

Review Article

Human Cytomegalovirus and Autoimmune Disease

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Received 27 January 2014; Accepted 17 March 2014; Published 29 April 2014

Academic Editor: Tsai-Ching Hsu

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Human cytomegalovirus (HCMV) represents a prototypic pathogenic member of the β -subgroup of the herpesvirus family. A range of HCMV features like its lytic replication in multiple tissues, the lifelong persistence through periods of latency and intermitting reactivation, the extraordinary large proteome, and extensive manipulation of adaptive and innate immunity make HCMV a high profile candidate for involvement in autoimmune disorders. We surveyed the available literature for reports on HCMV association with onset or exacerbation of autoimmune disease. A causative linkage between HCMV and systemic lupus erythematosus (SLE), systemic sclerosis (SSc), diabetes mellitus type 1, and rheumatoid arthritis (RA) is suggested by the literature. However, a clear association of HCMV seroprevalence and disease could not be established, leaving the question open whether HCMV could play a coresponsible role for onset of disease. For convincing conclusions population-based prospective studies must be performed in the future. Specific immunopathogenic mechanisms by which HCMV could contribute to the course of autoimmune disease have been suggested, for example, molecular mimicry by UL94 in SSc and UL83/pp65 in SLE patients, as well as aggravation of joint inflammation by induction and expansion of CD4⁺/CD28⁻ T-cells in RA patients. Further studies are needed to validate these findings and to lay the grounds for targeted therapeutic intervention.

1. Introduction

Autoimmune disease (AID) is a complex dysregulation of immunity, resulting in loss of self-tolerance and subsequent assault on endogenous tissue or cells. Onset of autoimmunity depends both on genetic and environmental factors (e.g., viruses) and is typically driven by antibodies or T-cells reacting against self-epitopes. Self-reactive immune responses can occur only transiently and may not necessarily cause overt disease, but in many cases self-destruction of initially healthy tissue gets permanently out of control, resulting in self-perpetuating clinical disease progressing in the absence of the triggering event.

Infection with Epstein-Barr virus (EBV), a human pathogenic γ -herpes virus, has been linked with the risk to develop multiple sclerosis (MS), an autoimmune disorder of the central nervous system characterized by the formation of lesions, inflammation, and the destruction of myelin sheaths of neurons [1]. A similar matter of recent debate is if and how infection with human cytomegalovirus (HCMV),

another human herpes virus, could be linked with certain autoimmune diseases and how both conditions could interfere with each other. Several features including its extensive manipulation of adaptive and innate immune functions [2–5], the very large coding capacity [6], its lytic replication in multiple tissues [7] both locally and systemically, its lifelong persistence during subsequent phases of latency and reactivation, and its ubiquitous prevalence in human populations readily explain why HCMV was frequently linked with AID but also with further acquired disorders like arteriosclerosis and vascular disease [8], immune aging [9], and certain types of tumors [10].

Hypothetically, the mutual influence of HCMV infection and autoimmunity could have different consequences. HCMV infection could cause, promote, or prevent AID, while conversely AID could inhibit or support HCMV reactivation from latency and/or replication. Given the fact that productive infection of HCMV usually results in cell death and thus impedes tissue integrity, HCMV replication

may enhance tissue damage caused by autoimmune pathologies. Conversely, anti-inflammatory activities known to be associated with HCMV infection could also exert protective effects on the course of autoimmune diseases. On the other hand, inflammation of tissues due to AID may generate an environment preventing the reactivation and growth of HCMV, or, depending on the prevailing factors, exert proviral effects and support productive infection.

While mutual influences of HCMV infection and established AID are consequently unavoidable, any causal relationship is much harder to substantiate. A frequently discussed phenomenon in the case of turning the immune system against self-epitopes is “molecular mimicry” [11, 12]. According to this concept pathogenic foreign epitopes are highly similar to host determinants and, therefore, after activation of the immune system result in self-attack. So far, a handful of pathogenic epitopes have conclusively been shown to trigger autoimmunity by molecular mimicry [13]. However, in many cases where viruses are found to coincide with the onset of autoimmune disease, such an epitope has not been identified. Apart from that, during infection the immune system will be strongly activated: cells destroyed by viruses or by immune attack can further activate dendritic cells and macrophages. Infected tissue and activated antigen presenting cells (APC) will attract immune cells producing high levels of cytokines and chemokines, which facilitate a so-called “bystander activation” and lower the threshold for a loss of tolerance.

This review attends to give an overview of the role of HCMV for initiation and/or exacerbation of autoimmune responses. The search for published data was performed using the PubMed database and entering the keywords “cytomegalovirus” and “autoimmunity.” The autoimmune diseases, which were found most often in combination with both keywords, were then searched again in combination with cytomegalovirus alone. These diseases were systemic lupus erythematosus (SLE), systemic sclerosis (SSc), type 1 diabetes (T1D), multiple sclerosis (MS), and rheumatoid arthritis (RA).

2. HCMV Pathogenesis and Modulation of the Immune System by HCMV

HCMV represents a human pathogenic herpes virus belonging to the subfamily of *Betaherpesvirinae*. As all herpes viruses HCMV have a large double-stranded DNA genome and possess a formidable coding capacity giving rise to more than 750 translational products [6] and a multitude of virus-encoded miRNAs in infected cells [14, 15], reflecting the exceptional power and ability of this virus to manipulate and cope with the host. During coevolution over millions of years HCMV adapted closely to the human host and today infects 40–99% of the adult populations depending on ethnic and socioeconomic conditions. Infection in immunocompetent individuals normally proceeds unperceived. After primary infection of diverse cell types (e.g., epithelial cells of the liver, lungs, kidney, salivary glands, large intestine, placenta endothelial cells, smooth muscle cells, fibroblasts, neuronal

cells, and various myeloid cells [7]), HCMV remains latent in CD34+ myeloid progenitors, from which reactivation and recurrent replication can emerge. Even though a healthy immune system controls HCMV replication, the infection can neither be eliminated by immune functions nor by antiviral drugs, precluding a state of sterile immunity. Upon failure or reduced efficiency of specific immune functions, opportunistic HCMV infections may lead to severe or even fatal illness. Common clinical findings in immunocompromised patients are fatigue, hepatitis, enterocolitis, encephalitis, pneumonitis, bone marrow failure and in AIDS patients also retinitis [16]. Moreover, HCMV infection is associated with a diminished graft survival in organ transplant recipients. Congenital HCMV infections are a leading cause of sensorineural hearing loss and permanent disability in infants [17].

Immune control of primary and latent HCMV infection is organized in a hierarchical but also redundant manner [18–20], with prominent roles for type I and type II interferons, NK cells, and CD8+ but also CD4+ T-cells, while antiviral antibodies are essential to restrict dissemination of recurrent virus. Even if a healthy immune system successfully controls infection, HCMV leads to permanent changes in the composition of immune cell populations. Steadily expanding CD8+ T-cells specific for a few HCMV epitopes dominating the memory CD8+ T-cell population is a hallmark of CMV infection and not observed for other viruses [21]. In the elderly HCMV-specific CD8+ T-cells may cover more than 20% of circulating CD8+ cells [22], a phenomenon called “memory inflation.” In addition, a higher frequency of HCMV specific CD4+ T-cells can be observed in HCMV positive persons. These cells exhibit a CD4+/CD28– phenotype and are classified as terminally differentiated effector memory cells [23]. Recently, a role for HCMV in early aging of the immune system or “immune risk phenotype” (IRP), measured as inverted CD4 : CD8 ratios, was linking HCMV to immunosenescence [24] and impaired responsiveness to vaccination [9], with possible effects seen already in young adults [25]. Moreover, induction of IL-6 and TNF α has been described in HCMV-positive persons [9].

Furthermore, HCMV infection results in expansion of a NK cell subset expressing activatory CD94/NKG2C receptors *in vivo* and *in vitro* [26, 27]. Independently, HCMV induces the expansion and differentiation of killer cell immunoglobulin like receptor (KIR)-expressing NK cells, manifesting as stable imprints in the NK cell repertoire. Obviously, HCMV-induced education by inhibitory KIRs is promoting a clonal-like expansion of NK cells, causing a bias for self-specific inhibitory KIRs [28]. *In vitro* analysis revealed also a HCMV-driven growth potential of additional NK cell subpopulations characterized by inhibitory KIR2DL1 and KIR2DL3 as well as activatory KIR3DS1 receptors [29].

