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REVIEW ARTICLE

The role of viral infections in the development of autoimmune diseases

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ABSTRACT

The exact aetiology of most autoimmune diseases remains unknown, nonetheless, several factors contributing to the induction or exacerbation of autoimmune reactions have been suggested. These include the genetic profile and lifestyle of the affected individual in addition to environmental triggers such as bacterial, parasitic, fungal and viral infections. Infections caused by viruses usually trigger a potent immune response that is necessary for the containment of the infection; however, in some cases, a failure in the regulation of this immune response may lead to harmful immune reactions directed against the host's antigens. The autoimmune attack can be carried out by different arms and components of the immune system and through different possible mechanisms including molecular mimicry, bystander activation, and epitope spreading among others. In this review, we examine the data available for the involvement of viral infections in triggering or exacerbating autoimmune diseases in addition to discussing the mechanisms by which these viral infections and the immune pathways they trigger possibly contribute to the development of autoimmunity.

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1. Introduction

The failure of immunologic tolerance, which leads to an immune response against the host antigens, is referred to as autoimmunity. Following tissue injury, usually caused by activation of self-reactive B and T-lymphocytes, autoimmunity can, in turn, develop into various disorders termed autoimmune diseases. A direct initiatory cause for most autoimmune diseases has not been defined yet; however, studies commonly suggest that a combination of factors is required for their initiation (Rose and Mackay 2014).

Autoimmune diseases represent a challenging clinical problem owing to their chronicity which necessitates an extended and often lifelong therapy that is relatively costly. Currently available therapeutic approaches rely on relieving symptoms rather than curing the disease. The multifactorial aetiologies underlying autoimmune diseases and the ambiguity of some of the mechanisms behind these diseases have hindered the development of curative therapeutic modalities.

Studies suggest that a combination of multiple factors is required for the initiation of autoimmunity; these include genetic predisposition, flawed immune regulation as well as particular environmental factors (Rahal et al. 2014; Ajib et al. 2005). On the other hand, a mutation in the autoimmune regulator (AIRE) gene is thought to be the single factor underlying the autoimmune poly-endocrine syndrome type 1 (APS-1) (Husebye et al. 2018). Viral infection has been associated with multiple autoimmune diseases. These infections typically trigger several immune processes some of which could overwhelm the immune regulatory mechanisms. This may result in immune reactions directed to viral as well as host antigens potentially resulting in tissue damage. Several mechanisms, including molecular mimicry, bystander activation of T-cells and epitope spreading have been the primary ways of explaining how a viral infection might induce a series of reactions resulting in an autoimmune disease.

2. Infections and autoimmunity

Bacterial, parasitic and viral pathogens are examples of environmental factors associated with the development of autoimmune diseases. Infection of the host with some of these pathogens can affect different arms of the immune system and result in the initiation of autoimmune reactions through multiple mechanisms

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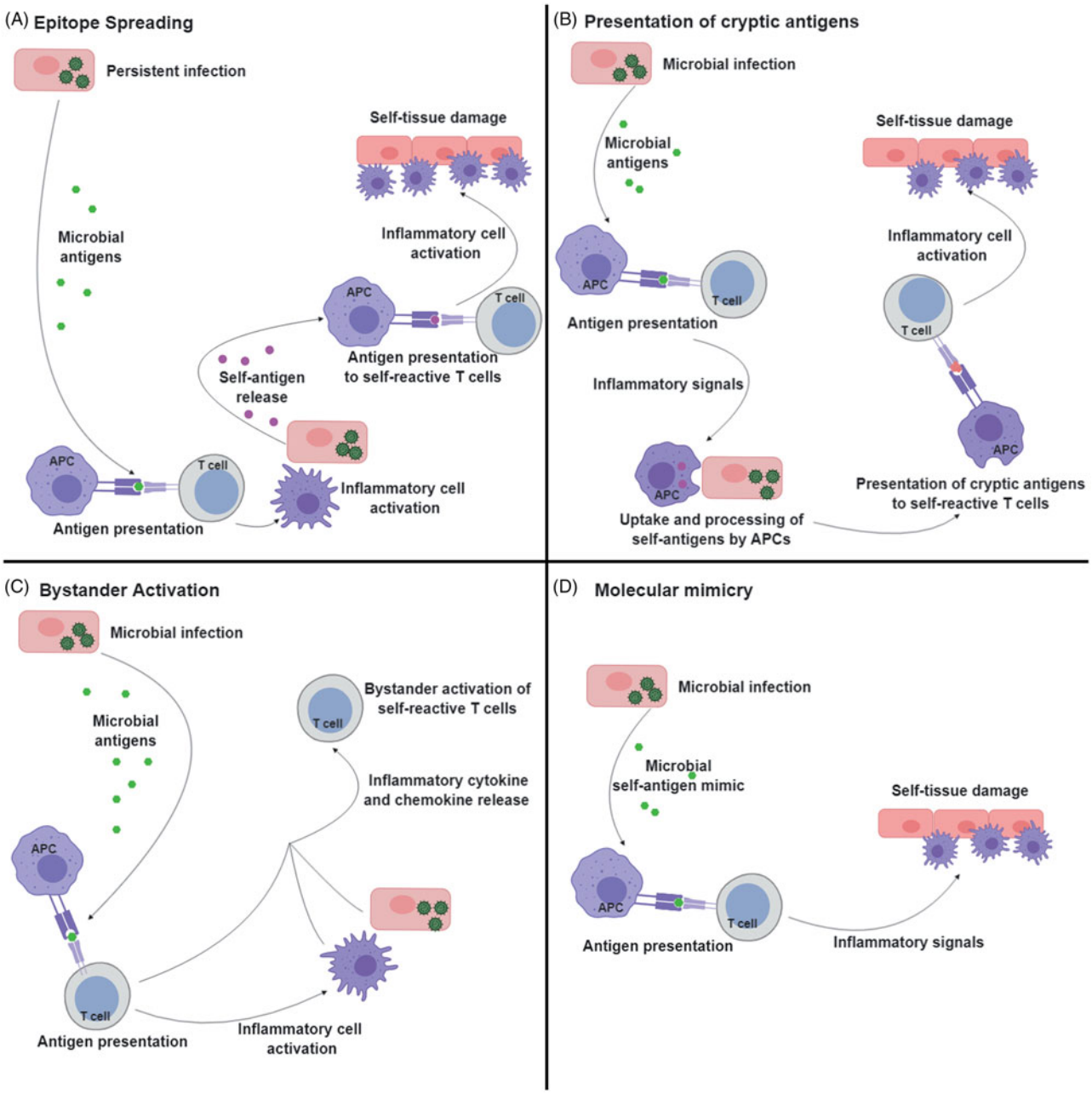

