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Review

Immunological Aspects of EBV and Oral Mucosa Interactions in Oral Lichen Planus

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Abstract: Oral lichen planus (OLP) is considered a T cell-mediated chronic inflammatory process activated by an unknown antigen, making basal keratinocytes vulnerable to a cytotoxic cell mediated immune response. The aim of this review is to summarize information on the role and pathways of Epstein–Barr virus (EBV) and immune cells in inducing OLP as an autoimmune lesion. The pathogenesis of OLP is analyzed from immunological aspects of interactions between EBV and oral mucosa. The results of the available studies allow us to assume that EBV can act both as an exogenous and an endogenous antigen in the pathogenesis of OLP. We emphasized the role of antigen-presenting cells (APC), such as dendritic cells (Langerhans cells, LC), in detecting and capturing antigens and modulating the adaptive immune response. Although EBV shows tropism for B cells and epithelial cells, under certain conditions it can infect monocytes, LCs, NK, and T lymphocytes. It means that under some circumstances of the chronic inflammatory process, EBV particles can react as endogenous agents. During the development of the autoimmune process, a decisive role is played by the loss of immune tolerance. Factors like the activity of cytokines, chemokines, and autoantibodies secreted by EBV-positive plasma cells, autoantigens formed due to virus protein mimicry of human proteins, new self-peptides released from damaged tissues, self-reactive B and T cells, dysregulation of LC function, the anti-apoptotic effect of EBV early lytic antigens, and an imbalance between inflammatory and anti-inflammatory immune cells facilitate the development of an autoimmune process.

Keywords: oral lichen planus; Epstein–Barr virus; chronic inflammation; oral epithelia; dendritic cells; immune cells; autoimmunity

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1. Introduction

Lichen ruber planus (LP) is a chronic, autoimmune, inflammatory mucocutaneus disease that influences the hair, skin, and nails, as well as the genital, oesophageal, laryngeal, conjunctival, and oral mucosa [1,2]. Mostly, it is isolated only in the oral cavity without involving the skin or other mucous membranes [3,4]. According to the literature data, oral lichen planus (OLP) affects 0.2–4% of people [5], occurs more often in individuals between the ages of 30 and 70, and has a female predominance with a ratio of 1.4:1 [6–8]. Some cases of the disease have been described in children, but it is not common [9,10].

The aetiology of OLP is unspecified, but an attempt has been made to identify and summarize the possible etiological factors [11]. Possible provocative factors are mentioned several systemic diseases, like hypertension, with chronic inflammation related to other cardiovascular risk factors: dyslipidemia, metabolic syndrome, thyroid and liver dysfunction, diabetes mellitus, kidney disease, celiac disease, and genetic susceptibility to cancer [12–14]. De Porras-Carrique et al. [15] stated that the current data regarding autoimmune diseases

such as Sjogren's syndrome, lupus erythematosus, and rheumatic conditions, dermatological diseases, fibromyalgia and gastrointestinal disorders do not allow conclude whether these diseases are really associated with OLP. Studies on the pathogenesis of OLP may be significantly influenced by Th17 cells and the IL17A polymorphism [15], but connections between 14 functional gene polymorphisms indicate that susceptibility to OLP might be linked to the TNFR2 +587 gene polymorphism [16]. There are studies on the role of vitamin and mineral (nutritional) deficiencies in the development of OLP, suggesting that the severity of OLP may be related to the presence of abnormally high blood homocysteine levels as well as deficiencies in Hb, iron, folic acid, and vitamin B12 [17]. Studies have shown that vitamin D receptor (VDR) variants could affect susceptibility to OLP, making VDR gene polymorphisms possible candidate susceptibility regions for the condition [18]. Wang et al. [19] clarified through meta-analysis that the profile of oxidative stress and antioxidant state markers in OLP patients has been elucidated, revealing heterogeneity among the studies and underscoring the necessity for additional research on oxidative stress and antioxidant systems in both saliva and blood. In recent years, there have been several studies and review articles analyzing the pathogenesis of OLP from a microbiological standpoint, considering the potential for a microbial etiology of the disease [20–22]. Conflicting studies exist on *H. pylori* involvement: no statistically significant correlation was found between the presence of the bacteria and OLP [23]. On the other hand, another study has shown a significant correlation between H. pylori infection and the pathogenesis of erosive OLP [24]. Many studies demonstrate that the influence of psychological factors (depression, anxiety, and stress) has not lost its relevance in OLP development, as proved by [25–27].

Payera et al. [28] expressed the opinion that various external agents, particularly viruses, as well as internal agents such as stress and heat shock protein (HSP) antigen expression, may contribute to the pathogenesis of the condition, whether associated or not, and can trigger OLP. Over the past 10 years, researchers have re-engaged in studies on the potential involvement of viruses in the pathogenesis of OLP [29–32].

Until now, the hepatitis-C virus (HCV) has been the most studied virus that is connected with the aetiology of OLP. There are a lot of studies devoted to the question of the hepatitis C virus link with LP [33–35]. It is established that in different geographical locations, the influence of environmental and genetic factors is also different. Studies show that the development of the disease is determined not by the direct effect of the virus but by the host's immune system responding to the presence of the virus particles. This means that the pathogenic pathways involved are not entirely clear [36].

