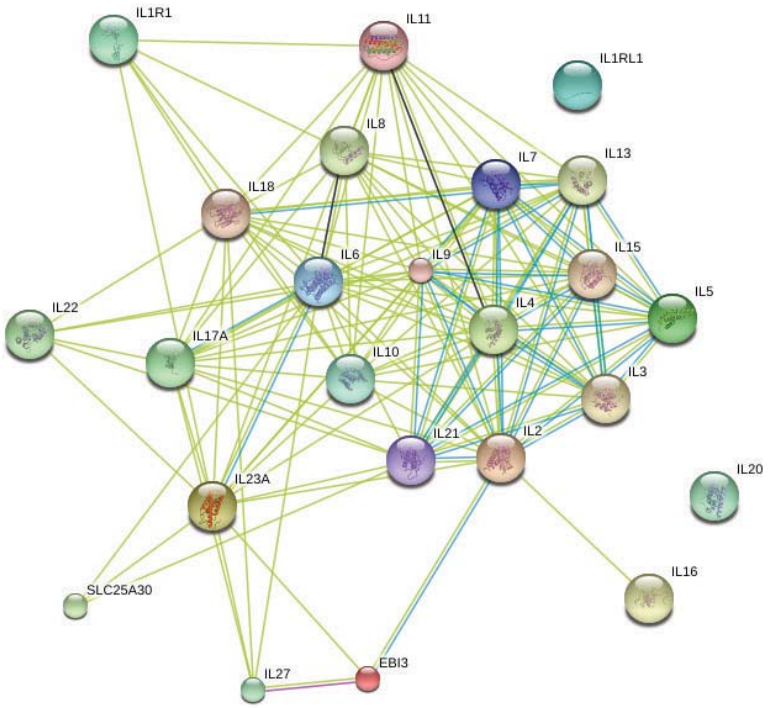

Figure 2. Cytokines in serum of SLE and eight cytokines (IL2, IL4, IL5, IL6,IL8, IL10, IL17, IL18) detected in OLP are circled.

However, with current controversies, much research in humans has suggested that serum levels of IL-10 are noticeably increased in patients with SLE.[76]

We have found no review of IL-10 in OLP, but found controversies in current studies.[35,42] In eight articles on this subject, three indicated an increased level of serum IL-10 and overexpression of its gene, two showed a decrease, and one study found no significant change.

As can be seen in this review, compared to SLE, there is a lack of research into some of the ILs in OLP, and there is no systematic review or meta-analysis on ILs of OLP. So, further investigations may illuminate the unknown aspects of the etiopathogenesis in OLP. For example, according to Table 4, IL21 is significantly increased in SLE. IL21 plays an important role in B cell proliferation, plasma cell differentiation, and immunoglobulin production.[32] Granular or homogeneous bands of immunoglobulin in the basement membrane zone have been verified in mucosa in SLE and DLE but only rarely in lichen planus.[78] An increased level of IL21 may be responsible for these differences in immunoglobulin deposition pattern. Further research into IL21 in OLP may provide new insights.

Current limitations in reviewed articles

1. Cytokines, like many other proteins have racial differences. In one meta-analysis of IL-6 polymorphisms in SLE, it was concluded that the IL-6 -174 G/C polymorphism may confer susceptibility to SLE in Europeans, and that the IL-6-572 G/C polymorphism is not related to susceptibility to SLE in Asians.[79]

Cytokine evaluation according to different populations may lead to more valuable results. Another good example is epidemiological studies which show significant geographical heterogeneity in the frequency of hepatitis C virus (HCV) infection in OLP patients. It suggests that in the pathogenesis of this type of OLP, host factors rather than viral factors play the main part. MHC class II alleles like HLA-DR6 influence the development of this subtype of OLP.[80–82] Assessment of interleukins in HCV-associated oral lichen planus may reveal new details about the role of interleukins.

2. Cytokines are pleiotropic and act in a complex network. The role of each cytokine should be assessed by its correlations and impact on other cytokines. For example, decreased production of IL-12 may be due to the inhibitory effect of increased IL-10 by monocytes in SLE patients.[60,62] On the other hand, the levels of IL-13 in patients with high levels of IL-12 are significantly lower than in patients with normal IL-12 levels.[61]

3. The final effect of cytokines is determined by several factors such as serum level of the cytokine, and the number and accuracy of certain receptors. For example, Hsieh SC and colleagues showed that irregular CXCR2 modulation and diminished cationic ion transporter expression cause a decrease in SLE-PMN responsiveness to IL-8.[17]

On the other hand, when cytokine levels are considered in serum, it is not possible to verify the origin of the cytokines. The serum cytokine levels are determined by several processes, for example production, tissue or cellular deposition, degradation, and elimination of these proteins. Comprehensive studies at the cellular level are therefore needed to explain cytokine levels.[75]

4. Chronic illnesses like autoimmune diseases have an unsteady process. These changes are determined by cytokine profiles and other factors. So, a certain cytokine has a dynamic process due to the stage of the disease. In studies where SLE patients were evaluated in separate groups of active and inactive disease, there were different results for each group. For example, higher levels of membrane-bound IL-15 were expressed in monocytes of active SLE compared with both inactive patients and healthy controls.[64]

5. The levels of interleukins, like other immunologic mediators, are changed by steroids like prednisolone. In many studies which have reviewed serum levels of interleukins in SLE patients, some patients were under steroid therapy, so studies with untreated (fresh) cases of SLE may have different results.

In conclusion, OLP is an autoimmune disease. Despite current knowledge and studies on interleukins such as IL2, IL4, IL5, IL6, IL8, IL10, IL17 and IL18 in OLP, compared to SLE as a prototypic autoimmune disease, there are many cytokines and interleukins which need to be investigated in OLP to reveal its pathogenesis.

Conflicts of Interest: There was no conflict of interest for this study.

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