Figure 1. Infection-associated mechanisms of autoimmunity. (A) Epitope spreading: a persistent infection results in the uptake of microbial antigens by antigen presenting cells (APCs) and presentation of these antigens to microbe-specific T cells. The subsequently activated inflammatory cascade to the persistently-infected site results in tissue damage and uptake of self-antigens by APCs. Presentation of these self-antigens to self-reactive T cells then results in an immune reaction against self-tissues. Therefore, the immune reaction spreads from being against microbial antigen epitopes to non-cross-reactive self-epitopes. (B) Presentation of cryptic antigens: upon a microbial infection, self-antigens may be uptaken and processed by APCs. Inflammatory signals may then result in altered processing of these self-antigens in a manner that exposes cryptic epitopes; these cryptic epitopes are then presented to self-reactive T cells hence initiating an autoimmune response. (C) Bystander activation: a microbial infection may trigger inflammatory signals that inadvertently result in the activation of self-reactive T cells, therefore, resulting in the activation of autoimmune processes. (D) Molecular mimicry: microbial antigens may share antigenic similarity with self-antigens. Upon presentation of these self-antigen mimics by APC to cross-reactive T cells that recognize both the microbial mimic and its respective self-antigen, an autoimmune reaction may ensue.

(Figure 1). In case of a persisting infection, the infectious agent may either cause damage directly to host tissue, or indirectly by triggering an immune response to the persisting pathogen. This damage results in the release of self-antigens that may then be taken up by immune cells and result in a reaction mounted against these self-antigens (Tuohy and Kinkel 2000). This mechanism is known as "epitope spreading" (Figure 1A).

Furthermore, the inflammatory microenvironment present in response to an infection may enhance the production of proteases and the processing of self-antigens by APCs. As opposed to dominant antigens, there exist subdominant cryptic antigens, which are unnoticed by the immune system under normal conditions. Thus, infections can also result in the development of autoimmune disorders by driving the APCs to process and display cryptic antigens (Lanzavecchia 1995) (Figure 1B). Alternatively, pathogens may contribute to an autoimmune disease through a mechanism referred to as "bystander activation" whereby the infection results in the activation of APCs that may, in turn, activate pre-primed auto-reactive T-cells. Following damage sustained by host tissues, APCs take up the released self-antigens and process them as pathogenic antigens, which triggers an immune response directed to the self (Fujinami et al. 2006) (Figure 1C). Additionally, in cases where some of the components of the infectious agent show a sufficient similarity between the structure or sequence of their amino acids and some of the host antigens, immune reactions directed against the antigens of the pathogen could affect those of the host; this mechanism is referred to as "molecular mimicry" (Ercolini and Miller 2009) (Figure 1D). The first studies that introduced the concept of molecular mimicry reported the presence of mouse antibodies reactive to host and viral (measles and HSV-1) intermediate filaments (Fujinami et al. 1983). In later studies, the same group described a possible role for T cell receptors (TCR), which are naturally specific for pathogenic antigens, in cross-reacting with molecularly resembling self-epitopes (Fujinami and Oldstone 1985, 1989).

While autoimmunity has been associated with many different pathogens, this review focuses on the role of prominent viruses, and on the mechanisms through which they interact with the infected host's immune system inducing inflammatory reactions that potentially lead to the development or exacerbation of autoimmune diseases (Table 1).

3. Viruses associated with autoimmunity

3.1. Epstein-Barr virus (EBV)

EBV, a herpesvirus that causes infectious mononucleosis (IM), has long been associated with autoimmune diseases such as systemic lupus erythematosus (SLE), a

Table 1. Summary of viruses with associated autoimmune diseases and possible underlying mechanisms.

Family	Virus	Associated diseases	Suggested mechanisms
Herpesviridae	Epstein-Barr virus	MS, SLE, RA, SS	BA (Serafini et al. 2007) , MM (Lang et al. 2002), "Mistaken self" (van Noort et al. 2000), ES (Pender 2003)
	Human Herpesvirus-6	MS, SLE, HT	MM (Tejada-Simon et al. 2003), BA (Kubo et al. 2006; Rizzo et al. 2016)
	Human Cytomegalovirus	SSc, SLE, T1D	MM (Lunardi et al. 2000; Hiemstra et al. 2001; Namboodiri et al. 2004; Lunardi et al. 2006), ES (Palafox Sánchez et al. 2009), BA (Bennett Jenson et al. 1980; Pak et al. 1988)
Retroviridae	Human T-Lymphotropic virus 1	HAM/TSP, SS, Uveitis, RA, SLE	BA (Vernant et al. 1988; Eguchi et al. 1992; Araújo et al. 2009; Best et al. 2009; Castro-Costa et al. 2009; Yamano et al. 2009; Romanelli et al. 2010; Nakamura et al. 2015)
Paramyxoviridae	Measles virus	MS	MM (Triger et al. 1974)
Picornaviridae	Enterovirus serotype CV	T1D, Chronic myocarditis	MM (Maisch 1986; Kaufman et al. 1992; Schwimmbeck et al. 1993; Root-Bernstein et al. 2009), BA (Blay et al. 1989; Horwitz et al. 2002; 2004; Li et al. 2018)
Togaviridae	Rubella virus	Thyroid diseases, T1D	MM(Ou et al. 2000), BA(Rabinowe et al. 1986; Ou et al. 2000; Banatvala and Brown 2004; Burgess and Forrest 2009)
Flaviviridae	Hepatitis C virus	HT, SS, RA	BA (Akeno et al. 2008), ES (Aktas et al. 2017)
	West-Nile virus, Yellow Fever virus, Dengue virus, Murray Valley Encephalitis virus, Kunjin virus	Encephalo-myelitis, polymyositis	BA (Bao et al. 1992)
	Japanese Encephalitis virus	Encephalo-myelitis, polymyositis	MM (Tseng et al. 2011), BA (Bao et al. 1992; Kalita and Misra 2002; Tsunoda et al. 2003; Swarup et al. 2007; Ghosh and Basu 2009)
Parvoviridae	Human Parvovirus B19	RA, SLE, SS, SSc, SD, Glm, SV, KD, HSP, DM, SJIA, GCA, PN	MM (Lunardi et al. 2008)