Once infected, cells become tightly controlled by HCMV, expressing numerous regulators of the cell cycle, apoptosis, cell signaling pathways, antigen presentation, and so forth (see Table 1). To date, the molecular understanding of HCMV interference with T cell responses, NK cell activation and effector function, IFN-induction, and IFN receptor signaling

TABLE 1: Immunomodulatory functions by HCMV.

Gene	Phenotype/suggested mechanism	Reference
T-cell responses		
US2	Degrades MHC class I and II	[30, 31]
US3	Retention of MHC class I complexes, mislocalization of MHC class II	[32, 33]
US6	Inhibits the peptide transporter TAP	[34, 35]
US11	Degrades MHC class I	[36]
US8	Binds MHC class I heavy chains, function unknown	[37]
UL18	Inhibits MHC I interaction with the PLC	[38]
miR-US4-1	Targets Erap1	[39]
?	Disturbed interaction between MHC class I and the PLC	[40]
UL11	Interacts with CD45	[41]
NK and NKT cell responses		
UL16	Intracellular retention of MICB and ULBP1 and 2	[42]
UL18	LIR-1 activation	[43]
UL40	Encodes a signal peptide for HLA-E	[44]
UL142	MICA and ULBP3 inhibition	[45, 46]
miR-UL112	MICB downregulation	[47]
UL83	Inhibition of NKp30	[48]
TRL11	Inhibition of CD16 activation	[49]
UL119-118; TRL11	Inhibition of CD16 activation	[49]
US10	Downregulates HLA-G	[50]
US2	Inhibits CD1d	[51]
Cytokines, chemokines, chemotaxis		
US28	Chemokine receptor; promotes chemotaxis; potential chemokine trap	[52, 53]
US27	Enhancement of CXCR4 signaling	[54]
UL33	GPCR family; modulates CCR5 and CXCR4	[55]
UL111a	vIL-10; hIL-10-like functions	[56, 57]
UL111a	LAvIL10; downregulates MHC class II expression	[58]
UL146	vCXCL1, hCXCR1/hCXCR2-specific chemokine; promotes neutrophil chemotaxis	[59]
UL147	IL-8 similarity	[60]
UL21.5	Sequesters RANTES; binds CCL5 and prevents host cell signalling	[61]
UL128	Increases TNF α and IL-6 expression by PBMC; promotes PBMC migration	[62]
UL78	GPCR family member; modulates CCR5 and CXCR4	[55]
Modulation of IFN and TNF signaling		
UL138	Upregulates TNF α R1	[63, 64]
UL144	TNFR homolog, inhibits T-cell prolif. via BTLA-4; induces CCL22	[65]
UL7	Inhibits inflammatory cytokine production	[66]
?	Jak1 degradation	[67]
?	STAT2 degradation	[68]
UL83	Suppresses type I IFN response and IRF3-induction	[69]
TRS1	Blocks PKR-mediated translation shut-off	[70]
UL126a	Inhibits OAS	[71]
UL123	Binds STAT2 and inhibits DNA binding; modulated phosphorylation state of IE1	[72]
UL122	Inhibitor of NF κ B; inhibition of IFN β transcription	[73]

TABLE 1: Continued.

Gene	Phenotype/suggested mechanism	Reference
Apoptosis		
UL37x1	Neutralizes Bax	[74]
UL36x1	Caspase-8 inhibitor	[75]
UL121/123	Inhibits apoptosis	[76]
Intrinsic immunity		
UL123	Disruption of ND10	[77]
UL82	Daxx inhibitor	[78–80]

as well as pathways of apoptosis is most advanced but is still representing only the tip of the iceberg.

The expression profile of infected cells becomes massively modified by HCMV due to (i) transcription of HCMV genes, (ii) extensive manipulation of the cellular transcriptome due to HCMV encoded transcription factors, and (iii) the expression of HCMV miRNAs which affect both HCMV and host transcription pattern. Thus HCMV infection must lead to extensive qualitative and quantitative changes of peptide ligands presented by MHC I and MHC II molecules which are not restricted to the emergence of viral epitopes but could include also novel endogenous self-epitopes on the cell surface. Given the massive interference of HCMV with host cell gene expression on the one hand and pathways of antigen presentation on the other hand the comprehensive analysis of MHC ligandomes is a paramount goal for future studies assessing potential pathogenic mechanisms that involve molecular mimicry between HCMV and individual self-peptides.

3. Prevalence of HCMV IgG in Patients with Autoimmune Disease

If HCMV plays any causative role for the pathogenesis and onset of autoimmunity, it should be expected that a higher prevalence of HCMV IgG antibodies is found in patients suffering from defined types of autoimmune diseases. To gain an overview of the frequency of HCMV infection in patients with autoimmune pathologies, published data were collected and HCMV seroprevalences in defined groups of patients in comparison to reported control groups were compiled (Table 2). In some of the listed reports HCMV was not the objective of the study but used as a control parameter for EBV seroprevalence. Most of the studies have been performed in patients suffering from SLE and MS, but also studies on SSc, T1D, RA, and Sjögren's syndrome (SS) have been reported. Taking all available studies into account it is conspicuous that no clear association of HCMV infection with a specific disease can be claimed. One difficulty in establishing a connection between AID and infection is the fact that HCMV is widespread in the human population while specific autoimmune diseases are rather rare, requiring large patient cohorts to provide sufficient statistical power. Since HCMV prevalence critically depends on factors like ethnicity, age, socioeconomic conditions, and sexual lifestyle it is of high importance to analyze appropriate control group matching

the patient cohort for all confounding factors. In many studies effort was given to control for age and ethnicity; however, in most cases the socioeconomic background was not accounted for. Moreover, the order of events (AID followed by HCMV infection versus HCMV infection followed by AID) was not distinguished in these studies.

3.1. *SSc*. The statistically highly significant association of HCMV infection in Swiss SSc patients (59% seropositivity in SSc patients compared with 12–21% in controls) [83] has not been observed in other studies so far [81, 82], even though higher HCMV antibody concentrations have been found in SSc patients [103, 104]. It should be mentioned that in SSc patients heterozygotes for *f* and *z* alleles of the Ig heavy chain an association with HCMV-specific antibodies was found, giving a hint for an important role of the genetic background [82].

3.2. *SLE*. Studies that found an association between HCMV and SLE disease were often performed in European countries [89–91]. Several other studies did not observe a direct association between HCMV seroprevalence and SLE [86–88]. In one of these studies HCMV seropositivity correlated significantly with Raynaud's phenomenon [90]. Further, another study reported on significantly more frequent HCMV specific IgM in SLE patients than in controls, but no difference in HCMV IgG prevalence was observed [85]. This finding could be an indication for more frequent HCMV reactivation events in SLE patients, which may occur as a result of immunosuppressive treatment. Also studies outside of Europe found higher frequencies of HCMV infection in SLE patients [81, 92] or higher HCMV IgG titers [105]. Moreover, in SLE patients with higher HCMV specific IgG titers more frequent autoantibodies could be detected [106]. It is peculiar however and not easily explainable that in that particular study a patient group positive for anti-HCMV IgM (and IgG) showed lower levels of autoantibodies against U1RNP/Sm and U1-70 k in comparison to the HCMV IgM(-)/IgG(+) group, suggesting a role for HCMV reactivation in regulation of autoantibodies.

Altogether, these findings are compatible with the notion that genetic factors in combination with HCMV infection play an important role for SLE disease onset.

3.3. *T1D*. In two independent Finnish studies no association between HCMV and onset of T1D in young children could

TABLE 2: Prevalence of HCMV specific IgG and IgM in autoimmune disease patients.