Contradictory studies have been conducted on the involvement of the Herpes group viruses (HSV) in the aetiology of OLP. For example, despite the positive HSV-PCR test and elevated HSV IgG level, no link between HSV and OLP was stated [37]. A study of HHV-7 supported the hypothesis mentioned by the authors on the association of this virus with lichen planus pathogenesis [38]. A significant association is found between human papilloma virus (HPV) and OLP, suggesting that there is evidence that HPV could have a significant causal role in both OLP and its malignant progression. Studies have shown that the extent of this correlation may vary depending on factors such as geographic population, clinical types of OLP, and HPV genotypes [39]. Additionally, there appears to be an increased risk of both Epstein–Barr virus (EBV) and HPV infection in individuals with OLP, as indicated by the study of Yildirim et al.'s [40] finding of statistical significance in the number of EBV (n = 23; 35%) and HPV (n = 14; 21%) infection positive cases in OLP, contrary to the number of HSV positive cases (n = 6; 9%). However, Lucchese et al. [31] found that after the review of the 43 chosen articles, direct activity could not be confirmed by EBV, HSV-1, cytomegalovirus (CMV), or HPV regarding the etiopathogenesis of oral lichen planus or its potential malignant transformation.

Nevertheless, relatively more studies have shown interest in the role of EBV in the origin of OLP [32,39,41–44]. It is still unclear what the target antigen is and how this process manifests itself at the molecular level. The purpose of this review is to provide

a summary of information supporting the role and pathways of EBV and other involved cells in inducing OLP as an autoimmune lesion.

2. Materials and Methods

A search was conducted across various online databases (including PubMed, Scopus, Research Gate, Web of Science, Science Direct, and Google Scholar) from their date of inception up until the year 2023. A total of 127 studies were identified that examined the potential correlation between Epstein–Barr virus (EBV) and oral epithelial cells with oral lichen planus. Articles in English were included in the review.

3. Currently Existing Pathogenesis of OLP

The exact pathogenesis of OLP remains unclear, although it is currently understood to be a chronic inflammatory process mediated by T cells. This process is initiated by an antigen or antigens that transform basal keratinocytes, rendering them vulnerable to cytotoxic immune responses from cells [45]. It has been established that OLP involves both innate and adaptive immune mechanisms [46,47]. The trigger factor can be an unknown endogenous or exogenous antigen. The first cells involved in antigen recognition are keratinocytes, which can perceive small molecular elements expressed by microorganisms known as pathogen-associated molecular patterns (PAMPs). Typical PAMPs are bacterial lipopolysaccharides (LPS), endotoxins, and viral-derived nucleic acids, which are identified by pattern-recognition receptors (PRRs) [45,48]. On the keratinocyte surface are located PRRs, to which belong toll-like receptors (TLRs), C-type lectin receptors, cytoplasmatic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and retinoic-acid-inducible gene I (RIG-I)-like receptors [49]. Keratinocytes have the capability to produce various pro-inflammatory cytokines and chemokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α [50], which promote the recruitment of immune cells such as neutrophils and T lymphocytes to the infection site. PRRs are recognized as endogenous factors, which are substances that are released due to damage to cells or tissues and are named danger-associated molecular patterns (DAMPs) [51]. TLRs are also expressed on the membranes of leucocytes, macrophages, dendritic cells, natural killer cells, T cells, and B cells and located on intracellular vesicles. In the literature review of Osorio-Osorno et al. [47], the authors focused on the interrelationship between toll-like receptors (TLRs) and OLP, with a focus on the molecular behavior of oral keratinocytes following the activation of TLR signals. Therefore, it can be assumed that if a foreign protein molecule acts as an antigen by reaching the physical barrier of the oral mucosa and coming into contact with oral keratinocytes, it will be recognized by TLRs and the immune cells will become activated. In the pathogenesis of OLP, both antigen-specific and non-specific mechanisms may be involved [52,53]. In the case of an antigen-specific mechanism, an antigen-peptide-loaded MHC I complex, located on basal keratinocytes, activates antigen-specific cytotoxic CD8+ T cells (CTL) with the following apoptosis of antigen-specific keratinocytes. This process is accompanied by the release by activated CD8+ T cells of cytokines such as granzymes, perforins, tumor necrosis factor alpha (TNF-a), Fas ligand (FAS-L), INF-gamma, IL-1, and IL-17 from other cells. This all promotes further inflammation [52,53]. The secretion of several pro-inflammatory cytokines activates epithelial Langerhans cells (LCs), also known as antigen-presenting cells (APCs), and the TLRs-dependent activation is required to induce dendritic cell maturation and migration to regional lymph nodes and naive T cell activation [54].

From APCs or an active T helper cell, requires co-stimulation on CD4+ T and CD8+ T cells located T cell receptor (TCR) complex activation. The TCR recognizes the antigen and the relevant antigen-presenting MHC complex [55]. The specific adaptive immune response is controlled by the T follicular helper (Tfh), cytotoxic T lymphocytes (CTLs), T cell subtypes Th1, Th2, T17, and regulatory T cell (Treg), which are distinguished by the types of cytokines they secrete [56]. According to Jin et al. [56], TLRs are also involved in T cell development and give a signal to reprogram Treg cells into helper cells [56]. T cell

subtypes Th1 and Th2 participate in the CD8+ T lymphocytes activation, thus helping the apoptosis of the keratinocytes [57].

Since all these processes activate TLRs, then through DAMPs or PAMPs, other keratinocytes may also be affected [58]. The inflammatory infiltrate consists mainly of cytotoxic CD+ T cells and is maintained by the released chemokines, which promote and sustain monocytes and polymorphonuclear cells attraction to the *lamina propria* and subsequent maintenance of inflammation [8]. It is noted that Th17 cells also play a pivotal role in the immune system, working on adaptative and innate responses [59].

All these mentioned processes are accompanied by mast cell degradation and matrix metalloproteinase (MMP) stimulation, the main reactions in the non-specific mechanisms in OLP pathogenesis [53]. CD4+ T lymphocytes clonally expand and maintain a pro-inflammatory state by releasing cytokines such as INF-γ and IL-2, leading to the activation and degranulation of mast cells. The number of mast cells in OLP is significantly increased, and the following degranulation releases TNF α, which upregulates endothelial cell adhesion molecule expression for lymphocyte adhesion and extravasation [60].