MM: Molecular mimicry; BA: Bystander activation; ES: Epitope spreading; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; SS: Sjögren's Syndrome; SSc: Systemic Sclerosis; HAM/TSP: HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis; T1D: Type 1 Diabetes; HT: Hashimoto's Thyroiditis; SD: Still's Diseases; Glm: Granulomatosis; SV: Systemic Vasculitis; KD: Kawasaki Disease; HSP: Henoch Schönlein Purpura; DM: Dermatomyositis; SJIA: Systemic Juvenile Idiopathic Arthritis; GCA: Giant Cell Arteritis; PN: Polyarteritis Nodosa.

disease that can affect multiple organs in addition to skin and joints, and is characterized by a butterfly-shaped rash on the face, and rheumatoid arthritis (RA), a disease affecting the synovial membrane of various joints causing pain and swelling. Studies have shown higher titres of EBV-directed antibodies in SLE and RA patients in addition to higher viral loads in peripheral blood mononuclear cells (PBMCs) from patients compared to relatively healthy controls (James et al. 2001; Poole et al. 2006). Moreover, viral capsid antigen (VCA), EBV nuclear antigen-1 (EBNA-1) and early antigen (EA)-directed antibodies have been detected with a higher frequency in sera of SLE patients. Studies on adult and paediatric SLE patients reported the detection of IgG and IgM antibodies to EBNA-1 and VCA in 100% of tested SLE patients, while only 66% of healthy controls were seropositive (James et al. 1997; 2001; McClain et al. 2006). Moreover, IgG antibodies to the early antigen/diffuse (EA/D), early antigen/restricted (EA/R), and the major DNA-binding protein BamHI A left frame transcript (BALF2) have been detected in high loads in ≈50% of SLE patients while only 8–17% of healthy controls were seropositive (Stratta et al. 1999; Berkun et al. 2009; Zandman-Goddard et al. 2009; Esen et al. 2012). Furthermore, elevated titres of EA/D-directed IgA have been observed in more than half of SLE patients while none were detected in healthy controls (Draborg et al. 2012). Additionally, increased level of mRNA expression of the viral antigens BamHI Z leftward open reading frame 1 (BZLF1), glycoprotein 350 (gp350), viral IL-10, latent membrane protein-1 (LMP-1), LMP2, and EBNA1 has been observed in SLE patients (Gross et al. 2005; Poole et al. 2009). It has also been demonstrated that EBV-directed $CD8^+$ T-cell activity, which plays a major role in killing EBV-infected cells, is diminished in SLE patients leading to an insufficient containment of the infection (Kang et al. 2004; Berner et al. 2005; Larsen et al. 2011).

Moreover, studies on synovial fluids and sera of RA patients have reported notably higher levels of EBNA1, EA/R, and VCA-directed antibodies than those in healthy controls (Alspaugh et al. 1981; McDermott et al. 1989; Mousavi-Jazi et al. 1998; Blaschke et al. 2000), and the number of EBV-infiltrated B-lymphocytes detected in RA patients has been found to be ten times higher in comparison with normal subjects (Balandraud et al. 2003). Furthermore, DNA from EBV was also detected in PBMCs, saliva, synovial tissues from a higher proportion of RA patients than controls (Takei et al. 1997; Saal et al. 1999; Blaschke et al. 2000; Takeda et al. 2000). Remarkably, a significant portion of the cyclic citrullinated peptide (CCP) antibody-producing plasma cells in synovial membranes and synovial fluids of RA patients have been found to contain EBV DNA (Croia et al. 2013). Additionally, the frequencies of CD8+ T-cells specific for the EBV lytic antigens HLA-A2-restricted GLC epitope and HLA-B8-restricted RAK epitope were not notably different in RA patients and healthy controls, however, the percentage of IFNγ-producing CD8+ T-cells directed against these antigens was found to be significantly lower in RA patients compared to controls, which indicates a defective IFNγ response to EBV proteins (Klatt et al. 2005). Another study reported that the reactivity of T-cells from the peripheral blood of RA patients to gp110, an EBV protein that plays an important role in viral entry to B-lymphocytes, was lower compared to healthy controls (Toussirot et al. 2000).

Multiple sclerosis (MS), an autoimmune disease that affects the central nervous system (CNS) potentially causing disability has also been associated with EBV. It has been shown that EBV infection in young adults leads to an increased risk of developing MS. This finding was confirmed by the proportional increase in the risk of developing MS with higher anti-EBV antibody titres (Pender and Burrows 2014). Moreover, Serafini et al. (2007) demonstrated that brain tissues of nearly all of the early onset MS subjects in the secondary progressive phase had dysregulated plasma cells infected with EBV. The study also reported increased proliferation of B-cells in addition to notable accumulation of EBV-encoded small RNA (EBER)+ cells in brain lesions from all MS patients tested, whereas patients suffering from other neuro-inflammatory diseases did not show any EBER + cells. Moreover, the EBV lytic protein BamHI F rightward open reading frame 1 (BFRF1) was detected in around 42% of intra-meningeal B-cells and plasma cells. Furthermore, cells expressing EBV latent proteins EBNA2 and LMP1 were detected in CNS lesions from 72% and 88% of MS patients tested respectively, whereas these proteins were not detected in CNS tissue from patients with other neuro-inflammatory diseases (Serafini et al. 2007).

Multiple mechanisms by which EBV contributes to the development of MS have been proposed. Through a process of molecular mimicry, T-cells exposed to EBV antigens may cross-react with antigens of the CNS, such as myelin antigens; for example T-cells from a subject with MS have been shown to react to both the DRB1*1501-restricted myelin basic protein (MBP) and the DRB5*0101-restricted Epstein-Barr virus (EBV) peptide (Lang et al. 2002). Serfani et al.'s (Serafini et al. 2007) findings, on the other hand, suggested that the immune response, represented by the expansion and increased activity of $CD8^+$ T-cells mainly targets EBV antigens, however, this attack leads to bystander

damage to the CNS (Serafini et al. 2007). Another study suggested that following exposure to EBV, and subsequent expression of the heat shock protein αB-crystallin in lymphoid cells, the immune system inadvertently attacks self-oligodendrocyte-derived αB-crystallin after mistaking it for a foreign antigen resulting in demyelination. The study distinctively refers to this mechanism as "mistaken self", whereby infected human lymphoid cells prime T-lymphocytes to αB-crystallin along with microbial antigens (van Noort et al. 2000). It has been also suggested that all human chronic autoimmune diseases, including MS, are caused by EBV infection of auto-reactive B-cells, which accumulate in the target organ where they produce pathogenic autoantibodies and provide costimulatory survival signals to auto-reactive T-cells that would otherwise die in the target organ by activation-induced apoptosis (Pender 2003). This hypothesis also proposed that the accumulation of EBV-infected auto-reactive B-cells in the target organ is due to a genetically determined defect in the elimination of EBV-infected B-cells by the cytotoxic $CD8^+$ T-cells that normally keep EBV infection under stringent control (Pender 2003). Ascherio and Munger (2007) also reported that the risk of MS is 20 times higher among people who have contracted IM, compared to seronegative individuals.