Nationality/ethnic background/group	Nr ^a	Age ^b	Disease		Group	Control group		HCMV seropositivity		Reference
			% IgG	% IgM		Nr	Age	% IgG	% IgM	
Systemic sclerosis										
Turkey	46	45	96		Primary antiphospholipid syndrome; healthy	38; 65	36; 35	95; 95		[81]
Caucasians	137		66		Patients with osteoarthritis, fibromyalgia, gout or regional musculoskeletal pain syndromes	145		69		[82]
Swiss	86	56	59	20	RA; osteoarthritis	43; 43	56	12; 21	7; 16	[83]
Systemic lupus erythematosus										
Turkey	198	38	100		Primary antiphospholipid syndrome; healthy	38; 65	36; 35	95; 95		[81]
French/inactive SLE; active SLE	76; 42	34; 35	76; 83		Healthy	31	33	58		[84]
Taiwanese	87		97	10	Cerebral vascular accident patients	97		100	1	[85]
variable	36	15	42		Matched sibling/relative/friend	36	16	47		[86]
African American	144		81	11	Randomly selected from driver's license agencies	72	Matched	79	8	[87]
White	86		55	9	Randomly selected from driver's license agencies	204	Matched	57	5	[87]
variable	196	45	66		Healthy	392	46	69		[88]
Norwegian	20	54	95	45	Healthy	26	49	69	4	[89]
Italian	60	41	82	5	Blood donors	100	40	69	3	[90]
British	97		91		RA; healthy	50; 97		64; 43		[91]
Variable	117	<20	36		Healthy	153	Matched	26		[92]
Type 1 Diabetes Mellitus										
Finnish	169	1.3	23		Healthy, matched for <i>HLA-DQB1</i>	791	1.3	26		[93]
Finnish	90	<7	47	4	Healthy	90	<7	42	4	[94]
Finnish	11	<2	18		Healthy siblings	11	<2	56		[94]
Multiple sclerosis										
Swedish	658	35	57		Healthy	786	36	65		[95]
Iranian	78	29	98		Healthy	123	29	52		[96]
Variable (USA)	189	15	28		Healthy	66	15	36		[97]
variable	144		50		Healthy	288		56		[1]
Norwegian	144	39	63		Traumatic fractures or rupture, gynaegological or plastic surgery disorder	170	40	69		[98]
Spanish	41	39	78		OND (other neurological disease)	31	48	85		[99]
Rheumatoid Arthritis										
German	202		57		Blood bank	272	Matched	54		[100]
Swiss	43	56	12	7	Osteoarthritis	43	56	21	16	[83]
English	50		64		Healthy	97		43		[91]

TABLE 2: Continued.

Nationality/ethnic background/group	Nr ^a	Age ^b	Disease		Group	Control group		HCMV seropositivity		Reference
			HCMV seropositivity % IgG	% IgM		Nr	Age	HCMV seropositivity % IgG	% IgM	
Autoimmune thyroid disease										
Greece	34	10	50		Healthy	31	9	55		[101]
Sjögren's syndrome										
English	24		79		Healthy (dental treatment)	24	Matched	63		[102]

^aNumber of subjects.

^bMedian age of subjects.

be established [93, 94]. This result confirms a Swedish study determining the prevalence of T1D after congenital HCMV infection [107]. A single case report has been published, in which a congenitally HCMV infected child developed T1D already at the age of 13 months [108]. Thus this might represent an isolated case that occurred in combination with other unknown factors. The reported frequent finding of HCMV genomes in PBMNCs of Canadian T1D patients [109] is therefore not supported by the Scandinavian studies mentioned above, suggesting that HCMV could display a risk only for a subpopulation of affected children, rather than playing a major role for the etiology of T1D.

3.4. MS. In several studies HCMV has been found to negatively associate with MS [95, 97, 110]. Only one out of six studies listed here noted a higher HCMV prevalence in MS patients [96]. Whether this is a specific property of the Iranian population or if other factors might have made an impact on this study is not clear. It is interesting though that in mice a protective role for mouse CMV (MCMV) on Theiler's murine encephalitis virus induced murine model of MS has been described. Improved motor performance and a significant reduction of brain infiltrating CD3+ cells were described as a result of MCMV infection [111].

3.5. RA. Only few studies were found that have determined HCMV seroprevalence in RA patients: whereas higher HCMV coincidence with RA was found in one report [91], the two others did not observe this [83, 100]. All studies were carried out in Europe.

3.6. SS. Using only a low number of subjects no significant correlation between HCMV seropositivity and Sjögren's syndrome could be established [102], whereas in another study with small numbers of study participants higher HCMV antibody titers were reported [112].

3.7. Summary. According to the studies evaluated here, there is no evidence that HCMV plays a role for the onset of T1D and MS. However, concerning SLE and SSc it cannot be ruled out that HCMV indeed may play an active role in the induction of disease depending on largely unknown genetic factors. A number of case reports underline this possibility (SSc: [113]; SLE: [114–116]). For a rejection or confirmation

of the HCMV hypothesis in the induction of SSC and SLE and a better clarification of HCMV-associated risk factors population-based prospective studies must be performed in the future.

4. Relevance of HCMV Molecular Mimicry and Bystander Effects in Autoimmune Disease

Crossreactive TCRs or immunoglobulins expressed by T- or B-cells, respectively, that have been primed against a pathogenic structure might recognize self-epitopes due to their sequence or structural similarity. This is the basis for molecular mimicry, which has been proposed to underlie aetiologically some autoimmune diseases initiated by pathogens [117]. It has been suggested that HSV-1 encoded UL6 (residues 299–314) induces autoreactive T-cells causing herpetic stromal keratitis [118]. It is a matter of debate, though, whether molecular mimicry is the key to disease development or if crossreactivity in combination with bystander functions and tissue damage is necessary to set off pathologic immune responses [119–121].

The DNA genome of HCMV encompasses about 230 kbp and was initially estimated to encode for around 200 proteins [122]. By ribosome profiling this number was recently readjusted to more than 750 encoded translational products [6]. In the context of productive infection, this massive number of proteins confronts the host with plenty of antigens, against which the immune system is simultaneously primed or boosted, thereby raising the likelihood of priming immune cells against a crossreactive epitope and taking the risk of bystander activation. So far, however, no HCMV encoded antigen has been clearly linked to an autoimmune disease.

4.1. HCMV and SSc. SSc is a connective tissue disorder with abnormal fibroblast cell proliferation. Endothelial cell activation leads to vascular pathology and over time to neointima formation in small and medium sized arteries. Typically, there is an increase in CD4+ and decrease in CD8+ T-cells numbers. Self-reactive antibodies against determinants of endothelial cells and topoisomerase have been shown to correlate with disease activity [123].

Interesting observations have been made concerning antibodies against the HCMV encoded protein UL94. Using

a random peptide library, a peptide sequence could be identified, against which 84 out of 90 SSc patients displayed antibodies. The purified antibody bound to the cellular integrin-NAG-2 complex and UL94 (possibly also hnRNP proteins and cytochrome C) [124]. However, when reactivity against the UL94-derived peptide was determined, only 55 out of 90 patients were found to have antibodies against the peptide, raising the question whether the SSc specific antibodies were crossreactive with UL94 rather than vice versa. Information about the HCMV serostatus of the patients was not provided.

The SSc antibody was found to bind to NAG-2 both on endothelial cells and fibroblast, which resulted in major changes of the expression pattern that could be linked to previous observations in SSc patients [125]. Antibody binding to NAG-2 on endothelial cells leads to apoptosis, whereas apoptosis was not induced in fibroblasts [124, 125].

Further, the level of UL94-reactive antibodies was analysed in patients with diffuse (more prominent vascular disease) and limited forms of SSc [126]. Patients with diffuse SSc had significantly higher levels of the UL94-reactive antibody, pointing at a possible role for HCMV in disease aggravation. However, again, the HCMV serostatus of these patients was not reported. In addition to the possibility that a *de novo* antibody response against UL94 upon HCMV infection is the reason for these antibodies to arise, it is also possible that the patients might have developed these antibodies independently of HCMV, or the patients were prone to develop the antibodies and HCMV lowered the threshold and caused loss of tolerance. In the latter case, it could be possible that also another pathogen might induce such an event. To corroborate this sequence of events, further studies are needed. It should be established whether the UL94-reactive antibody is actually a true anti-UL94 antibody and, hence, associated with a positive HCMV serostatus. Are these antibodies also found in healthy HCMV positive persons and, furthermore, do HCMV negative SSc patients have less or no activity against NAG-2 and UL94?

Analysis of peptides recognized by antitopoisomerase I antibodies revealed a homologous peptide sequence present in the UL70-encoded polypeptide [127]. Experimental data that this peptide is indeed recognized by such autoantibodies is not available so far.

