

Review Article

A Review of T and B Cell Responses Against Epstein–Barr Virus in the Pathogenesis of Primary Sclerosing Cholangitis

Carlos Y. Chui^{1*}

1. Latin American Cooperative Oncology Group (LACOG), Oncoclínicas, Porto Alegre, Brazil

* Correspondence: carloschui2021@gmail.com

Abstract: Primary sclerosing cholangitis (PSC) is an incurable, progressive inflammatory disease of the bile ducts for which the etiology remains poorly understood. Recent advances in molecular immunology and large-scale epidemiological data have provided compelling evidence linking the Epstein–Barr virus (EBV) to the pathogenesis of PSC. This review synthesized these findings, focusing on the adaptive immune responses mediated by T and B cells. A robust epidemiological association demonstrates that a symptomatic primary EBV infection, specifically infectious mononucleosis, is associated with a 12-fold increased risk of developing PSC. Immunological profiling of patients reveals a unique, convergent T and B cell response targeting EBV proteins, particularly those expressed during the lytic, or reactivated, phase of the virus. These EBV-specific T-cell responses are restricted by specific human leukocyte antigen (HLA) susceptibility alleles, which are also known to increase PSC risk, suggesting a precise genetic and environmental interaction. Furthermore, a higher burden of anti-EBV antibodies is found in PSC patients, with EBV-specific B cells isolated directly from the diseased livers. This collective evidence supports a pathogenic model in which a genetically predisposed host mounts a persistent, pathological immune response to reactivating EBV, which subsequently drives chronic inflammation in the bile ducts, potentially through a mechanism such as molecular mimicry. The findings represent a significant paradigm shift, offering new avenues for developing targeted diagnostics, preventive strategies, and effective therapies for this debilitating disease.

Keywords: T and B cell responses, Epstein–Barr virus, pathogenesis, primary sclerosing cholangitis

1. INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare, idiopathic, and progressive disease characterized by chronic inflammation of the intra- and/or extrahepatic bile ducts [1]. This inflammatory process leads to multifocal biliary strictures and fibrosis, which progressively obstruct the flow of bile, eventually resulting in biliary cirrhosis, liver failure, and an increased risk of malignancy, including cholangiocarcinoma. The disease is often asymptomatic in its early stages, with a diagnosis frequently made incidentally following abnormal liver function tests, such as elevated alkaline phosphatase (ALP) levels. A defining clinical feature of PSC is its strong association with inflammatory bowel disease (IBD), particularly ulcerative colitis, with approximately 60%–80% of PSC patients also having a concurrent IBD diagnosis [2]. Despite decades of research, the precise etiology of PSC remains elusive. The leading pathogenic theories suggest a complex interplay between a host's genetic predisposition and environmental triggers that instigate an aberrant immune response. As of now, there are no effective medical therapies to slow or halt the progression of PSC, and liver transplantation remains the only definitive curative treatment option for patients with end-stage disease [3]. The urgent need for a deeper understanding of the disease's origins to inform new therapeutic strategies underscores the

importance of investigating potential environmental cofactors, such as viral infections. The Epstein–Barr virus (EBV), also known as human herpesvirus 4, is a ubiquitous member of the herpesvirus family [4]. It is estimated that over 95% of the world's population is infected with EBV, typically acquiring the infection in childhood. While early childhood infections are often asymptomatic, infection delayed until adolescence or adulthood frequently leads to a symptomatic illness known as infectious mononucleosis [5]. Following primary infection, EBV establishes a lifelong latent presence within host B cells, with the ability to periodically reactivate into a lytic, or productive, phase. The virus has long been recognized for its capacity to alter host immune responses and evade total elimination, positioning it as a plausible trigger for a variety of immune-mediated disorders. Indeed, EBV has been consistently implicated in the development of numerous autoimmune diseases, including multiple sclerosis (MS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [6]. Its role in these conditions has spurred a growing interest in its potential link to other autoimmune diseases of unknown etiology, such as PSC. Given the autoimmune nature of PSC and the well-established role of EBV as a trigger for other autoimmune conditions, recent large-scale research efforts have been directed at systematically investigating a potential etiological link. This review article aims to provide a comprehensive and critical synthesis of the latest evidence regarding the adaptive immune responses to EBV in PSC patients. Specifically, it will focus on T and B cell responses, as these are the primary mediators of adaptive immunity against viral pathogens. The review's objective is to integrate recent epidemiological, genetic, and immunological findings to construct a cohesive pathogenic hypothesis, moving beyond mere association to a more mechanistic understanding of PSC.