Despite the substantial amount of evidence in the literature pointing at an association between EBV and MS, some studies investigating samples from MS patients countered this belief. One study reported that no trace of EBV was detected in tested white matter lesion samples from MS patients compared to EBV-positive controls and only 2 out of 12 tested MS meningeal samples showed EBV-infected cells (Willis et al. 2009). Moreover, Sargsyan et al. (2010) did not detect EBV RNA in MS cerebrospinal fluid (CSF) and found only (EBER)-1 in rare active MS plaques. Therefore, this association is rather debatable (Lassmann et al. 2011).

Additionally, EBV has been associated with Sjögren's syndrome (SS), an autoimmune disease characterized by dry eyes and dry mouth in addition to joint pain and fatigue. SS patients had higher EBV viral loads (Fox et al. 1986; Saito et al. 1989; Mariette et al. 1991; Pflugfelder et al. 1994; Wen et al. 1996) and EBV-directed antibodies (Miyasaka et al. 1989; Inoue et al. 1991; Toda et al. 1994; Pasoto et al. 2013). In addition to the viral particle, EBV DNA has been detected in high levels in epithelial cells and B-lymphocytes from salivary glands of SS patients (Fox et al. 1986; Mariette et al. 1991; Pflugfelder et al. 1994; Wen et al. 1996). Moreover, lacrimal glands of SS patients have been found to contain EBV DNA in addition to EBV latent and lytic proteins (Pflugfelder et al. 1994). Furthermore, high loads of EBNA, VCA, and EA-directed antibodies in the serum of SS patients were reported in multiple studies (Miyasaka et al. 1989; Inoue et al. 1991; Toda et al. 1994). Additionally, one study found that the percentage of anti-EA/D IgG antibodies in SS patients (36%) is significantly higher compared to controls (4.5%) (Pasoto et al. 2013).

We have previously reported that EBV DNA stimulates the production of the pro-inflammatory cytokine interleukin-17A (IL-17A) in mice (Rahal et al. 2015). IL-17A is known to play a substantial role in the development of autoimmune diseases (Tabarkiewicz et al. 2015). In a follow-up study, we demonstrated that TLR9 was involved in the increase in IL-17A production, since treatment with the TLR9 inhibitor ODN 2088 led to a significant drop in IL-17A levels. This enhancement in IL-17A production observed in mice following EBV DNA treatment was validated in human subjects whereby RA patients showed a propensity for linearity in the correlation between the EBV DNA load and IL-17A levels as opposed to controls. In addition, we have demonstrated that EBV DNA modulates regulatory T-cell markers with a notable inhibitory effect on the expression of the CTLA4 gene, while enhancing the expression of Th17 markers (Salloum et al. 2018).

Worth noting is that EBV is a widespread virus infecting around 90% of the human population. This fact raises a relevant question: if EBV is capable of triggering a large number of autoimmune mechanisms, why is only a relatively small fraction of individuals affected? An answer to this question might be underscored by the fact that many other elements that vary among individuals could affect the development of autoimmunity. These elements include environmental and lifestyle factors such as climate, nutritional habits, vitamin D levels, stress and cigarette smoking among others (Jörg et al. 2016). Moreover, a 2018 study showed through novel computational methods that the EBNA2 protein binds approximately 50% of SLE genetic risk loci, which demonstrates a non-random gene-environment interaction. Such associations with EBNA2 were also observed in other autoimmune diseases such as inflammatory bowel disease, type 1 diabetes (T1D), celiac disease, juvenile idiopathic arthritis, Kawasaki disease, RA and MS (Harley et al. 2018).

3.2. Human herpesvirus 6 (HHV-6)

HHV-6 establishes latency in lymphocytes, monocytes, bone marrow and the CNS with potential later reactivations. This virus can cause exanthema subitum or

roseola infantum in children less than two years old (Friedman et al. 1999; Grinde 2013). It has also been associated with seizures (Caserta et al. 1994), disseminated demyelination (Kamei et al. 1997) and infarction of the basal ganglia in children (Webb et al. 1997), in addition to encephalitis in both adults and children (McCullers et al. 1995; Isaacson et al. 2005). Two variants of HHV-6 were identified in 1993; HHV-6A and HHV-6B (Álvarez-Lafuente R et al. 2004; De Bolle et al. 2005). These two variants have highly similar genomes but are different biologically and immunologically (Pietiläinen et al. 2010). HHV-6 has also been shown to be associated with autoimmune disease development. The first evidence of such an association was provided by a study reporting the presence of a HHV-6A antigen in oligodendrocytes from MS patients, and its absence in control subjects (Challoner et al. 1995). Other subsequent studies continued to demonstrate this association by showing high levels of HHV-6A/B-directed antibodies in MS patients compared to healthy controls in addition to detecting HHV-6A/B DNA in the brains, CSF and serum from MS patients (Soldan et al. 1997; Ablashi et al. 1998; Fillet et al. 1998; Kim et al. 2000; Chapenko et al. 2003; Hafler 2004; Rotola et al. 2004; Donati et al. 2005; Opsahl and Kennedy 2005; Voumvourakis et al. 2010).