The major product of mast cells is chymases, which, through direct or indirect activation of T cells, secrete and activate matrix metalloproteinases 9 (MMP-9) and damage the epithelial basement membrane [8,53,60]. The chronic nature of the process creates and promotes further accumulation of T cells in the superficial *lamina propria*, the arrival of immune cells in the epithelia, and the apoptosis of keratinocytes [52,53]. The degradation of basement membrane structural proteins by mast-cell-derived chymase and tryptase is a crucial step in the pathogenesis of OLP. This enzymatic breakdown can cause disruptions in the epithelial basement membrane, leading to the infiltration of cytotoxic CD8+ T lymphocytes into the epithelial layer through breaks in type IV collagen created by tryptase [61].

4. Characteristics of Langerhans Cells

Other cells in the epithelium that are also involved in antigen presentation are Langerhans cells, which belong to dendritic cells (DCs). The oral mucosa contains a rather complicated immune system to ensure and maintain immunological homeostasis. Dendritic cells, being divided into conventional DCs (cDCs) and plasmacytoid DCs (pDCs), play the most important roles in the initiation of immunity and the maintenance of tolerance [62]. The oral cavity is composed of various mucosal surfaces, each exhibiting a distinct distribution of dendritic cell (DC) subsets, indicating that in addition to tissue-specific properties, the local distribution of DCs provides different outcomes for the immune system, with subsequent translation into a general immune response in the lymph nodes. DCs play a crucial role in inducing accurate and efficient pathogen-specific immunity by adapting their immune response to the type of pathogen [63].

According to Hovav [64], the murine mucosal epithelia model demonstrates that LCs arise and are continuously renewed from circulating pre-dendritic cells and monocytes arising in bone marrow. This indicates the plasticity of LC differentiation, but the differentiation of mouth mucosal LCs is regulated by epithelial differentiation signals. Several studies have identified that oral mucosal LCs are composed of three distinct subsets, including CD103+LC1, CD11b+LC2, and moLC [65].

Previously conducted studies report that the average number of LCs in stratified squamous epithelium is 160–550 cells/mm^2; in non-keratinized epithelia of the oral mucosa, it is 508 $\pm$ 110 cells/mm^2, but the lowest density is in the keratinized mucosa of the hard palate [66]. In buccal mucosa, LCs are found predominantly in suprabasal layers, through the length of the epithelium, but with the tendency to form clusters at the top of the connective tissue papillae [67]. LCs were found to be located in the basal and suprabasal layers of the oral mucosa, arranged linearly along the length of the epithelium. In the lateral border of the tongue and floor of the mouth, LCs were located on the basal and suprabasal layers, while in the hard palate, they were predominantly found in the stratum spinosum and basal layer [68]. Studies from later years confirm that the highest numbers include the vestibulum, buccal mucosa, hard and soft palate, and tongue, while smaller numbers have

been observed in the sublingual area and gingiva. With the aid of E-cadherin, Langerhans cells and the surrounding keratinocytes, form a tight network with one another, which is indispensable to maintain LCs in the epidermis but does not regulate LC maturation, migration, or function [69,70].

The dendritic outgrowths of LCs are directed toward the epithelial surface, providing an effective function by capturing invading external pathogens—bacteria or virus-derived peptides—acting as an antigen or allergen [69,71]. This control and sample collection from the surrounding environment are provided by already mentioned PRRs like C-type lectin receptors (CLR) and TLRs [72]. The cDC contains TLR2 and TLR4 receptors and expresses interleukin 6 (IL-6), interleukin 12 (IL-12), TNF, and chemokines [73].

Another essential role in extracellular antigen presentation and initiating immune responses is played by major histocompatibility complex II (MHC II) molecules, located on dendritic cells as well as on B cells, mononuclear phagocytes, some endothelial cells, and thymic epithelial cells [74]. In this process, immature dendritic cells phagocytose the pathogen, degrade their proteins into small fragments in a lysosome, and then, upon maturation, display the small pieces as MHC II molecules. The MHC II molecule moves to the surface of APCs to deliver the antigen to T helper cells. The process is accompanied by the release of cytokines. After TLR's recognition of an invading pathogen, it results in activating antigen-presenting cells (APCs) and/or providing co-stimulatory signals to T cells, resulting in the induction of both innate and adaptive immune responses [56]. The immature Langerhans cells become activated and, carrying a specific quantity of peptide-MHC complexes, accompanied by cytokines and costimulatory molecules, move to the lymph nodes, where they interrelate with T and B cells to activate the adaptive immune response [73]. Scientific studies have found that the oral environment is known to create conditions that enhance the T cell co-stimulation capacity of oral LCs compared to their skin counterparts [75].

5. Role of Langerhans Cells in Oral Lichen Planus Pathogenesis

An increase and higher concentration of LCs, as stated in OLP, are associated with the severity of the inflammatory response compared with healthy subjects [76]. This indicates the LCs in OLP play a pivotal role in antigen identification and subsequent presentation to T lymphocytes [77]. The study by Kulkarni et al. [77] by assessing expression of Langerhans cell membrane protein CD1a found that in normal mucosal epithelium, LCs formed an intraepithelial webwork for better synchronization of antigen capture, but in OLP, LCs are the main immunoregulators in the oral epithelium. The authors believe that LC plays a crucial role through the activation of naïve T cells and the initiation of a secondary immune response via antigen-specific T cell clones. This statement about LC's role in the attraction of CD4+ and CD8+ cells in the subepithelial region and in the apoptosis of keratinocytes was also confirmed by the recent studies of Kumar et al. [78]. Moreover, the authors found that in the case of OLP, the number of dendritic processes in CD1a-positive LCs also increased, which is probably caused by the increasing amount of antigens and cytokines secreted by keratinocytes [78]. Immunohistochemically CD1a-positive LCs were stated in the upper spinous layer with a mild distribution, intense and moderate in the mid-spinous layers, and moderate as well as mild in the suprabasal layers of OLP. When another marker, the cell membrane receptor Langerin (CD207), was applied to determine the density of LC cells intraepithelially in OLP, a significant increase in the density of CD207+ cells in the oral epithelium was found. In addition, it was found in a significant density already in the case of reticular oral lichen planus, which is clinically characterized by fewer subjective symptoms compared to erosive oral lichen planus [79]. This increase in LC in OLP was observed not only intraepithelially but also in *lamina propria* and is associated with enhanced recruitment of dendritic cell precursors [80].