Evidence for association of HCMV with SSc disease is still diffuse. However, Pandey and LeRoy hypothesized HCMV to be an amplifier of SSc in a review of possible mechanisms by which HCMV could contribute to autoimmune vasculopathies [128]. Interestingly, mice with a deficiency in IFN- γ signaling (IFN- γ R KO) and increased susceptibility to MCMV showed signs of neointima formation [129]. If SSc-like disease manifestations could be found in this situation, this model could provide insight into the pathophysiology of HCMV infection eventually leading to SSc disease.

4.2. HCMV and SLE. Characteristic for SLE is apoptosis of endothelial cells and following atherosclerotic plaque development. Autoantibodies directed against nuclear structures (e.g., antinuclear antibodies, ANA and anti-dsDNA) are detectable years before onset of disease [130] and their levels

correlate with disease severity. It is not clear though to what extent DNA antibodies contribute to the disease but immune complexes are found in temporal and spatial association with glomerular inflammation. Notably, antinuclear and anti-dsDNA antibodies were found in patients suspected to have an onset of SLE as a consequence of HCMV infection [131].

The UL83-encoded pp65 matrix protein has been linked to autoantibodies in SLE patients. Elevated levels of anti-pp65 antibodies were found in SLE patients compared to controls and CTD (connective tissue disease) as well as RA patients. However, in SLE patients also elevated levels of another tegument protein, pp150, were found [132], raising the possibility that anti-CMV antibodies were generally induced in these patients. In this particular publication it was also reported that an UL83-encoding plasmid used for immunization of NZB/W F1 mice caused production of anti-dsDNA and antinuclear antibodies, leading to more severe signs of glomerulonephritis than control plasmid immunization [132].

In a second study it was found that ca 75% of pp65 reactive antibodies from controls (healthy, RA, SS, and SSc patients) recognized the N-terminus, whereas antibodies from SLE patients were predominantly (70%) reactive against the C-terminus (amino acids 336–379) of pp65 [133]. BALB/c mice were immunized with peptides corresponding to the amino acids 1–167 or 336–439 of pp65 together with the complement component C3d as an adjuvant and the crossreactivity of the raised antibodies was analyzed. Antinuclear and anti-dsDNA antibody activity could be measured and mice immunized with the C-terminal peptide showed signs of IgG deposition on glomeruli. The C-terminal peptide resulted in antibodies reactive against HeLa cell lysates (as a measure of crossreactivity); it should be noted though that the reactivity against lysates from HCMV infected cells was also higher for these antibodies [133].

It would be of high priority to learn whether possible crossreactivity also exists for anti-pp65 antibodies isolated from the SLE patients, especially the C-terminal reactive antibodies, which showed a higher incidence in SLE patients.

In addition, a HCMV gB expressing adenovirus induced antibodies against dsDNA and the U1-70 kDa spliceosome (U1-70 k) protein in immunized mice [134]. In humans, however, conflicting data are reported on U1-70 k autoantibodies in healthy HCMV positive persons. Serum from healthy persons screened within a vaccination study was tested for the presence of U1-70 k autoantibodies and an increase in frequency and quantity in HCMV positive persons was found [135]. The authors suggested that HCMV may play a role in inducing autoimmune disease in a subset of these individuals. In contrast, in a following study no indications for a higher frequency of SLE autoantibodies were found in sera from healthy volunteers vaccinated with the Towne strain [136]. This latter finding was confirmed by a study applying vaccination using soluble recombinant gB in combination with an adjuvant MF59 and gB expressed by a recombinant canarypox virus [137], leaving the question concerning the relation between gB antibodies and autoantibodies open.

4.3. HCMV and T1D. So far unknown mechanisms by which HCMV could interfere with immunity and cause T1D have been postulated. For instance, HCMV inclusion bodies were found in pancreatic islet of children with fatal HCMV infection [138], suggesting that HCMV infection may cause immune reactions and destruction of these cells. However in other autopsy samples of pancreas tissue from T1D patients no indication for HCMV infection was found by nested PCR [139], even though the ability of HCMV to infect β -cells *in vitro* has been reported [140]. While HCMV- or immune-mediated cell death is a possible outcome of abortive HCMV infection, the data should be carefully interpreted since only IE1/pp72 and pp65 proteins were detected in these cultures. Firstly, pp65 protein is abundantly present in the HCMV particle and therefore viral *de novo* gene expression is not necessarily needed for detection of pp65 and, secondly, IE/pp72 expression is in most cases possible to detect after virus entry in various cells, also in nonpermissive cell types, but does not necessarily implicate successful HCMV replication. To prove this assumption, evidence of late gene expression or release of infectious viral progeny should be provided.

Moreover, mice vaccinated with the HCMV strain AD169 were found to produce antibodies against a 38 kDa human islet cell protein [141]. There is no further follow-up on this finding reported and the HCMV antigen possibly causing the crossreactive antibodies (the antigen should be a virion component since HCMV does not replicate in mouse cells) was not identified and it is also not clear with which host protein the antibodies may crossreact and whether the antibodies have indeed the potential to induce autoimmunity.

T-cells play a major role in destruction of pancreatic β -cells in T1D patients [142] and there is a strong correlation of T1D disease with certain alleles in the highly polymorphic MHC II locus [143]. It has been shown that GAD65 (glutamic acid decarboxylase) specific autoreactive CD4+ T-cells involved in T1D and stiff-man syndrome also recognize a HCMV UL57 derived peptide. The UL57 peptide can be processed and presented by dendritic cells, suggesting a potential involvement in loss of CD4+ T-cell tolerance to GAD65 [144].

5. T-Cells, HCMV, and RA

CD8+ T-cells are of particular importance to control HCMV replication. A hallmark of HCMV infection is the extraordinary expansion of HCMV specific CD8+ T-cells. It is becoming evident though that CD4+ T-cells might be even more important to prohibit HCMV associated disease [145] and that HCMV specific CD4+ T-cells are found in HCMV positive persons at a high frequency. These T-cells are typically end-differentiated effector memory cells, which have lost expression of CD27 and CD28, but express CD45RA and are therefore classified as effector memory or EMRA cells. HCMV specific CD4+ CD28⁻ CD27⁻ T-cells express granzyme B and have been shown to possess both cytotoxic activity and the ability to express IFN γ upon encountering of HCMV antigens [23, 146]. Similarly, expanded CD4+ T-cell populations are also documented in patients with

various autoimmune diseases, including RA [147, 148], MS [149], and Wegener's granulomatosis [150]. However, there is growing evidence that the HCMV seropositive population of the patients is causing the association with disease and is responsible for the extraordinary expansion of CD4+ CD28⁻ T-cells [100, 148, 151–153].

5.1. CD4+ T-Cells in HCMV Infected RA Patients. In RA patients T-cells are strongly implicated in disease pathogenesis. This is characterized by a large and stable clonal expansion of T-cells and increased frequencies (up to 10%) of CD4+ CD28⁻ cells [154–156]. Expansion of the CD4+ CD28⁻ subset was particularly pronounced in HCMV positive RA patients [100, 148, 152, 153], indicating that the disease *per se* is probably not the cause for the strong expansion of CD4+ CD28⁻ cells, but the coincidence of disease and HCMV infection. Actually it was observed that the CD4+ CD28⁻ T-cell population was about 3-fold higher in HCMV positive RA patients than in healthy HCMV positive subjects [100], suggesting that the disease contributes essentially to the expansion of CD4+ CD28⁻ T-cells.

The majority of the CD4+ CD28⁻ cells were found to be HCMV-specific [148] and no autoreactivity could be measured in that particular study, although CD4+ CD28⁻ T-cells in RA patients were found to be autoreactive in a previous study [156] and the CD4+ CD28⁻ cells were only partially susceptible to the control by regulatory T-cells. Interestingly, it was recently suggested that HCMV-specific CD4+ CD28⁻ CD27⁻ cells are able to function as regulatory T-cells downregulating both HCMV-specific and to a lesser extent unrelated immune responses. This function was shown to be dependent on granzyme B and to some extent on TGF β [157]. If indeed the HCMV specific CD4+ CD28⁻ CD27⁻ cells are by themselves, at least partly, able to confer regulatory T cell functions, additional downregulation might not be easy to detect.