Moreover, exacerbations in cases of relapsing-remitting MS coincided with increased viral titers in both serum and PBMCs, indicating that the relapse might be linked to the reactivation of the latent HHV-6 (Wilborn et al. 1994; Soldan et al. 1997; Chapenko et al. 2003). Furthermore, HHV-6 DNA was more frequently present in MS lesions compared to normal regions within the same brains. Moreover, through immunohistochemical studies on brains from MS patients, viral proteins have been detected in astrocytes and oligodendrocytes, and more frequently in demyelinating lesions compared to normal areas of the same brains (Sanders et al. 1996; Fillet et al. 1998; Álvarez-Lafuente et al. 2004). Interestingly, a study reported that there is a shared peptide sequence between the HHV-6A protein U24 and human myelin basic protein (MBP), consisting of seven identical amino acid residues. Remarkably, the immune reactions mediated by antibodies and T-cells directed towards this sequence were high in MS patients (Tejada-Simon et al. 2003), suggesting a mechanism of molecular mimicry to be occurring. However, the HHV6/MS association has been challenged by multiple studies (Leibovitch and Jacobson 2014). One study detected anti-HHV6 IgM in only 1 of 198 MS patients while 1.8% of patients were positive for the virus and had very low median viral load of 2.2 copies/ml (Simpson et al. 2014). Another study detected HHV6 DNA in the blood of only 3.2% of tested MS patients (Hon et al. 2014). The frequency of serum HHV6 DNA detection in MS patients was low as well (2.2%) in another study (Gustafsson et al. 2014). The reason for this discordance remains to be investigated, however, one of the possible factors could be the different genetic profiles of studied patients since each of the aforementioned studies challenging the HHV6/MS association was conducted in a cohort of a particular nationality.

Furthermore, elevated HHV-6 antibody titres in collagen vascular disease patients suggest that viral reactivations are frequent compared to controls (Krueger et al. 1991). Frequent HHV-6A/B reactivation has also been detected in SLE among other autoimmune connective tissue diseases (ACTDs) (Broccolo et al. 2009; 2013).

Studies on tissues from Hashimoto's thyroiditis patients reported the detection of HHV-6 in these tissues (Scotet et al. 1999). Another study compared fine needle aspirates (FNAs) from thyroids of HT patients and healthy controls and found that 82% of the studied HT specimens contained HHV-6A compared to only 10% of controls. In addition, 100% of HHV-6A-containing HT FNAs coincided with the lytic phase of the infection while positive samples from controls harboured only latent HHV-6A (Caselli et al. 2012). Furthermore, Rizzo et al. (Rizzo et al. 2016) have shown that the antibody response specifically directed against the HHV-6 U94/Rep protein was more prevalent (100% vs 75%) and in higher titers in HT patients compared to controls, (Rizzo et al. 2016). HT patients also differed from controls in the numbers of specific NK cell types. One criterion based on which NK cells can be grouped is the amount of CD56 present on the cell surface; cytotoxicity is more associated with $CD56^{low}$ NK cells while $CD56^{high}$ NK cells produce more cytokines including the pro-inflammatory cytokine IFN-γ (Cooper et al. 2001). Samples from HT patients showed higher numbers as well as higher activity of $CD56^{high}$ NK cells compared to controls, whereas no variation was observed in $CD56^{low}$ NK cells between samples from HT patients and controls (Rizzo et al. 2016). These findings represented an additional validation for a previous study by Kubo and colleagues on the CSF and serum of a female infant suffering from HHV-6-associated acute necrotizing encephalopathy reporting higher numbers of $CD56^{high}$ NK cells and increased pro-inflammatory cytokine levels (Kubo et al. 2006).

3.3. Human cytomegalovirus (HCMV)

HCMV is another human herpesvirus that has been associated with certain autoimmune diseases. In most

cases, immunocompetent HCMV-infected individuals show little or no symptoms. However, HCMV infections can lead to serious systemic manifestations such as colitis, nephritis, splenomegaly, retinitis and encephalitis mostly in subjects with compromised immunity (Schottstedt et al. 2010). Several characteristics of HCMV can qualify the virus to contribute to the development of autoimmunity including its worldwide prevalence, its wide range of target cells and tissues (Sinzger et al. 2008), its remarkable ability to modulate immune functions (Babić et al. 2011; Amsler et al. 2013) and its persistence through alternate phases of latency and lytic replication (Sinclair 2008).

HCMV has been associated with systemic sclerosis (SSc) (or scleroderma), a chronic connective tissue disease characterized by abnormal fibroblast proliferation, vascular injury, accumulation of extracellular matrix proteins in the skin, increase in the number of CD4+ T-cells and a decrease in the number of CD8+ T-cells (Yamamoto 2009). Studies have reported that HCMV antibody concentrations are higher in SSc patients compared to controls (H Vaughan et al. 2000; Arnson et al. 2009). Interestingly, the occurrence of HCMV-directed antibodies has been associated with heterozygosity for the *f* and *z* alleles of the IgG heavy chain in SSc patients, indicating a key role for the genetic profile of the patient in contributing to disease development (Pandey 2004). A study conducted on 90 SSc patients indicated that about 93% had antibodies to a peptide sequence shared by the HCMV protein UL94 and novel antigen-2 (NAG-2), a cell surface protein belonging to the transmembrane-4 superfamily (Lunardi et al. 2000). In an *ex vivo* assessment, the incubation of human dermal fibroblasts and human umbilical cord endothelial cells with anti-UL94 antibodies led to the binding of NAG-2 by this antibody resulting in apoptosis in endothelial cells but not in fibroblasts (Lunardi et al. 2000; 2006). Moreover, the levels of antibodies against UL94 were found to be substantially higher in patients with a more systemically diffuse form of the disease (Namboodiri et al. 2004) which is consistent with the hypothesis suggested by Pandey and LeRoy stating that HCMV acts as an enhancer of SSc (Pandey and LeRoy 1998).

In addition to SSc, HCMV has also been associated with SLE, however, studies that found a link between HCMV and SLE are relatively scarce compared to studies correlating SLE with EBV. One study documented a correlation between increased levels of anti-HCMV IgM antibodies in patients with SLE compared to healthy controls, however, levels of anti-HCMV IgG antibodies were the same in both groups tested (Su et al. 2007); this finding indicates that it is more likely that latent HCMV reactivation is occurring in SLE patients, due to the treatment with immunosuppressive drugs, rather than HCMV being a trigger of SLE (Halenius and Hengel 2014). Other studies reported that SLE patients had increased levels of anti-HCMV IgG antibodies compared to healthy controls (Barzilai et al. 2007), and that the occurrence of HCMV infections was higher in SLE patients compared to controls (James et al. 1997; Esen et al. 2012). Chen et al. (2015) reported that CMV-directed IgG and IgM levels in SLE patients were significantly higher than those detected in control patients. In addition, the frequency of detection of the HCMV gene *UL55*, which encodes glycoprotein B, in the peripheral blood leukocytes of SLE patients was significantly higher than controls (Chen et al. 2015).