OLP pathogenesis primarily involves a cell-mediated type of immunological reaction, as was already found by the study of Sloberg et al. [81]. In their study, the authors stated that compared to healthy oral mucosa, in OLP, Langerhans cells express large amounts of

immune-associated (Ia) responses like antigen, a membrane protein and product of the MHC. It is also expressed by subepithelial T cells.

Both cDCs and pDCs are also observed in OLP and are found adjacent to mature DCs [82]. LCs role in OLP pathogenesis confirms studies of OLP biopsies, finding out that in the submucosa, together with lymphocytes, mature LC and DC accumulate [76,83], and that there is a quantitative increase of immature LCs in antigen perception and demonstrating to T cells, as well as ongoing interactions with T lymphocytes in the subepithelial area [77]. When evaluating the amount of Langerin expression by all APCs in OLP and normal oral mucosa, a significantly higher number of MHCII+ APCs were found in OLP, both in the epithelium and in the lamina propria, compared to the normal oral mucosa [80]. Recent studies show that the immune system regulatory function of LCs is also manifested in the activation and propagation of regulatory T cells (Tregs) [80]. LCs, as a specialized subset of APC both in the skin and in the oral mucosa, are one of the main players in detecting and capturing antigens on the body's barrier surfaces and initiating an immune response. LCs can migrate to lymph nodes and interact with T cells, thereby modulating the adaptive immune response. Upadhyay et al. [67] demonstrated that LCs can also take up epithelial antigens from apoptotic cells. Chandavatkar et al. [84] give a comprehensive overview of current understanding of Langerhans cells, including their historical point of view, origin, structure, function, and phenotypic expression. The authors analyze the role of LCs in different oral mucosal lesions and give their immunological characteristics based on current knowledge. It is concluded that LCs act as immune mediator cells and vectors of infected and phagocytic cells.

Comparing the presence of Langerhans cells (LCs; CD1a), T cells (CD3), and B cells (CD20) in inflammatory processes in the cases of OLP and oral leukoplakia (OL), a noticeably elevated number of CD3+ and CD20+ cells in the submucosa of OLP compared to OL ($p < 0.01$) was stated. In the epithelium of OLP, the number of $CD3^+$ cells was noticeably higher than in OL ($p < 0.05$). In OLP, there was evidence of immune activation involving both T cells and B cells [85].

6. Characterization of EBV and Its Potential Action as Exogenous and Endogenous Antigens in the Pathogenesis of OLP

Epstein–Barr virus (EBV), also known as Human herpesvirus 4 (HHV-4), is a member of the Herpesviridae family and the subfamily Gammaherpesvirinae, genus Lymphocryptovirus. EBV is a widely distributed double-stranded DNS virus [86]. Primary infection is asymptomatic or mildly symptomatic and usually happens in childhood [87]. It can cause infectious mononucleosis, oral hairy leukoplakia, and various non-epithelial and epithelial tumors, among which the most known are Burkitt's lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and gastric cancer in adults and adolescents [88,89]. EBV primary infects B cells and epithelial cells, but under certain conditions, it can also affect monocytes, Langerhans cells, NK and T lymphocytes, and smooth muscle cells and induce oncogenesis in all these cell types [90,91]. There are two genotypes of EBV: EBV is classified into two types, EBV-1 and EBV-2, which differ in their DNA sequences of several genes and their oncogenic potential [92]. Between individuals, EBV is transmitted by saliva, and before infecting B lymphocytes, the virus must first cross the tonsillar epithelium [87]. There is a possible variant when the virus infects only the epithelium [93]. The prevalence of latent EBV infection among adults worldwide is more than 90%, and after primary infection, the virus persists throughout life in memory B lymphocytes [89]. B lymphocytes and oral squamous epithelial cells are the typical sites where EBV can replicate. Reactivation of the latent phase of EBV can lead to productive infection, resulting in the release of infectious EBV particles in saliva [89]. Studies have shown that stratified epithelia can be infected only from the apical surface and not from the basal surface. They are not found in the lower basal and parabasal layers. It is stated that the basal epithelial cells consistently proved resistant to infection [94,95]. To infect oral epithelim, the fusion of the EBV envelope with the cell membrane and transport of the virus into the cell are required, which are