2. THE EPIDEMIOLOGICAL AND GENETIC FOUNDATION: A COMPELLING LINK

A pivotal epidemiological finding has provided a strong foundation for the link between EBV and PSC. A comprehensive analysis of a vast database of over 116 million electronic health records was conducted to assess disease associations. The analysis revealed a striking association: individuals with a documented history of infectious mononucleosis were found to be 12 times more likely to develop PSC compared to those who had not experienced the infection [7]. This odds ratio is noteworthy, as it is six times higher than the twofold increased risk for multiple sclerosis, another disease for which EBV has a well-established association [8]. The robust nature of this finding suggests that the severity and specific characteristics of the initial EBV infection play a crucial role in disease initiation. The fact that most people are infected with EBV asymptotically, but only those who experience the more severe, inflammatory response of infectious mononucleosis have such a dramatically increased risk of PSC, points to a hypothesis where the intense immune "storm" accompanying the symptomatic infection is a critical cofactor in disease pathogenesis. A simple exposure to the virus is not sufficient; rather, it is the host's specific, and potentially dysregulated, response to that infection that appears to set the stage for PSC. The pathogenesis of PSC is not solely an environmental affair; it is also rooted in the host's genetic makeup [9]. While genetic variants identified to date account for only a fraction of the disease's heritability, they provide crucial clues about the underlying mechanisms. Notably, many of the genetic variants linked to a higher risk of PSC are related to the immune system's ability to recognize and respond to EBV, indicating a specific molecular vulnerability [10]. The connection between EBV, genetics, and PSC is further solidified by the discovery that PSC-associated T-cell receptor (TCR) clonotypes are restricted by known PSC risk alleles of the human leukocyte antigen (HLA) system. Specifically, the HLA-B*08:01 and HLA-DRB1*03:01 alleles, which are strongly associated with PSC, appear to be the platforms that present EBV-derived antigens to the immune system in a way that contributes to the disease [11]. This finding is significant because it moves beyond a generalized genetic susceptibility and points to a "two-hit" model of pathogenesis. A single genetic risk factor or a single environmental trigger is not enough to cause a rare disease like PSC. Instead, a host with a specific genetic predisposition (the HLA "lock") encounters a specific environmental trigger (the EBV antigen

"key"), which together initiate the cascade of immune events that culminates in disease. This provides a compelling explanation for why only a small subset of the globally infected population develops PSC.

Table 01: Finding in PSC Patients and their Significance

Feature	Finding in PSC Patients	Significance
Infectious Mononucleosis History	12x higher risk for PSC	Strong clinical and epidemiological link between symptomatic EBV infection and disease development
Genetic Predisposition	Genetic variants related to immune recognition of EBV	Suggests a molecular vulnerability in a specific subset of the population
HLA Alleles	PSC-associated TCR clonotypes restricted by HLA-B08:01, HLA-DRB103:01	Provides evidence for a "two-hit" model where a specific genetic profile interacts with an EBV trigger

3. THE ADAPTIVE IMMUNE RESPONSE: A CONVERGENT ATTACK ON EBV

To investigate the immunological mechanisms underlying the epidemiological and genetic links, researchers performed a large-scale analysis of T-cell repertoires in PSC patients. By profiling blood samples from 504 individuals with PSC and 904 healthy controls, a total of 1,008 T-cell receptor (TCR) clonotypes were identified that were significantly associated with PSC [12]. The presence of these clonotypes was not only more frequent in PSC patients but was also specific to this disease, as they were not similarly elevated in other autoimmune liver diseases such as primary biliary cholangitis (PBC) or autoimmune hepatitis (AIH). A crucial discovery was that a substantial fraction of these PSC-associated clonotypes were known to target Epstein–Barr virus epitopes. This finding provides a direct molecular link between the T-cell-mediated immune response in PSC and a specific viral pathogen. The immune response was found to be particularly directed against the EBV lytic-phase master regulator protein BZLF1 [13]. The significance of this lies in the fact that the immune system targets different proteins during the latent (dormant) versus lytic (reactivated) phases of the virus [14]. An immune response that is robustly directed at lytic-phase proteins indicates that the virus is not simply dormant, but is actively and chronically reactivating, providing a persistent antigenic stimulus that drives the ongoing inflammation characteristic of PSC. This distinguishes the PSC immune response from the normal, quiescent immune surveillance that occurs in most EBV-infected individuals. The T-cell findings are not an isolated phenomenon; they are corroborated by a parallel investigation into the humoral immune response. Using a high-throughput antigenic screening approach known as phage-immunoprecipitation sequencing (PhIP-Seq), a higher burden of anti-EBV responses was detected in the antibody repertoires of 120 PSC patients compared to 202 healthy controls [15]. This finding indicates a significantly higher prevalence of EBV-specific antibody production in individuals with PSC, confirming a heightened immune response at the B-cell level as well. The research further identified the specific EBV antigens targeted by these antibodies, including lytic-phase proteins such as BFRF3 (small capsid protein) and BMRF1, as well as the latent-phase protein EBNA1. The most compelling evidence of a direct pathogenic role, however, came from the isolation of EBV-specific monoclonal antibodies directly from B cells located within the inflamed liver tissue of PSC patients [16]. This discovery is profoundly significant. While elevated antibodies in the blood suggest a systemic response, finding the B cells that produce them at the physical site of disease provides a strong indication of a localized pathological process. It suggests that these immune cells have migrated to the liver and are