The first discovered autoantibody in an SLE patient was identified by Tan and Kunkel (Tan and Kunkel 1966) in 1966 and is known as anti-Sm. Sm consists of seven proteins involved in multiple mRNA processing functions. The Sm proteins interact with the small nuclear RNAs (snRNAs) U1, U2, U4, U5 and U6 to form a highly stable small nuclear ribonucleoprotein (snRNP) core (J & Y 2016). One study indicated that the detection of autoantibodies was more frequent in SLE patients having higher levels of anti-HCMV IgG antibodies (Palafox Sánchez et al. 2009).

Whereas multiple studies have shown no association between HCMV and T1D (Hiltunen et al. 1995; Aarnisalo et al. 2008), a study conducted in Sweden indicated an association between congenital infections with HCMV and the occurrences of T1D (Ivarsson et al. 1993) while another report documented the case of a new-born with HCMV infection developing T1D roughly one year after birth (Ward et al. 1979). Despite these isolated reports, several groups have attempted to uncover a potential etiologic relation between HCMV infection and T1D onset. Bennett Jenson et al. 1980) found HCMV inclusion bodies in the islets of Langerhans of paediatric patients severely infected with HCMV (Bennett Jenson et al. 1980). Later, through dot and *in-situ* hybridization, Pak and colleagues (Pak et al. 1988) found that the lymphocytes of around 15% of T1D patients contained the genome of HCMV. Moreover, the group found autoantibodies against islet cells in sera of T1D patients, indicating a possible association between HCMV infection and T1D development. CD4+ T-cells involved in T1D pathogenesis have also been demonstrated to target the HCMV peptide UL57 and to be cross-reactive to glutamic acid decarboxylase-65 (GAD65); an enzyme that catalyzes the decarboxylation of glutamate to γ-aminobutyric acid and CO_2

(Hiemstra et al. 2001). These findings may indicate that a strong immune reaction to HCMV could have a destructive effect on the host pancreatic tissue contributing to T1D development. However, examination of post-mortem pancreatic samples by nested PCR in one study did not find any sign of HCMV infection (Foulis et al. 1997). The inconsistency in the observations among different studies is possibly due to genetic variations affecting immune components between different individuals or populations.

3.4. Human T lymphotropic virus type 1 (HTLV-1)

HTLV-1 is mostly known for causing HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) but has also been associated with the development of other diseases such as SS and uveitis (Gessain et al. 1985; Romanelli et al. 2010). A possible trigger for these diseases could be the infection of CD4+ T-cells by HTLV-1, leading to changes in the levels and/or activity of key transcription factors and mediators of signalling pathways mainly due to the activity of Tax, an HTLV-1 protein that plays a key role in viral transcription and affects the expression of several cellular transcription factors such as activator protein 1 (AP-1), serum response factor (SRF), NF-κB and cAMP response element binding protein (CREB) (Best et al. 2009; Satou and Matsuoka 2010; Fuzii et al. 2014).

Several groups studied HAM/TSP patients and found that the level of expression of the Treg-defining transcription factor forkhead box P3 (FOXP3) gene was low in these subjects consequently resulting in decreased levels of anti-inflammatory cytokines produced by Tregs such as IL-10 and TGF-β (Brito-Melo et al. 2007; Toulza et al. 2008; Yamano et al. 2009; Satou and Matsuoka 2010). One study suggested an association between a Tax-mediated persistent immune response in HAM/TSP patients and the simultaneous decline in the numbers of $FoxP3^{+}$ Tregs and expansion of $FoxP3^{-}$ Tregs capable of secreting the pro-inflammatory cytokine IFN-γ (Yamano et al. 2009). Other autoimmune-related cytokines were found to be increasingly secreted by HAM/TSP-derived CD4+ T-cells infected with HTLV-1 including IL-1, IL-6 and TNF-α (Araújo et al. 2009; Best et al. 2009; Castro-Costa et al. 2009; Romanelli et al. 2010).

Moreover, HTLV-1 infected T-cells and DNA from HTLV provirus were detected in the synovium and synovial fluid of RA patients. Increased anti-HTLV-1 antibody titers have also been noticed in RA and ACTD patients (Nishioka et al. 1993; Eguchi et al. 1996; Yakova et al. 2005; Brzustewicz and Bryl 2015). In addition, examination of patients suffering from HTLV-1-related diseases of the joint found Tax mRNA to be expressed in their synovial cells (Nishioka et al. 1993).

One study found that, after co-culture of salivary gland epithelial cells (SGECs) with HTLV-1-producing HCT-5 cells, HTLV-1 pro-viral DNA was determined to be present in SGECs by in-situ PCR and some of the SGECs became positive for nuclear NF-kB p65, a transcription factor known to be activated by HTLV-1. In addition, a higher expression of pro-inflammatory cytokines and chemokines including chemokine C-C motif ligand 5 (CCL5) and C-X-C motif chemokine 10 (CXCL10) also known as IFN-γ induced protein 10 (IP-10) was observed (Nakamura et al. 2015), indicating that HTLV-1 infects and induces alterations in SGECs, which may demonstrate its possible involvement in the development of SS. On the other hand, a potential role for HTLV-1 in exacerbating SS has been indicated by studies showing a higher level of mononuclear cell proliferation in HTLV1-infected individuals compared to non-infected SS patients (Vernant et al. 1988; Eguchi et al. 1992; Nakamura et al. 2015). Furthermore, multiple studies have also associated HTLV-1 with SLE while others found no link between the virus and this disease. Thus, this association remains a matter of debate (Olsen et al. 1987; Magistrelli et al. 1999; Akimoto et al. 2007; Sugimoto et al. 2007; Shirdel et al. 2013, p. 20).

3.5. Measles virus (MV)

MV has been mostly associated with MS. Studies have reported the presence of anti-MV antibodies in the CSF of around 75% of MS patients (Reiber et al. 1998; Ahlgren et al. 2011). Other groups found that MV-directed antibody titres were higher in sera of MS patients compared to healthy controls (Adams et al. 1970; Panelius et al. 1973; Ahlgren et al. 2011). Normally, anti-MV IgG antibody levels decrease with age in the aftermath of either a measles infection or vaccination (Krugman 1983; Davidkin et al. 2008), however, one study found that MV antibody levels in both serum and CSF increased over time in MS patients (Ahlgren et al. 2012). In addition to MS, the occurrence of high anti-MV antibody titres has been reported by multiple groups in patients suffering from different diseases including discoid lupus erythematosus (Phillips and Christian 1970; Hollinger et al. 1971; Kalliomäki and Halonen 1972; Laitinen and Vaheri 1974) and chronic active hepatitis (Triger et al. 1972; Closs et al. 1973; Laitinen and Vaheri 1974). In the latter, an association has been made between the increased MV antibody titres, and the presence of anti-nuclear antibody in

addition to autoantibodies targeting the smooth muscle (Triger et al. 1974).