ensured by cell surface receptors, integrins, and mediating cell-extracellular matrix and cell-cell adhesion. It is provided by the direct interaction of EBV glycoproteins gH/gL with integrins αv-6 and αv-8 on epithelial cells [96] and the transmembrane glycoprotein BMRF2 interaction with integrins 1 and α5 [94]. In addition, Xiao et al. [94] showed that BMRF2 is being transported to the basolateral membranes of polarized oral epithelial cells, localized by β1 integrin. Such abundant BMRF-2 accumulation was observed in the epthelium of patients with oral hairy leukoplakia (OHL). It was also stated that epithelial αvβ6 integrin of oral mucosa plays an important role as a mediator of stem cell quiescence and immune surveillance through activation of TGF-β [97]. The virus released by stratified epithelium is highly infectious to B cells but not to epithelial tissue. To infect B lymphocytes, the EBV glycoprotein complex gH/gL/gp42 is required, as is the binding of glycoproteins gp350/220 to the cell surface receptor CR2-type 2 complement receptor (CD21) [19,98]. This mechanism ensures EBV's continuous movement between B lymphocytes and epithelial cells, thus maintaining the persistence of the infection process. In a series of studies by Xiao et al., it was shown that interaction between EBV BMRF-2 and integrins is decisive for EBV infection in oral epithelial cells [94]. BMRF-2 is a ligand for β1, α5, α3, and αv integrins and demonstrates the role of BMRF 2 in the lytic stage of infection, but the absence of BMRF-2 results in an approximately 50% reduction in EBV attachment to oral epithelial cells [99]. It is suggested that BMRF-2 may also play a crucial role in facilitating the spread of EBV progeny virions through the oral epithelial lateral membranes to other cells [100].

EBV has two life cycles, consisting of a latent cycle, a condition with persistent infection without productive viral replication, and a lytic cycle, a state in which new virions are produced [92]. EBV multiplies in oropharyngeal epithelial cells and establishes latency III, II, and I infections in B lymphocytes in primary infection, which is required for viral persistence, subsequent replication in epithelial cells, and the shedding of infectious virus in saliva. Latency II is possible only in epithelial cells, and latency II infection of oral epithelial cells and NK or T cells can lead to malignancies characterized by EBV genome presence and gene expression [101]. During EBV latent infection, three EBV-encoded latent proteins (LMP 1–3) and six EBV core antigens (EBNA 1–6) are expressed. B cell immortalization and cell cycle progression depend on EBNA-LP, EBNA2, and EBNA3C [88]. These latent proteins can also pathologically affect various molecular processes and pathways of the cell, thus playing a role in the pathogenesis of EBV-related cancers [102]. The process in the lytic cycle can be divided into three temporal and functional stages: immediate, early, and late [92]. Rta (encoded by BRLF1) and Zta (encoded by BZLF1) are viral transcription factors that mediate the transition from latent EBV infection to lytic viral replication. The viral transcription factors Rta (encoded by BRLF1) mediate the switching from latent EBV infection to lytic viral replication (encoded by BRLF1) and Zta (encoded by BZLF1). Rta is the main transactivator in epithelial cells, and Zta supports DNA replication and co-activates a subset of early promoters along with Rta. Both Rta and Zta are immediate early transcription factors that activate EBV-lytic gene expression. The products of the early genes are mainly involved in viral DNA replication, while the products of the late genes mainly support the formation of viral particles [103]. The lytic cycle of EBV is triggered when EBV-infected memory B cells differentiate into plasma cells, simultaneously stimulating productive EBV replication by releasing large amounts of EBV fragments that directly infect epithelial cells of the oropharynx. The new virions further multiply and spread to other cells [104]. In oral saliva are found exosomes and microvesicles secreted by oral and tonsillar epithelial cells that promote intercellular communication. An examination of cultured oral epithelial cells reveals that the epithelium-specific miR-200 family of microRNAs releases a specific signal that initiates EBV lytic replication [105]. It should be noted that latent infection is recognized as the most important mode of infection in EBV-related cancers, and limited expression of a specific group of latent genes contributes to the disorder's development. In recent years, studies have shown that the EBV lytic phase may play a substantial role in EBV lytic gene expression, and its involvement in EBV tumorigenesis is often disclosed in tumor tissues and cell lines [106].

One of the EBV manifestations on the tongue, known as oral hairy leukoplakia, is clinically well diagnosed in immunosuppressed patients. In this case, EBV lytically infects normal differentiated oral epithelial cells of the *stratum spinosum* and the *stratum granulosum*. The desquamating cells containing infectious virions shed into saliva [107,108]. EBV replication in the oral epithelium is determined by the factors that will lead to OHL, which include the correlation of the local immune response, local environmental factors, and the EBV gene expression profile [108]. In HIV-seronegative immunocompetent patients, productive EBV replication in the epithelial cells of the tongue does not often take place [109]. Multiple strains of EBV, as inter- and intrastrain reincorporations, have been found in cells of oral hairy leukoplakia lesions [92]. In situ hybridization studies demonstrated abundant mRNA expression of the BMRF-2 gene in OHL in the more differentiated cell layers of the *stratum spinosum* [110]. A crucial role in mediating the reactivation of lytic in OHL-differentiated epithelial cells also plays transcription factor Krüppel-like factor 4 (KLF4) and suppressor of transcription B lymphocyte-induced maturation protein 1 (BLIMP1) [107].

According to Tonoyan et al. [30], there are multiple factors that suggest EBV's potential involvement in the pathogenesis of OLP: the high prevalence of EBV infection worldwide; the fact that it is diagnosed in saliva and oral epithelial cells; and the fact that it is often found in inflammatory lesions of the oral cavity, including autoimmune lesions. EBV is considered to have oncogenic properties and has been associated with the development of malignancies in epithelial cells, which may also play a role in the pathogenesis of OLP. CD8+ cytotoxic T cells induce apoptosis in virus-infected cells. During the lytic cycle, there is active replication of EBV in OLP, which is clinically associated with an acute exacerbation of the disease. Raybaud et al. [42] found in their study, that the number of EBV+ infected cells correlated with the severity of OLP disease. The degree of EBV infection in OLP can vary, and as the condition advances, for example, in the erosive form, the number of EBV+ positive cells increases significantly. In contrast, in the case of the reticular form of OLP, some cells were uninfected or showed only moderate levels of EBV infection.