The question remains whether the HCMV-specific CD4+ CD28⁻ cells play a role for the course of the disease. Although no significant increase in HCMV seroprevalence was observed in RA patients, a significant association of HCMV IgG and progression of joint destruction and number of required surgical procedures could be determined [100]. It was put forward that the increased CD4+ CD28⁻ T-cell population in these patients might be involved in aggravated joint disease, as expanded CD4+ CD28⁻ T-cells have been found to cause a significantly faster progression of joint destruction [158]. Despite the fact that CD4+ CD28⁻ T-cells are also associated with severe extra-articular disease [159], this association was not noted for HCMV seropositivity [160].

5.2. Role for CD8+ T-Cells in RA. Studies on CD8+ T-cells from inflamed lesion of RA patients revealed enrichment of EBV and HCMV specific CD8+ T-cells in comparison to cells from peripheral blood. Although the ratio of EBV and HCMV specific synovial lymphocytes to blood lymphocytes was conspicuously higher in RA patients, the presence of

virus specific T-cells was also found in inflamed lesions of patients suffering from various autoimmune diseases (psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis, and arthrosis) [161]. These findings prompted the authors of the study to propose that the virus specific CD8+ T-cells do not play a role for initiation of disease but rather are a consequence of preferential homing of the cells to inflamed tissue after virus reactivation. Furthermore, whereas the virus-specific CD8+ T-cells were readily observed in chronic stages, they were not found in samples drawn early after onset of disease, again arguing against a role in initiation of the disease process [161].

These HCMV specific CD8+ T-cells might contribute to RA-induced inflammation in the tissue by local release of proinflammatory cytokines. Recently, a possible TCR-independent proliferation of HCMV-specific CD8+ T-cells was proposed [162]. Particularly T-cells (CD8⁺ CD45RO⁺) specific for HCMV antigens presented by HLA-A*02:01, but not by HLA-B*07:01, were found to proliferate in an IL-15 dependent fashion [162]. This is interesting because high expression of IL-15 is found both in the synovial fluid and serum of RA patients and has been found to attract and activate T-cells, thereby contributing to the pathogenesis of RA [163]. It is therefore tempting to speculate that the high prevalence of HCMV-specific CD8+ T-cells in the joints of RA patients might be connected to IL-15 expression.

In light of this, it should not escape our attention that pp65 specific, HLA-C restricted CD8+ T-cells were found to crossreact with an HLA-DR4 alloantigen [164], demonstrating an additional level, at which loss of immune tolerance can occur in HCMV infection. Moreover, it might be a unique characteristic of CMV infections that CD8+ T-cells are activated against highly promiscuous epitopes presented by MHC class II molecules, as demonstrated in rhesus cytomegalovirus infection [165]. This might provide additional challenges for the immune system concerning the maintenance of immune tolerance. The existence of such MHC II-restricted CD8+ T-cell responses in humans remains to be demonstrated.

Final Remarks

At first glance a number of HCMV's characteristic attributes appear to predispose this particular virus to be more likely involved in the induction of autoimmune disorders than many other pathogens. Commonly found in all human populations, lasting throughout life in alternating cycles of productive and latent infection, establishing lytic replication in multiple tissues, expressing a plethora of antigens, manipulating extensively intrinsic, innate, and adaptive immune functions, HCMV infection should hazard many opportunities to induce a loss of immunological tolerance and cause autoimmune disease. On the other hand, the cospeciation of HCMV with its human host over millions of years has obviously led to an optimally adapted opportunist which does little harm and avoids clinical symptoms in the immunocompetent host. Evidently, anti-inflammatory

strategies of HCMV [57, 166] can effectively counterbalance immune activation and tissue damage.

We have surveyed the currently available literature for evidence on HCMV association with onset or exacerbation of certain autoimmune disease. While a causative linkage between HCMV and systemic lupus erythematosus, systemic sclerosis, diabetes mellitus type 1, and rheumatoid arthritis is suggested by some findings reported by the literature, the overall evidence does not convincingly support this notion. Albeit an association of HCMV seroprevalence and AID could not be established, HCMV could still play a coresponsible role for the onset of disease, disease progression, or amelioration. For convincing conclusions population-based prospective studies are urgently needed in the future.

Several studies provide evidence for an exciting interplay between adaptive immune responses to HCMV and manifestations of certain autoimmune disorders, for example, in RA and SLE. Specifically, immunopathogenic mechanisms by which HCMV could contribute to the course of autoimmune disease have been indicated, for example, molecular mimicry by the UL94 antigen in SSc patients and UL83/pp65 in SLE patients, as well as aggravation of joint inflammation by induction and expansion of CD4⁺/CD28⁻ T-cells in HCMV infected RA patients. Future studies should provide more detailed insight into the immunopathological potential of HCMV-reactive immune cells to develop potential new strategies of targeted therapeutic intervention.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

This work was supported by VISTRIE (BMBF/Helmholtz VH-VI-424-2 to AH and HH).

References

- [1] A. Ascherio, K. L. Munger, E. T. Lennette et al., "Epstein-Barr virus antibodies and risk of multiple sclerosis: a prospective study," *Journal of the American Medical Association*, vol. 286, no. 24, pp. 3083–3088, 2001.
- [2] H. Hengel, W. Brune, and U. H. Koszinowski, "Immune evasion by cytomegalovirus—survival strategies of a highly adapted opportunist," *Trends in Microbiology*, vol. 6, no. 5, pp. 190–197, 1998.
- [3] M. Babić, A. Krmpotić, and S. Jonjić, "All is fair in virus-host interactions: NK cells and cytomegalovirus," *Trends in Molecular Medicine*, vol. 17, no. 11, pp. 677–685, 2011.
- [4] L. Amsler, M. C. Verweij, and V. R. DeFilippis, "The tiers and dimensions of evasion of the type I interferon response by human cytomegalovirus," *Journal of Molecular Biology*, vol. 425, no. 24, pp. 4857–4871, 2013.
- [5] B. P. McSharry, S. Avdic, and B. Slobedman, "Human cytomegalovirus encoded homologs of cytokines, chemokines and their receptors: roles in immunomodulation," *Viruses*, vol. 4, no. 11, pp. 2448–2470, 2012.