actively participating in the bile duct inflammation, perhaps as antigen-presenting cells or by producing local autoantibodies. The convergence of T- and B-cell responses at the site of inflammation against the same viral proteins provides a potent and cohesive picture of a targeted, organ-specific autoimmune attack on the bile ducts.

4. PUTATIVE MECHANISMS: FROM VIRAL REACTIVATION TO AUTOIMMUNITY

The collective immunological data—specifically, the T-cell and B-cell responses targeting lytic-phase EBV proteins—strongly support the hypothesis that EBV reactivation is a central pathological event in PSC [17]. EBV reactivation is the process by which the virus breaks latency and enters a productive cycle, generating new virions. In PSC patients, this reactivation appears to provide a persistent antigenic stimulus that sustains a chronic inflammatory response. This mechanism is not unique to PSC; EBV reactivation has been implicated in other chronic inflammatory and autoimmune diseases, paralleling findings in multiple sclerosis and rheumatoid arthritis [18]. The question then becomes: what triggers this reactivation? One plausible trigger is the gut microbiome. The gut microbiome is known to be altered in both PSC and its co-morbid condition, IBD. It has been shown that various stimuli, including pathogenic infections and commensal microbiomes, can induce EBV reactivation from its latent state [19]. This suggests a fascinating mechanistic bridge, or a gut-liver axis connection, where a dys biotic microbiome in an IBD-afflicted patient could produce metabolites or present antigens that trigger EBV reactivation in B cells. This, in turn, could initiate the autoimmune cascade that leads to the specific pathology of PSC, providing a potential explanation for the well-documented clinical link between the two diseases. With a pathological immune response to EBV established, the question shifts to how this response translates into an attack on the bile ducts. The most widely accepted model is molecular mimicry. This mechanism describes a situation where an immune response to a foreign antigen mistakenly targets a host's own tissues due to a structural or sequence similarity between the foreign and self-antigens. In other EBV-associated autoimmune diseases, this has been a well-documented process. For example, in multiple sclerosis, the EBV nuclear antigen (EBNA1) is known to mimic the host protein glial cell adhesion molecule (Glial CAM), leading to a cross-reactive immune attack on the central nervous system [20]. For PSC, the hypothesis is that the robust T and B cell responses to specific EBV antigens—such as BFRF3, BMRF1, and BZLF1—are cross-reactive with proteins on the surface of cholangiocytes. When the immune system mounts a sustained attack against these reactivated viral proteins, it simultaneously damages the bile duct cells that bear the mimicking self-antigens. The presence of EBV-specific B cells and monoclonal antibodies within the liver itself further supports this theory, indicating that the misguided immune attack is occurring directly at the site of the pathology. However, while this hypothesis is mechanistically sound and supported by compelling associative evidence, a critical missing link remains: the direct identification of a specific cholangiocyte autoantigen that is structurally mimicked by an EBV protein. Discovering this precise molecular relationship is the crucial next step in proving causality.