However, there are several other aspects that should be considered when evaluating the potential involvement of EBV in the pathogenesis of OLP. It is related to the changes in the oral microenvironment with age, which are influenced by hormonal levels and the aging of oral cavity structures and epithelium constituent cells [111]. The average age of OLP development is around 56 years [112], when a decrease in mitotic activity can already begin, epithelial cells remain larger and wider, cell density and number of layers decrease, and tissue elasticity changes [113,114]. A study by Thomasini RL et al. (2017) [115] demonstrated that EBV reactivation, based on the presence of virus-positive antibodies IgG+ in the blood plasma, was higher (30%) in elderly women (age 60–80) compared to young women (age 18–30), making up 15% This means that age is correlated with the frequency of EBV reactivation but not the viral load, possibly indicating an inability of CD8+ T cells to control the infection [115]. EBV reactivation can also be provoked by cellular and psychological stressors, a detailed overview of which is given by Sausen DG et al. (2021) [116].

7. Role of LCs in EBV Infection

The currently existing publications demonstrate that dendritic cells, including LCs, are activators and regulators of the immune response and play a vital role in the progression of various oral pathologies. LCs, as APCs are one of the first cells to receive antigens, thus also a viruses. In the case of the herpes simplex virus, there is evidence of incomplete maturation in dendritic cells after infection. Further DC maturation, IL-12 secretion, and induction of primary and secondary T cell responses are faulty by hypo-polysaccharides (LPS). As a result, cell apoptosis is asynchronous and delayed. However, it turns out that cells adjacent to functionally altered DCs can take over their function by cross-presentation of HSV antigens [117]. Previous studies also revealed the so-called EBV transition model, where EBV are capable of latently infecting blood-borne mononuclear cells, precursors of LCs, during their migration from the blood to the epithelium, where they differentiate into oral Langerhans cells [118]. A broader study of HSV, varicella zoster virus (VZV),

and HIV revealed that these viruses interact with LCs at the very early stages of infection. However, the effects of infection can be different, determined by the nature of the respective virus and the pathways of pathogenesis. For instance, in the situation of HIV, capture of HIV by LCs is followed by degradation of these cells. Another possibility is that under specific circumstances, de novo infection may be observed, as HIV has the ability to use LCs to transmit to CD4 lymphocytes located in the submucosa, leading to subsequent dissemination. Another study previously confirmed that, for example, in cases of HIV-associated oral hairy leukoplakia, a reduction in the LC cell count occurs, resulting in the suppression of EBV-specific cytotoxic CD8+ T lymphocyte responses [119]. As mentioned above in connection with HSV, VZV also causes DC maturation disorders and possible apoptosis. However, it is recognized that once DCs are infected, they can present both HIV and VZV as antigens to CD4+ Tly and CD8+ Tly and induce an immunological response [69]. Based on the above opinion and knowing that EBV latently infects immediate precursors of LCs and then both productively and latently infects resident LCs in the oral epithelium, we could explain the mode of action of EBV as an endogenous antigen.

One of the immunodominant epitopes of EBV nuclear antigen 1(EBNA1) is the peptide sequence GLCTLVAML, which can bind to MHC class I molecules and be presented on the cell surface to cytotoxic T lymphocytes (CTLs).

8. Possible Autoimmune Pathway in Oral Lichen Planus

At present, the autoimmune pathogenic process leading to the formation of OLP at the molecular level is still poorly understood, and the target antigen(s) are unknown. However, the current results of the available studies allow us to assume that under certain conditions, EBV particles, the specificity of cell infection mechanisms, reproduction, and metabolic products can create conditions for the initiation of an autoimmune process. Schifter [120] believes that the processes involved in the aetiopathology of OLP are synergistically multifactorial, involving the following processes: (1) antigen-specific cellular immune response; (2) the nature of the humoral immune reaction; (3) non-specific immune mechanisms; (4) the production of autoantibodies targeting self-antigens, leading to the promotion of autoimmune responses; (5) loss of tolerance; and (6) genetic factors. If the immune tolerance is damaged and the elimination of B and T lymphocytes with potential self-peptide reactivity no longer takes place, then the self-reactive lymphocytes react pathologically to autoantigens. The forming autoantibodies play a crucial role in the pathogenesis of several diseases and mediate the subsequent systemic inflammation and tissue damage [121]. Through the presentation of self-antigens to T cells, resulting in the production of proinflammatory cytokines and/or autoantibodies, B cells could be directly or indirectly engaged in the pathophysiology of autoimmunity [122]. Additionally, altered functions of dendritic cells play a significant role in the pathogenesis of various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and idiopathic inflammatory myopathy. It is indicated by alterations in tissue DC populations, damaged removal of apoptotic cells, disbalance of certain cytokine production, and deformed movement of DCs from the sites of inflammation. DC subsets differentially affect autoimmune disorders and excel with heterogeneity and remarkable functional diversity in different pathologies [123]. It is found that LCs play a relevant role in the activation of the immune reaction hostile to foreign antigens while at the same time determining tolerance against self-antigens. The LCs membrane protein CD1a is capable of presenting diverse types of self and microbial lipid antigens to T lymphocytes. Lukose et al. [124,125] believe that LCs are the main factor involved in the autoimmune pathogenesis of OLP due to dysregulated LC function, which is the initial event of pathogenesis. According to the authors, the initiation and persistence of disease are determined by two processes: continual stimulation of autoreactive T cells and redirecting the inflammatory cytokine profile towards a Th1-type immune response. The two CD4+ T cell subpopulations, Th17, secreting pro-inflammatory cytokines, and regulatory T cells (Treg), also called “suppressor” T cells, provide the critical tolerance mechanism by which immune cells are able to distinguish invading cells from “self”.