- [6] N. Stern-Ginossar, B. Weisburd, A. Michalski et al., "Decoding human cytomegalovirus," *Science*, vol. 338, pp. 1088–1093, 2012.
- [7] C. Sinzger, A. Grefte, B. Plachter, A. S. H. Gouw, T. Hauw The, and G. Jahn, "Fibroblasts, epithelial cells, endothelial cells and smooth muscle cells are major targets of human cytomegalovirus infection in lung and gastrointestinal tissues," *Journal of General Virology*, vol. 76, no. 4, pp. 741–750, 1995.
- [8] Y. N. Ji, L. An, P. Zhan, and X. H. Chen, "Cytomegalovirus infection and coronary heart disease risk: a meta-analysis," *Molecular Biology Reports*, vol. 39, no. 6, pp. 6537–6546, 2012.
- [9] G. Pawelec, J. E. McElhaney, A. E. Aiello, and E. Derhovanessian, "The impact of CMV infection on survival in older humans," *Current Opinion in Immunology*, vol. 24, pp. 507–511, 2012.
- [10] C. S. Cobbs, "Cytomegalovirus and brain tumor: epidemiology, biology and therapeutic aspects," *Current Opinion on Oncology*, vol. 25, pp. 682–688, 2013.
- [11] R. S. Fujinami, M. B. Oldstone, Z. Wroblewska, M. E. Frankel, and H. Koprowski, "Molecular mimicry in virus infection: crossreaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 80, no. 8, pp. 2346–2350, 1983.
- [12] J. B. Zabriskie and E. H. Freimer, "An immunological relationship between the group A streptococcus and mammalian muscle," *Journal of Experimental Medicine*, vol. 124, no. 4, pp. 661–678, 1966.
- [13] N. R. Rose and I. R. Mackay, "Molecular mimicry: a critical look at exemplary instances in human diseases," *Cellular and Molecular Life Sciences*, vol. 57, no. 4, pp. 542–551, 2000.
- [14] S. Pfeffer, A. Sewer, M. Lagos-Quintana et al., "Identification of microRNAs of the herpesvirus family," *Nature Methods*, vol. 2, no. 4, pp. 269–276, 2005.
- [15] T. J. Stark, J. D. Arnold, D. H. Spector, and G. W. Yeo, "High-resolution profiling and analysis of viral and host small RNAs during human cytomegalovirus infection," *Journal of Virology*, vol. 86, no. 1, pp. 226–235, 2012.
- [16] T. Crough and R. Khanna, "Immunobiology of human cytomegalovirus: from bench to bedside," *Clinical Microbiology Reviews*, vol. 22, no. 1, pp. 76–98, 2009.
- [17] A. Ludwig and H. Hengel, "Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe," *Euro Surveillance*, vol. 14, no. 9, pp. 26–32, 2009.
- [18] R. M. Presti, J. L. Pollock, A. J. Dal Canto, A. K. O'Guin, and H. W. Virgin, "Interferon γ regulates acute and latent murine cytomegalovirus infection and chronic disease of the great vessels," *Journal of Experimental Medicine*, vol. 188, no. 3, pp. 577–588, 1998.
- [19] B. Polić, H. Hengel, A. Krmpotić et al., "Hierarchical and redundant lymphocyte subset control precludes cytomegalovirus replication during latent infection," *Journal of Experimental Medicine*, vol. 188, no. 6, pp. 1047–1054, 1998.
- [20] M. J. Reddehase, "Erratum: the immunogenicity of human and murine cytomegaloviruses," *Current Opinion in Immunology*, vol. 12, no. 6, p. 738, 2000.
- [21] A. W. Sylwester, B. L. Mitchell, J. B. Edgar et al., "Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects," *Journal of Experimental Medicine*, vol. 202, no. 5, pp. 673–685, 2005.
- [22] Q. Ouyang, W. M. Wagner, A. Wikby et al., "Large numbers of dysfunctional CD8+ T lymphocytes bearing receptors for a single dominant CMV epitope in the very old," *Journal of Clinical Immunology*, vol. 23, no. 4, pp. 247–257, 2003.
- [23] E. M. M. van Leeuwen, E. B. M. Remmerswaal, M. T. M. Vossen et al., "Emergence of a CD4+CD28- granzyme B+, cytomegalovirus-specific T cell subset after recovery of primary cytomegalovirus infection," *Journal of Immunology*, vol. 173, no. 3, pp. 1834–1841, 2004.
- [24] A. Wikby, B. Johansson, J. Olsson, S. Löfgren, B.-O. Nilsson, and F. Ferguson, "Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study," *Experimental Gerontology*, vol. 37, no. 2-3, pp. 445–453, 2002.
- [25] J. E. Turner, J. P. Campbell, K. M. Edwards et al., "Rudimentary signs of immunosenescence in Cytomegalovirus-seropositive healthy young adults," *Age*, vol. 36, pp. 287–297, 2014.
- [26] M. Gumá, A. Angulo, C. Vilches, N. Gómez-Lozano, N. Malats, and M. López-Botet, "Imprint of human cytomegalovirus infection on the NK cell receptor repertoire," *Blood*, vol. 104, no. 12, pp. 3664–3671, 2004.
- [27] M. Gumá, M. Budt, A. Sáez et al., "Expansion of CD94/NKG2C+ NK cells in response to human cytomegalovirus-infected fibroblasts," *Blood*, vol. 107, no. 9, pp. 3624–3631, 2006.
- [28] V. Beziat, L. L. Liu, J. A. Malmberg et al., "NK cell responses to cytomegalovirus infection lead to stable imprints in the human KIR repertoire and involve activating KIRs," *Blood*, vol. 121, pp. 2678–2688, 2013.
- [29] H. N. Charoudeh, G. Terszowski, K. Czaja et al., "Modulation of the natural killer cell KIR repertoire by cytomegalovirus infection," *European Journal of Immunology*, vol. 43, no. 2, pp. 480–487, 2013.
- [30] R. Tomazin, J. Boname, N. R. Hedge et al., "Cytomegalovirus US2 destroys two components of the MHC class II pathway, preventing recognition by CD4+ T cells," *Nature Medicine*, vol. 5, no. 9, pp. 1039–1043, 1999.
- [31] E. J. H. J. Wiertz, D. Tortorella, M. Bogoy et al., "Sec61-mediated transfer of a membrane protein from the endoplasmic reticulum to the proteasome for destruction," *Nature*, vol. 384, no. 6608, pp. 432–438, 1996.
- [32] D. C. Johnson and N. R. Hegde, "Inhibition of the MHC class II antigen presentation pathway by human cytomegalovirus," *Current Topics in Microbiology and Immunology*, vol. 269, pp. 101–115, 2002.
- [33] T. R. Jones, E. J. H. J. Wiertz, L. Sun, K. N. Fish, J. A. Nelson, and H. L. Ploegh, "Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class I heavy chains," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 21, pp. 11327–11333, 1996.
- [34] K. Ahn, A. Gruhler, B. Galocha et al., "The ER-luminal domain of the HCMV glycoprotein US6 inhibits peptide translocation by TAP," *Immunity*, vol. 6, no. 5, pp. 613–621, 1997.
- [35] H. Hengel, J.-O. Koopmann, T. Flohr et al., "A viral ER-resident glycoprotein inactivates the MHC-endocytic peptide transporter," *Immunity*, vol. 6, no. 5, pp. 623–632, 1997.
- [36] T. R. Jones, L. K. Hanson, L. Sun, J. S. Slater, R. M. Stenberg, and A. E. Campbell, "Multiple independent loci within the human cytomegalovirus unique short region down-regulate expression of major histocompatibility complex class I heavy chains," *Journal of Virology*, vol. 69, no. 8, pp. 4830–4841, 1995.