5. DISCUSSION AND CLINICAL IMPLICATIONS

The synthesis of recent epidemiological and immunological research paints a unified and compelling picture of PSC pathogenesis. The data suggest a multi-step process. First, a genetically susceptible individual, possessing high-risk HLA alleles like HLA-B*08:01, encounters the Epstein–Barr virus [21]. A particularly inflammatory initial response, such as infectious mononucleosis, appears to be a critical event that primes the immune system for a pathological trajectory. This trajectory is perpetuated by chronic EBV reactivation, which is possibly triggered by environmental factors like a dys biotic gut microbiome, an especially relevant consideration given the strong co-occurrence of PSC with IBD [22]. The persistent viral reactivation provides a continuous antigenic stimulus that drives a robust, yet misguided, T and B cell response targeting lytic-phase EBV proteins [23]. This immune response, via a

mechanism of molecular mimicry, then mistakenly targets and destroys the cells lining the bile ducts, leading to the chronic inflammation and fibrosis that define PSC. This model moves the understanding of PSC from a purely "idiopathic" disease to one with a potentially identifiable, multi-layered root cause.

This new pathogenic framework offers a paradigm shift in how PSC could be managed in the future, opening up novel therapeutic and preventive avenues.

1. **EBV Vaccination:** The strong association between infectious mononucleosis and PSC suggests that an effective EBV vaccine, a long-standing goal of virology research, could serve as a preventative measure for PSC [24]. By preventing or mitigating the severity of the primary EBV infection, a vaccine could eliminate the critical triggering event and significantly reduce the likelihood of a person with genetic risk factors developing PSC.
2. **Targeted Antiviral and Immunotherapies:** For patients with established PSC, the identification of chronic viral reactivation and EBV-specific B cells within the diseased liver suggests that therapies targeting EBV-infected cells or the virus itself could be a new treatment modality [25]. This could include new antiviral agents designed to prevent reactivation or immunotherapies that specifically target and deplete EBV-infected B cells without causing broad immunosuppression.
3. **Precision Medicine:** The combination of genetic markers and the EBV-specific immune signature found in PSC patients provides a foundation for a precision medicine approach [26]. Future diagnostics could screen for high-risk HLA alleles and a specific EBV-driven immune profile to identify patients most likely to respond to a targeted therapy. This would enable clinicians to move away from a one-size-fits-all approach and offer personalized treatment strategies.

6. Limitations and Future Research Directions

While the findings are compelling, a direct causal relationship has not yet been proven [27]. The current evidence establishes a strong association, but further research is required to fully elucidate the pathogenic mechanisms and translate these findings into clinical practice.

Future studies must focus on several critical areas:

- The search for the precise molecular targets of mimicry is paramount. Researchers need to identify a specific amino acid sequence or structural motif on an EBV protein that is shared with a protein on a cholangiocyte. The identified antigens such as BFRF3, BMRF1, and BZLF1 provide excellent starting points for this investigation [28].
- The role of the gut microbiome in triggering EBV reactivation needs to be thoroughly investigated, particularly in the context of PSC and IBD. Understanding this relationship could lead to new therapies that modulate the microbiome to prevent viral reactivation [29].
- Prospective studies are needed to track individuals who have had infectious mononucleosis and carry high-risk HLA alleles to validate the predictive power of these associations and to monitor the early stages of disease development [30].

6. CONCLUSION

The recent convergence of epidemiological and immunological evidence represents a significant breakthrough in our understanding of Primary Sclerosing Cholangitis. The discovery of a powerful link between infectious mononucleosis and PSC, coupled with the identification of a specific T- and B-cell-mediated immune response targeting reactivating EBV, provides a solid foundation for a new pathogenic model. This model posits that a genetically predisposed host's persistent, pathological

immune response to a reactivating EBV infection drives the chronic inflammation of the bile ducts. While the definitive causal relationship and the precise molecular mechanisms, such as molecular mimicry, require further investigation, these findings offer renewed hope for the development of targeted diagnostics, preventive strategies, and, most importantly, effective therapies for a disease that has long evaded medical intervention.