Transforming growth factor beta 1 (TGF-β1), a multifunctional cytokine, contributes to the development of oral tolerance and mucosal immunity by inducing these cells. Studies in vitro revealed that neutralization of TGF-β1 inhibits the differentiation of helper T cells into Th17 cells. This suggests that the imbalance of inflammatory and anti-inflammatory immune cells can be an important link to autoimmunity [126]. Studies on animal models revealed that deficiencies in TGF-β1 can impact various immunological pathways and lead to the development of autoimmune diseases: (1) increased MHC I and II expression and activation on APCs; (2) elevated IL-2, IL-4, IL-10, and IFN gamma levels; (3) high levels of IgM, IgE, IgG, and low levels of IgA; (4) impaired Tregs; (5) increased apoptosis of T cells and inflammatory response; and (6) increased expression of ICAM-1 on affected tissue and LFA-1 on T cells [127].

The interplay of various mediators, genetic factors, environmental triggers, and immune dysregulation contributes to the development of autoimmune diseases. The specific mediators involved can vary depending on the particular autoimmune disease. IL-1 is produced by various cells, including macrophages and monocytes. IL-1 can promote the activation of immune cells and the production of other pro-inflammatory mediators. Interleukin-23 (IL-23): IL-23 is a cytokine that is closely associated with the pathogenesis of autoimmune diseases mediated by Th17 cells. B lymphocyte stimulator (BLyS/BAFF): BLyS is a cytokine that regulates the survival and activation of B cells, which are involved in antibody production. Interleukin-10 (IL-10): while IL-10 is generally considered an anti-inflammatory cytokine, dysregulation of IL-10 production or signaling can contribute to the development of autoimmune diseases.

Several viral epitopes are structurally similar to a human protein (molecular mimicry), so enhanced antibody production against viral proteins can cause a cross-reaction with self-peptide, resulting in autoimmunity. Autoantigen-reactive T and B cells can also be activated through the recognition of new self-epitopes that are released from damaged tissues, a phenomenon known as epitope spreading [128]. Smatti et al. [129] believe that viral infections (specifically EBV) are major triggers of autoimmunity via multidirectional processes: (1) epitope spreading; (2) bystander activation; (3) immortalization of infected B cells; and/or (4) molecular mimicry. Since plasma cells are important in maintaining inflammation, the discovery that the increased accumulation of EBV+ plasma cells in OLP tissues and the autoantibodies released by them can contribute to the development of the autoimmune process [42]. EBV can infect different types of cells, but basically it translocates between epithelial and B cells, establishing and maintaining a chronic and recurrent state. Therefore, autoimmune diseases related to EBV infection of epithelial cells, such as systemic lupus erythematosus (SLE) and Sjögren's syndrome, and in the case of B cell infection, rheumatoid arthritis (RA) and multiple sclerosis, are currently more studied [130]. This is revealed by Smati et al. [129] in their review by collecting data on the probable association and cellular pathways of viruses that could cause autoimmunity. It is stated that in the case of SLE, high EBV load, increased EBV mRNA expression, and high titres of anti-early antigen (Ea) IgG and IgA are found in the blood, but in the case of RA and Sjögren's syndrome—frequent virus reactivation—one can detect an increase in EBV viral load, elevated levels of EBV antibodies, and an impaired cell-mediated immune response against EBV. Early lytic antigen (Ea) complexes that diffuse (Ea-D) detectable both in the cytoplasm and nucleus, and are restricted (Ea-R), detectable only in the cytoplasm, have multiple functions. They are responsible for replication, metabolism, and blocking antigen processing [92]. Therefore, for example, Adtani and Malathi [131] believe that EBV screening and detection are mandatory in patients diagnosed with OLP and RA and that antiviral drugs should be included in addition to conventional treatment methods.

Two early lytic antigen products are BHRF1 and BALF1, which are functionally homologous to Bcl-2. BHRF1 is known to have high anti-apoptotic activity. Less is known about BALF1, whether it has more pro- or anti-apoptotic activity. It may suggest that anti-apoptotic action can also result in a breakdown of immune tolerance and a possible initiation of the autoimmune process [132]. Zhang [124] suggests a two-step process

when evaluating the action of EBV in the formation of an autoimmune reaction. In some cases, EBV can serve as an initiator, causing permanent changes to genetic material and thereby increasing autoimmune risks, but mostly, EBV acts as a promoter by forming cells susceptible to autoimmunity. Expression of viral or self-antigens and facilitation of the development of autoreactive B and T cells as well as proliferation are facilitated due to the high expression of human leukocyte antigens (HLA) on type III latency cells and APCs function [133]. The process is reinforced by III-latency cell-mediated cytokine production. However, Zhang [124] notes that it is obvious that the onset of a particular autoimmune disorder is not determined by one unified EBV action model. Figure 1 demonstrates the hypothetical pathway of EBV infection in the pathogenesis of OLP:

1. After primary infection, infected B cells migrate through the bloodstream to the regional lymph nodes, where they stimulate the activation of CD8+ and CD4+ cells. As a result of the activation of CD4+ cells, B cells become active, which in turn become plasma cells. The lytic cycle is switched on by releasing a large number of EBV particles, which are able to directly infect oral epithelial cells. The spread of the newly produced virions to other cells and intercellular communication are probably provided by exosomes and microvesicles present in tissues and saliva;
2. Under certain conditions of the oral microenvironment and simultaneously with virus reactivation, the virus or virus-derived peptides present in saliva can be detected with the help of toll-like receptors (TLRs) and major histocompatibility complex I (MHC I) located on parakeratinized epithelium. If *str. spinosum* superficial cell layers become infected, then the information, possibly also with the help of exosomes and microvesicles, is transferred to LCs belonging to antigen-presenting cells (APCs) and containing TLRs as well as major histocompatibility complex II (MHC II);
3. Activation of TLRs causes LC maturation and migration to the regional lymph node, with subsequent interaction with T and B cells and the release of antigen-specific T cell clones. The release of cytokines and chemokines under the epithelial basal membrane begins;
4. If the basal keratinocyte becomes infected, the viral epitope peptide binds to the extracellular portion of the MHC class I molecule, presented to antigen-specific cytotoxic CD8+ T cells, with the following apoptosis of the antigen-specific keratinocyte. This process is accompanied by the abundant release of cytokines and chemokines;
5. The proinflammatory status activates and then degrades mast cells. Chymase, the product of mast cells, damages the epithelial basement membrane through direct or indirect activation of T cells secreting and activating matrix metalloproteinases 9. This opens the way for CD8+ T lymphocytes to enter the epithelium. LCs can perceive epithelial antigens from apoptotic cells;
6. EBV is able to latently infect LC precursors in the circulation during their migration from the blood to the epithelium, where they differentiate into oral LCs. Infected LCs can present antigen to CD4+ T ly and CD8+ T ly and trigger an immunological response. Functionally altered LC functions can take over neighboring cells through the cross presentation of antigen;
7. Intensely damaged tissue can produce self-antigens that are recognized by LCs while activating autoreactive T cells. Enhanced development and formation of autoreactive B and T cells deepen tissue destruction, promoting the formation of autoimmune processes.

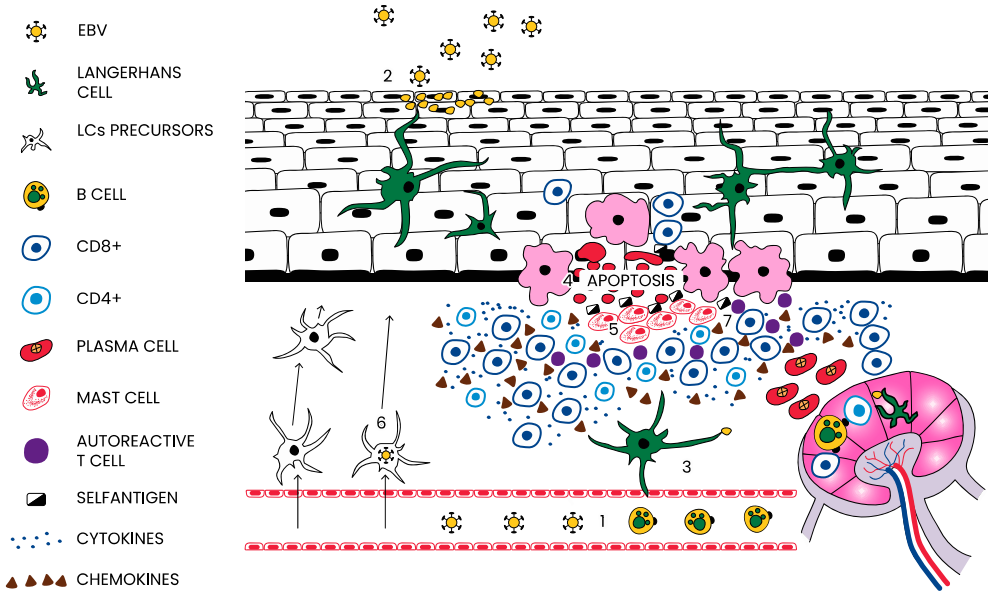

Figure 1. A possible hypothetical pathway of EBV infection in the pathogenesis of OLP (scheme in the case of non-keratinized buccal epithelium).

9. Conclusions

OLP is a chronic inflammatory disease with an unknown aetiology; however, there is some information on the involvement of EBV and other human herpesviruses in the aetiology of OLP. Despite the fact that there are quite a lot of articles in the scientific literature on the etiological factors of OLP, their relation to other systemic diseases, diagnostic options, clinical description, and treatment, the main limitation of this review is the inclusion of a small number of published articles on EBV as a possible etiological factor in the OLP pathogenesis because there are simply very few such articles. Therefore, the objective of this article was to find out the possible involvement of EBV as an antigen from immunological aspects and oral mucosa interactions in OLP. In this review, we tried to emphasize the main role of LCs as a specialized subset of APC in detecting and capturing exogenous and endogenous antigens and initiating an immune response in the case of OLP. When LCs migrate to lymph nodes, they interact with T cells, thereby modulating the adaptive immune response. For more effective antigen capture and process regulation, not only LC dendritic density increases but also density in the intraepithelial and lamina propria, by recruiting dendritic cell precursors. Such an active process indicates the presence of a possibly increased amount of antigen and an increased number of cytokines secreted by the involved cells. It is possible that the involvement of EBV in the pathogenesis of OLP encompasses its dual role as both an exogenous and endogenous antigen, affecting various cell types and immune mechanisms. Although EBV shows tropism for B cells and epithelial cells, under certain conditions it can infect monocytes, LCs, NK, and T lymphocytes. This means that autoantibodies secreted by EBV+ plasma cells; autoantigens are formed as a result of virus protein mimicry of human proteins; new self-peptides are released from damaged tissues; self-reactive B and T cells; dysregulation of LC function occurs; and the anti-apoptotic effect of EBV early lytic antigen. All of this facilitates the development of an autoimmune process. All this is encouraged and reinforced by the activity of cytokines and chemokines, as well as the imbalance between inflammatory and anti-inflammatory immune cells.

However, the performed literature review indicates that it would be desirable to perform a more comprehensive literature review where the role of EBV in the pathogenesis of OLP is analyzed from more various aspects: oral microenvironment, clinical, morphological, and molecular aspects, to the description of the involved cells and their functional activity. In addition, the role of EBV should be studied and evaluated in the context of

other human herpesviruses, which may also play a significant role in the development of OLP and other oral pathologies.

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