- [37] R. S. Tirabassi and H. L. Ploegh, "The human cytomegalovirus US8 glycoprotein binds to major histocompatibility complex class I products," *Journal of Virology*, vol. 76, no. 13, pp. 6832–6835, 2002.
- [38] Y. Kim, B. Park, S. Cho et al., "Human cytomegalovirus UL18 utilizes US6 for evading the NK and T-cell responses," *PLoS Pathogens*, vol. 4, no. 8, Article ID e1000123, 2008.
- [39] S. Kim, S. Lee, J. Shin et al., "Human cytomegalovirus microRNA miR-US4-1 inhibits CD8⁺ T cell responses by targeting the aminopeptidase ERAP1," *Nature Immunology*, vol. 12, no. 10, pp. 984–991, 2011.
- [40] A. Halenius, S. Hauka, L. Dölken et al., "Human cytomegalovirus disrupts the major histocompatibility complex class I peptide-loading complex and inhibits tapasin gene transcription," *Journal of Virology*, vol. 85, no. 7, pp. 3473–3485, 2011.
- [41] I. Gabaev, L. Steinbrück, C. Pokoyski et al., "The human cytomegalovirus UL11 protein interacts with the receptor tyrosine phosphatase CD45, resulting in functional paralysis of T cells," *PLoS Pathogens*, vol. 7, no. 12, Article ID e1002432, 2011.
- [42] C. Dunn, N. J. Chalupny, C. L. Sutherland et al., "Human cytomegalovirus glycoprotein UL16 causes intracellular sequestration of NKG2D ligands, protecting against natural killer cell cytotoxicity," *Journal of Experimental Medicine*, vol. 197, no. 11, pp. 1427–1439, 2003.
- [43] D. Cosman, N. Fanger, L. Borges et al., "A novel immunoglobulin superfamily receptor for cellular and viral MHC class I molecules," *Immunity*, vol. 7, no. 2, pp. 273–282, 1997.
- [44] M. Ulbrecht, S. Martinozzi, M. Grzeschik et al., "Cutting edge: the human cytomegalovirus UL40 gene product contains a ligand for HLA-E and prevents NK cell-mediated lysis," *Journal of Immunology*, vol. 164, no. 10, pp. 5019–5022, 2000.
- [45] N. J. Bennett, O. Ashiru, F. J. E. Morgan et al., "Intracellular sequestration of the NKG2D ligand ULBP3 by human cytomegalovirus," *Journal of Immunology*, vol. 185, no. 2, pp. 1093–1102, 2010.
- [46] N. J. Chalupny, A. Rein-Weston, S. Dosch, and D. Cosman, "Down-regulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142," *Biochemical and Biophysical Research Communications*, vol. 346, no. 1, pp. 175–181, 2006.
- [47] N. Stern-Ginossar, N. Elefant, A. Zimmermann et al., "Host immune system gene targeting by a viral miRNA," *Science*, vol. 317, no. 5836, pp. 376–381, 2007.
- [48] T. I. Arnon, H. Achdout, O. Levi et al., "Inhibition of the NKp30 activating receptor by pp65 of human cytomegalovirus," *Nature Immunology*, vol. 6, no. 5, pp. 515–523, 2005.
- [49] R. Atalay, A. Zimmermann, M. Wagner et al., "Identification and expression of human cytomegalovirus transcription units coding for two distinct Fcγ receptor homologs," *Journal of Virology*, vol. 76, no. 17, pp. 8596–8608, 2002.
- [50] B. Park, E. Spooner, B. L. Houser, J. L. Strominger, and H. L. Ploegh, "The HCMV membrane glycoprotein US10 selectively targets HLA-G for degradation," *Journal of Experimental Medicine*, vol. 207, no. 9, pp. 2033–2041, 2010.
- [51] J. Han, S. B. Rho, J. Y. Lee et al., "Human cytomegalovirus (HCMV) US2 protein interacts with human CD1d (hCD1d) and down-regulates invariant NKT, (iNKT) cell activity," *Molecules and Cells*, vol. 36, no. 5, pp. 455–464, 2013.
- [52] D. N. Strelbow, C. Soderberg-Naucler, J. Vieira et al., "The human cytomegalovirus chemokine receptor US28 mediates vascular smooth muscle cell migration," *Cell*, vol. 99, no. 5, pp. 511–520, 1999.
- [53] C. Weber, C. von Stülpnagel, K. S. C. Weber, H. Hengel, and P. C. Weber, "Association of myocardial infarction with mononuclear cell expression of the cytomegalovirus chemokine receptor US28 in patients with NIDDM," *Experimental and Clinical Cardiology*, vol. 6, no. 2, pp. 105–108, 2001.
- [54] K. L. Arnolds, A. P. Lares, and J. V. Spencer, "The US27 gene product of human cytomegalovirus enhances signaling of host chemokine receptor CXCR4," *Virology*, vol. 439, pp. 122–131, 2013.
- [55] K. Tadagaki, D. Tudor, F. Gbahou et al., "Human cytomegalovirus-encoded UL33 and UL78 heteromerize with host CCR5 and CXCR4 impairing their HIV coreceptor activity," *Blood*, vol. 119, pp. 4908–4918, 2012.
- [56] S. V. Kottenko, S. Saccani, L. S. Izotova, O. V. Mirochnitchenko, and S. Pestka, "Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10)," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 4, pp. 1695–1700, 2000.
- [57] J. V. Spencer, J. Cadaoas, P. R. Castillo, V. Saini, and B. Slobedman, "Stimulation of B lymphocytes by cmvIL-10 but not LAcmvIL-10," *Virology*, vol. 374, no. 1, pp. 164–169, 2008.
- [58] C. Jenkins, A. Abendroth, and B. Slobedman, "novel viral transcript with homology to human interleukin-10 is expressed during latent human cytomegalovirus infection," *Journal of Virology*, vol. 78, no. 3, pp. 1440–1447, 2004.
- [59] H. R. Lüttichau, "The cytomegalovirus UL146 gene product vCXCL1 targets both CXCR1 and CXCR2 as an agonist," *The Journal of Biological Chemistry*, vol. 285, no. 12, pp. 9137–9146, 2010.
- [60] M. E. T. Penfold, D. J. Dairaghi, G. M. Duke et al., "Cytomegalovirus encodes a potent α chemokine," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 17, pp. 9839–9844, 1999.
- [61] D. Wang, W. Bresnahan, and T. Shenk, "Human cytomegalovirus encodes a highly specific RANTES decoy receptor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 47, pp. 16642–16647, 2004.
- [62] Q. Zheng, R. Tao, H. Gao, J. Xu, S. Shang, and N. Zhao, "HCMV-encoded UL128 enhances TNF-α and IL-6 expression and promotes PBMC proliferation through the MAPK/ERK pathway in vitro," *Viral Immunology*, vol. 25, no. 2, pp. 98–105, 2012.
- [63] V. T. K. Le, M. Trilling, and H. Hengel, "The cytomegalovirus protein pUL138 acts as potentiator of tumor necrosis factor (TNF) receptor 1 surface density to enhance ULB'-encoded modulation of TNF-α signaling," *Journal of Virology*, vol. 85, no. 24, pp. 13260–13270, 2011.
- [64] C. Montag, J. A. Wagner, I. Gruska, B. Vetter, L. Wiebusch, and C. Hagemeyer, "The latency-associated ul138 gene product of human cytomegalovirus sensitizes cells to tumor necrosis factor alpha (TNF) signaling by upregulating tnf receptor 1 cell surface expression," *Journal of Virology*, vol. 85, no. 21, pp. 11409–11421, 2011.
- [65] C. A. Benedict, K. D. Butrovich, N. S. Lurain et al., "Cutting edge: a novel viral TNF receptor superfamily member in virulent strains of human cytomegalovirus," *Journal of Immunology*, vol. 162, no. 12, pp. 6967–6970, 1999.
- [66] P. Engel, N. Pérez-Carmona, M. M. Albà, K. Robertson, P. Ghazal, and A. Angulo, "Human cytomegalovirus UL7, a homologue of the SLAM-family receptor CD229, impairs cytokine production," *Immunology and Cell Biology*, vol. 89, no. 7, pp. 753–766, 2011.