3.6. Enteroviruses

Enterovirus B serotype (CV-B), a group of the *Enterovirus* CV serotype formerly referred to as Coxsackievirus, has been associated with T1D (Hyöty and Taylor 2002). Similar to HCMV, CV-B4 infection triggers the autoreactivity of T-cells through a mechanism of molecular mimicry, likely due to the homology between sequences of the CV-B4 P2-C protein and GAD, a protein of the human islets of Langerhans (Kaufman et al. 1992). Bystander immune system activation was also proposed to play a role in CV-B4-induced T1D, since the increased phagocytosis of CV-B4-infected islet cells and consequent presentation of host islet antigens by APCs is believed to lead to an immune response directed towards islet cells causing damage that subsequently leads to the development of T1D (Horwitz et al. 2002; 2004).

Multiple studies have reported the occurrence of anti-CV-B3 IgM antibodies in a higher percentage of patients suffering from chronic myocarditis and other diseases of the heart muscle than in other patients with cardiomyopathies related to different causes (Maisch et al. 1979; 1982; McCartney et al. 1986). Molecular mimicry may also play a role in CV-B3-triggered cardiomyopathies since auto-antibodies targeting heart tissues in patients with heart muscle diseases could be separated from patient sera by using CV-B viral particles as adsorbents (Maisch 1986) suggesting the presence of epitopes possessing similar amino acid sequences in CV-B and heart tissue antigens. Many studies have since examined the involvement of enteroviruses in autoimmunity, particularly CV-B, through different approaches. Using a mouse model, a study in 1987 identified cardiac myosin as the prime target for autoantibodies induced by CV-B3 infection (Alvarez et al. 1987). Interestingly, another group adsorbed lymphocytes from CV-B3-infected mice to monolayers of myocytes among other cell types and transferred the adherent population into non-infected mice, which subsequently developed myocarditis and pancreatitis. In this study, CD4+ cells were determined to be the mediators of CV-B3-induced inflammation, which was confirmed by positive selection of lymphocyte subpopulations prior to transfer (Blay et al. 1989). Later, antigenic determinants of the adenine nucleotide translocator (ANT) were also reported to have an undetermined degree of homology with those of CV-B3 (Schwimmbeck et al. 1993). Moreover, different CV-B proteins were found to have different degrees of sequence homology (all >50%) with human actins A, B and C; a list of these sequences can be found in a study by Root-Bernstein and colleagues (Root-Bernstein et al. 2009). Recently, a study indicated that Progranulin, an endogenous antagonist of TNF receptor signalling, attenuates CV-B3-induced myocarditis in a mouse model by downregulating Th1 and Th17 cell responses, suggesting that Th1 and Th17 play a major role in the development of CV-B3-induced myocarditis and pointing at a potential new therapeutic target and biomarker for inflammation to monitor in human disease (Li et al. 2018).

3.7. Rubella virus (RV)

Infection with RV leads to the development of Rubella (also referred to as German measles), a self-limited disease with mild symptoms such as low-grade fever, lymphadenopathy and a characteristic rash (Parkman 1996). RV has been linked with autoimmune diseases including diseases of the thyroid (Takasu et al. 2005; Tozzoli et al. 2008); however, it has mostly been associated with T1D (Ginsberg-Fellner et al. 1984; Banatvala and Brown 2004). Transmission of RV from the mother to the fetus mostly during the first trimester may lead to the development of congenital rubella syndrome (CRS) where anomalies in the formation of different organs occur (Webster 1998). Increased prevalence of the HLA-DR3 haplotype in CRS patients represents strong genetic evidence of T1D association, (Rubinstein et al. 1982; Banatvala and Brown 2004) since HLA-DR3 is considered to be a predisposing haplotype to autoimmune T1D development (Dembic 2015). Other studies on CRS/T1D patients found self-reactive antibodies targeting pancreatic tissues (Ginsberg-Fellner et al. 1984; Rabinowe et al. 1986). Animal studies have also demonstrated that diabetes can be triggered in hamsters through infection of neonates with RV (Rayfield et al. 1986). Similar to HCMV and *Enterovirus* CV serotype, a mechanism of molecular mimicry has been proposed to govern the harmful inflammatory process mediated by RV whereby T-cells from CRS/T1D patients are reactive to two RV peptide sequences RVE1[157→176], RVE2[87→;107] in addition to the human GAD protein (Ou et al. 2000). On the other hand, the development of pulmonary and skin pathological changes in paediatric CRS patients in addition to lymphocyte infiltration found in post-mortem pancreatic samples from paediatric CRS patients may indicate that particular autoimmune processes take place in these subjects (Rabinowe et al. 1986; Ou et al. 2000;

Banatvala and Brown 2004; Burgess and Forrest 2009). Furthermore, one study investigated the presence of RV-directed antibodies in patients with different autoimmune diseases and found a notable higher frequency of IgM and IgG rubella-directed antibodies in these tested individuals compared to healthy control subjects (Altman et al. 2012), however, the study does not specify whether tested patients were undergoing immunosuppressive therapy, which can significantly affect the observations made.

3.8. Flaviviruses

3.8.1. Hepatitis C virus (HCV)

Multiple studies have shown an association between HCV and Hashimoto's thyroiditis (HT), a chronic inflammatory disease of the thyroid that mainly causes hypothyroidism (Huang et al. 1999; Salazar et al. 2010; Choubey and Moudgil 2011). A substantial fraction of chronically HCV-infected individuals has been reported to have mild hypothyroidism (Preziati et al. 1995; Marazuela et al. 1996). Upon studying the pathophysiology of HCV-related diseases of the thyroid, Akeno et al. (Akeno et al. 2008) detected the expression of the HCV receptor CD81 on thyroid cells. The study also found that incubation of thyroid cells with E2, a glycoprotein from the HCV envelope, leads to the attachment of E2 to the cells and subsequent release of IL-8, a chemokine that plays a key role in the development of inflammation (Akeno et al. 2008).