REFERENCES

- [1] Pathogenesis and clinical spectrum of primary sclerosing cholangitis - PMC, accessed August 8, 2025.
- [2] Abdul Mumin, Abdullah Al Amin, A.K.M. Shahriar Kabir, Rifat Ara Noor & Urmi Rahman (2024). Role of C- Reactive Protein (CRP) and Neutrophil Lymphocyte Ratio (NLR) in detecting severity & Predicting outcome of Acute Pancreatitis patients. *Dinkum Journal of Medical Innovations*, 3(01):01-12.
- [3] Pathogenesis and clinical spectrum of primary sclerosing cholangitis, accessed August 8, 2025,
- [4] T and B cell responses against Epstein-Barr virus in primary sclerosing cholangitis., accessed August 8, 2025,
- [5] Johanna Carlbring & Lasse Bosse (2025). A Review on Mental Health Integration and Digital Therapeutics in Primary Care. *Dinkum Journal of Medical Innovations*, 4(05):298-305.
- [6] Bikramaditya Prasad Sah (2025). Outcome Comparison in Microscopic and Endoscopic Trans-Sphenoidal Pituitary Adenoma Surgery in Terms of Extent of Resection. *Dinkum Journal of Medical Innovations*, 4(04):165-176.
- [7] The Role of Microbiota in Primary Sclerosing Cholangitis and Related Biliary Malignancies, accessed August 8, 2025,
- [8] Chronic Bile Duct Inflammation Linked to Epstein-Barr Virus Reactivation, accessed August 8, 2025,
- [9] Valérie Oneko (2025). A Review on HIV Vaccine & limitations of long-acting PrEP with a focus on Lenacapavir. *Dinkum Journal of Medical Innovations*, 4(02):48-52.
- [10] Protective function of sclerosing cholangitis on IBD - Gut, accessed August 8, 2025,
- [11] Primary sclerosing cholangitis (PSC) – What you should know | Crohn's & Colitis Foundation, accessed August 8, 2025
- [12] Terrie D.Taylor (2025). Critical Analysis of the Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis . *Dinkum Journal of Medical Innovations*, 4(02):63-68.
- [13] Epstein-Barr Virus as a Trigger of Autoimmune Liver Diseases - PMC, accessed August 8, 2025,
- [14] Chronic Bile Duct Inflammation Linked to Epstein-Barr Virus ..., accessed August 8, 2025,
- [15] Epstein–Barr Viruses: Their Immune Evasion Strategies and Implications for Autoimmune Diseases - MDPI, accessed August 8, 2025
- [16] Mononucleosis linked to higher risk of developing PSC: Study - Liver Disease News, accessed August 8, 2025
- [17] Epstein–Barr virus - Wikipedia, accessed August 8, 2025
- [18] Researchers have found a link between mono and the liver disease PSC, accessed August 8, 2025,
- [19] EBV Reactivation: Symptoms, Treatment, and More - WebMD, accessed August 8, 2025,
- [20] How Does Epstein–Barr Virus Interact With Other Microbiomes in EBV-Driven Cancers?, accessed August 8, 2025,
- [21] Rajendra Bhandari, Prasanna Bahadur Amatya, Nabin Kumar Sinjali Magar & Ram Bahadur KC (2024). Association between Serum CRP Level and CURB-65 Score in Community Acquired Pneumonia Patients. *Dinkum Journal of Medical Innovations*, 3(09):656-669.

- [22] Identifying the key regulators orchestrating Epstein-Barr virus reactivation - Frontiers, accessed August 8, 2025, A Common Mechanism Links Epstein-Barr Virus Infections and Autoimmune Diseases, accessed August 8, 2025.
- [23] Nujhat Minhaj, Mohasin Mia & Rukhshana Afroz Afrin (2024). Level and Pattern of Cervical Lymph Node Metastasis from Gingivo Buccal Sulcus & Palatal Mucosa of Maxilla in Oral Squamous Cell Carcinoma. Dinkum Journal of Medical Innovations, 3(08):570-580.
- [24] HLA-DPA1*02:01~B1*01:01 is a risk haplotype for primary sclerosing cholangitis mediating activation of NKp44+ NK cells | Gut, accessed August 8, 2025
- [25] T and B cell responses against Epstein–Barr virus in primary sclerosing cholangitis - PMC, accessed August 8, 2025.
- [26] Sandesh Doranga, Yugadi Gurung, Sandip Shrestha, Susan Pradhan & Ajay K.C. (2024). Efficacy of Tamsulosin in the Expulsion of Lower Ureteral Calculi. Dinkum Journal of Medical Innovations, 3(07):523-532.
- [27] Role of microbiome in autoimmune liver diseases - PMC - PubMed Central, accessed August 8, 2025,
- [28] Dr. Zahidur Rahman Khan & Dr. Sabrina Tymee (2024). Evaluation of Prognostic Role of Serum CRP in Acute Stroke Patients. Dinkum Journal of Medical Innovations, 3(06):460-468.
- [29] (PDF) T and B cell responses against Epstein–Barr virus in primary sclerosing cholangitis, accessed August 8, 2025,
- [30] Awakening the sleeping giant: Epstein–Barr virus reactivation by biological agents | Pathogens and Disease | Oxford Academic, accessed August 8, 2025,