An HCV association with other autoimmune diseases, such as SS and RA, is not very well-established. Sporadic studies attempted to find a potential link between HCV and SS, however, these attempts resulted in linking HCV infection to sialadenitis; a condition that is comparable to SS clinically and histologically (Koike et al. 1997; Scott et al. 1997). Multiple other studies have reached similar conclusions indicating that it is difficult to specify whether HCV plays a role in the development of SS itself, or merely an SS-like condition (reviewed in (Carrozzo 2008). More recently, a study in Spain found HCV IgG antibodies in 13% of tested SS patients (Brito-Zerón et al. 2015) and another nationwide population-based study on a large number of subjects in Taiwan showed a significant correlation between the occurrence of SS and infection with HCV (Yeh et al. 2016). On the other hand, a study by Zehairy et al. (2012) examined HCV-infected arthropathic patients and other HCV-free RA patients and found a fundamental disparity between RA and HCV-associated arthropathy, which has been confused before for HCV-associated RA. The study also determined that the best way to identify RA is by anti-CCP antibody detection, which in this case was above 80% in RA patients and lower than 5% in HCV-infected subjects suffering from diseases of the joints (Zehairy et al. 2012). Several mechanisms have been proposed to explain HCV-associated joint diseases; the most prominent two being HCV mixed cryoglobulinemia and cytokine-induced inflammatory response triggered by direct synovial invasion by the virus (Aktas et al. 2017).

3.8.2. Other flaviviruses

The main finding providing a link between Flaviviruses and autoimmunity is the increase in MHC-I expression on the surface of different types of host cells following infection with West Nile virus (Lobigs et al. 1996; Kesson et al. 2002), Yellow Fever virus, Dengue virus, Murray Valley Encephalitis virus, Kunjin virus and Japanese Encephalitis virus (JEV) (Lobigs et al. 1996). It has been suggested that due to high levels in MHC-I expression, auto-reactive cytotoxic T-cells are activated and subsequently mount an attack against host tissues leading to the development of autoimmune diseases such as polymyositis (Bao et al. 1992).

A study reported the discovery of T-lymphocytes responding by expansion when stimulated with MBP in addition to anti-myelin antibodies in mice infected with JEV (Tseng et al. 2011). This finding may explain typical observations in the CNS of JEV-infected mice such as encephalomyelitis encompassing different regions of the brain and the spinal cord (Kalita and Misra 2002; Ghosh and Basu 2009), whereby death of neurons with subsequent demyelination and axonal injury can be observed (Tsunoda et al. 2003). Another possible explanation for loss of myelin could be the JEV-induced death of oligodendrocytes responsible for myelin formation (Mason et al. 2000). Swarup et al. (2007) also showed that JEV infection markedly decreases the levels of the anti-inflammatory cytokine IL-10 in the CNS of mice, and that this decrease correlates directly with neuronal death in addition to a subsequent increase in IL-1β and TNF-α levels thus inducing/exacerbating inflammatory reactions in the CNS.

3.9. Parvovirus B19 (PVB19)

PVB19 has been often associated with multiple types of autoimmune diseases including RA (White et al. 1985; Kerr et al. 1996; Murai et al. 1999), SLE (Chassagne et al. 1993; Tanaka et al. 1998; Dorsch et al. 2002; Sève et al. 2004), SS (Ramos-Casals et al. 2000), SSc (Ferri et al. 1999; 2002; Zakrzewska et al. 2009), Still's disease (Blidi et al. 1996), granulomatosis (Nikkari et al. 1994),

systemic vasculitis (Chakravarty and Merry 1999), Kawasaki disease (Nigro et al. 1994; Yoto et al. 1994), Henoch-Schönlein purpura (Diaz and Collazos 2000; Cioc et al. 2002; Quéméneur et al. 2002), dermatomyositis (Lewkonia et al. 1995; Chevrel et al. 2000; Crowson et al. 2000), systemic juvenile idiopathic arthritis (Godeau et al. 1995; Longo et al. 1998), giant cell arteritis (Gabriel et al. 1999; Salvarani et al. 2002), and polyarteritis nodosa (Corman and Dolson 1992). Moreover, numerous studies have demonstrated the presence of autoantibodies against various host antigens such as anti-reticulin, smooth muscle and parietal cell antigens-directed auto-antibodies (Kerr et al. 1996b), anti-host DNA (Soloninka et al. 1989), anti-phospholipid (Johnston et al. 2000; Landenberg et al. 2003), anti-nuclear and rheumatoid factor auto-antibodies (Sasaki et al. 1989) in patients infected with PVB19. Furthermore, antibodies against the PVB19 proteins Vp1 and Vp2 have been shown to cross-react with multiple host antigens, such as human cytokeratin and GATA1 in addition to murine collagen, cardiolipin, keratin and denatured DNA (Lunardi et al. 2008).

4. Conclusion

The development of autoimmunity mostly depends on a combination of different factors such as genetic predisposition, a defective immune response and environmental triggers such as viral infections. The level of contribution of each of these factors, including viral infections, to the initiation of autoimmune diseases, is still not clear and current evidence is still unable to irrefutably indicate the degree of involvement of each element. As discussed above, conflicting data have been reported for some viruses. Lack of reproducibility and weak study design, such as, small cohort sizes in certain cases, have complicated establishing associations. It is also worth noting that a large portion of autoimmune disease patients are treated with immunosuppressive medications, which could contribute to the exacerbation of an infection or creating a suitable environment for a latent virus to reactivate and replicate hence creating the impression that the development of the disease in question is associated with this particular pathogen in non-longitudinal studies. Therefore, the reliance on prospective cohort studies may circumvent some of the problems in the study design. Whether a certain pathogen contributes to the rise of an autoimmune disease or not, the sizeable amount of evidence associating the viral infections discussed within this review indicates that these viruses are at least capable of exacerbating a developing self-directed immune reaction.

On the other hand, the literature on autoimmune diseases mostly consists of studies that are based in Europe and the United States (Ramos-Casals et al. 2015; Vento and Cainelli 2016). Given the differences in genetic background across different populations and the triggers, viral or otherwise, these populations are exposed to; associations that are quite well-established in the developed world may not apply in less well-studied populations and countries. Therefore, research efforts attempting to further our understanding of the different triggers and enhancers of autoimmune pathways are crucial at this stage; such efforts may elucidate possible preventative measures as well as treatments that account for infections that may initiate or exacerbate autoimmune processes.

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