- [67] D. M. Miller, B. M. Rahill, J. M. Boss et al., "Human cytomegalovirus inhibits major histocompatibility complex class II expression by disruption of the Jak/Stat pathway," *Journal of Experimental Medicine*, vol. 187, no. 5, pp. 675–683, 1998.
- [68] V. T. K. Le, M. Trilling, M. Wilborn, H. Hengel, and A. Zimmermann, "Human cytomegalovirus interferes with signal transducer and activator of transcription (STAT) 2 protein stability and tyrosine phosphorylation," *Journal of General Virology*, vol. 89, no. 10, pp. 2416–2426, 2008.
- [69] D. A. Abate, S. Watanabe, and E. S. Mocarski, "Major human cytomegalovirus structural protein pp65 (ppUL83) prevents interferon response factor 3 activation in the interferon response," *Journal of Virology*, vol. 78, no. 20, pp. 10995–11006, 2004.
- [70] K. A. Cassady, "Human cytomegalovirus TRS1 and IRS1 gene products block the double-stranded-RNA-activated host protein shutoff response induced by herpes simplex virus type 1 infection," *Journal of Virology*, vol. 79, no. 14, pp. 8707–8715, 2005.
- [71] J. C. G. Tan, S. Avdic, J. Z. Cao et al., "Inhibition of 2',5'-oligoadenylate synthetase expression and function by the human cytomegalovirus ORF94 gene product," *Journal of Virology*, vol. 85, no. 11, pp. 5696–5700, 2011.
- [72] C. Paulus, S. Krauss, and M. Nevels, "A human cytomegalovirus antagonist of type I IFN-dependent signal transducer and activator of transcription signaling," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 10, pp. 3840–3845, 2006.
- [73] R. T. Taylor and W. A. Bresnahan, "Human cytomegalovirus IE86 attenuates virus- and tumor necrosis factor alpha-induced NFκB-dependent gene expression," *Journal of Virology*, vol. 80, no. 21, pp. 10763–10771, 2006.
- [74] V. S. Goldmacher, "vMIA, a viral inhibitor of apoptosis targeting mitochondria," *Biochimie*, vol. 84, no. 2-3, pp. 177–185, 2002.
- [75] A. Skaletskaya, L. M. Bartle, T. Chittenden, A. L. McCormick, E. S. Mocarski, and V. S. Goldmacher, "A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 14, pp. 7829–7834, 2001.
- [76] H. Zhu, Y. Shen, and T. Shen, "Human cytomegalovirus IE1 and IE2 proteins block apoptosis," *Journal of Virology*, vol. 69, no. 12, pp. 7960–7970, 1995.
- [77] F. Koriath, G. G. Maul, B. Plachter, T. Stamminger, and J. Frey, "The nuclear domain 10 (ND10) is disrupted by the human cytomegalovirus gene product IE1," *Experimental Cell Research*, vol. 229, no. 1, pp. 155–158, 1996.
- [78] S. R. Cantrell and W. A. Bresnahan, "Human cytomegalovirus (HCMV) UL82 gene product (pp71) relieves hDaxx-mediated repression of HCMV replication," *Journal of Virology*, vol. 80, no. 12, pp. 6188–6191, 2006.
- [79] C. M. Preston and M. J. Nicholl, "Role of the cellular protein hDaxx in human cytomegalovirus immediate-early gene expression," *Journal of General Virology*, vol. 87, no. 5, pp. 1113–1121, 2006.
- [80] R. T. Saffert and R. F. Kalejta, "Inactivating a cellular intrinsic immune defense mediated by Daxx is the mechanism through which the human cytomegalovirus pp71 protein stimulates viral immediate-early gene expression," *Journal of Virology*, vol. 80, no. 8, pp. 3863–3871, 2006.
- [81] B. A. Esen, G. Yilmaz, S. Uzun et al., "Serologic response to Epstein-Barr virus antigens in patients with systemic lupus erythematosus: a controlled study," *Rheumatology International*, vol. 32, no. 1, pp. 79–83, 2012.
- [82] J. P. Pandey, "Immunoglobulin GM genes and IgG antibodies to cytomegalovirus in patients with systemic sclerosis," *Clinical and Experimental Rheumatology*, vol. 22, no. 3, pp. S35–S37, 2004.
- [83] M. Neidhart, S. Kuchen, O. Distler et al., "Increased serum levels of antibodies against human cytomegalovirus and prevalence of autoantibodies in systemic sclerosis," *Arthritis & Rheumatology*, vol. 42, pp. 389–392, 1999.
- [84] M. Larsen, D. Sauce, C. Deback et al., "Exhausted cytotoxic control of Epstein-Barr virus in human lupus," *PLoS Pathogens*, vol. 7, no. 10, Article ID e1002328, 2011.
- [85] B. Y.-J. Su, C.-Y. Su, S.-F. Yu, and C.-J. Chen, "Incidental discovery of high systemic lupus erythematosus disease activity associated with cytomegalovirus viral activity," *Medical Microbiology and Immunology*, vol. 196, no. 3, pp. 165–170, 2007.
- [86] M. T. McClain, B. D. Poole, B. F. Bruner, K. M. Kaufman, J. B. Harley, and J. A. James, "An altered immune response to Epstein-Barr nuclear antigen 1 in pediatric systemic lupus erythematosus," *Arthritis & Rheumatism*, vol. 54, no. 1, pp. 360–368, 2006.
- [87] C. G. Parks, G. S. Cooper, L. L. Hudson et al., "Association of Epstein-Barr virus with systemic lupus erythematosus: effect modification by race, age, and cytotoxic T lymphocyte-associated antigen 4 genotype," *Arthritis & Rheumatism*, vol. 52, no. 4, pp. 1148–1159, 2005.
- [88] J. A. James, B. R. Neas, K. L. Moser et al., "Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure," *Arthritis & Rheumatism*, vol. 44, pp. 1122–1126, 2001.
- [89] S. Bendiksen, M. van Ghelue, O. P. Rekvig, T. Gutteberg, H.-J. Haga, and U. Moens, "A longitudinal study of human cytomegalovirus serology and viraemia fails to detect active viral infection in 20 systemic lupus erythematosus patients," *Lupus*, vol. 9, no. 2, pp. 120–126, 2000.
- [90] P. Stratta, C. Canavese, G. Ciccone et al., "Correlation between cytomegalovirus infection and Raynaud's phenomenon in lupus nephritis," *Nephron*, vol. 82, no. 2, pp. 145–154, 1999.
- [91] J. R. Rider, W. E. R. Ollier, R. J. Lock, S. T. Brookes, and D. H. Pamphilon, "Human cytomegalovirus infection and systemic lupus erythematosus," *Clinical and Experimental Rheumatology*, vol. 15, no. 4, pp. 405–409, 1997.
- [92] J. A. James, K. M. Kaufman, A. D. Farris, E. Taylor-Albert, T. J. A. Lehman, and J. B. Harley, "An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus," *Journal of Clinical Investigation*, vol. 100, no. 12, pp. 3019–3026, 1997.
- [93] J. Aarnisalo, R. Veijola, R. Vainionpää, O. Simell, M. Knip, and J. Ilonen, "Cytomegalovirus infection in early infancy: risk of induction and progression of autoimmunity associated with type 1 diabetes," *Diabetologia*, vol. 51, no. 5, pp. 769–772, 2008.
- [94] M. Hiltunen, H. Hyoty, J. Karjalainen et al., "Serological evaluation of the role of cytomegalovirus in the pathogenesis of IDDM: a prospective study," *Diabetologia*, vol. 38, no. 6, pp. 705–710, 1995.
- [95] E. Sundqvist, T. Bergstrom, H. Daialhosein et al., "Cytomegalovirus seropositivity is negatively associated with multiple sclerosis," *Multiple Sclerosis Journal*, 2013.
- [96] N. Sanadgol, N. Ramroodi, G. A. Ahmadi et al., "Prevalence of cytomegalovirus infection and its role in total immunoglobulin

- pattern in Iranian patients with different subtypes of multiple sclerosis," *New Microbiologica*, vol. 34, no. 3, pp. 263–274, 2011.
- [97] E. Waubant, E. M. Mowry, L. Krupp et al., "Common viruses associated with lower pediatric multiple sclerosis risk," *Neurology*, vol. 76, no. 23, pp. 1989–1995, 2011.
- [98] K.-M. Myhr, T. Riise, E. Barrett-Connor et al., "Altered antibody pattern to Epstein-Barr virus but not to other herpesviruses in multiple sclerosis: A population based case-control study from western Norway," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 64, no. 4, pp. 539–542, 1998.
- [99] J. Gutiérrez, M.-J. Vergara, M. Guerrero et al., "Multiple sclerosis and human herpesvirus 6," *Infection*, vol. 30, no. 3, pp. 145–149, 2002.
- [100] M. Pierer, K. Rothe, D. Quandt et al., "Association of anticytomegalovirus seropositivity with more severe joint destruction and more frequent joint surgery in rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 64, pp. 1740–1749, 2012.
- [101] D. Thomas, F. Karachaliou, K. Kallergi et al., "Herpes virus antibodies seroprevalence in children with autoimmune thyroid disease," *Endocrine*, vol. 33, no. 2, pp. 171–175, 2008.
- [102] C. Scully, "Sjogren's syndrome: No demonstrable association by serology of secondary sjorgen's syndrome with cytomegalovirus," *Journal of Oral Pathology and Medicine*, vol. 19, no. 1, pp. 43–44, 1990.
- [103] Y. Arnson, H. Amital, S. Guiducci et al., "The role of infections in the immunopathogenesis of systemic sclerosis-evidence from serological studies," *Annals of the New York Academy of Sciences*, vol. 1173, pp. 627–632, 2009.
- [104] J. H. Vaughan, P. X. Shaw, M.-D. Nguyen et al., "Evidence of activation of 2 herpesviruses, Epstein-Barr virus and cytomegalovirus, in systemic sclerosis and normal skins," *Journal of Rheumatology*, vol. 27, no. 3, pp. 821–823, 2000.
- [105] O. Barzilai, Y. Sherer, M. Ram, D. Izhaky, J. M. Anaya, and Y. Shoenfeld, "Epstein-Barr virus and cytomegalovirus in autoimmune diseases: Are they truly notorious? A preliminary report," *Annals of the New York Academy of Sciences*, vol. 1108, pp. 567–577, 2007.
- [106] C. A. Palafox Sánchez, M. Satoh, E. K. Chan et al., "Reduced IgG anti-small nuclear ribonucleoprotein autoantibody production in systemic lupus erythematosus patients with positive IgM anti-cytomegalovirus antibodies," *Arthritis Research & Therapy*, vol. 11, no. 1, p. R27, 2009.
- [107] S.-A. Ivarsson, B. Lindberg, K. O. Nilsson, K. Ahlfors, and L. Svanberg, "The prevalence of Type 1 diabetes mellitus at follow-up of Swedish infants congenitally infected with cytomegalovirus," *Diabetic Medicine*, vol. 10, no. 6, pp. 521–523, 1993.
- [108] K. P. Ward, W. H. Galloway, and I. A. Auchterlonie, "Congenital cytomegalovirus infection and diabetes," *The Lancet*, vol. 1, no. 8114, p. 497, 1979.
- [109] C. Y. Pak, R. G. McArthur, H.-M. Eun, and J.-W. Yoon, "Association of cytomegalovirus infection with autoimmune type 1 diabetes," *The Lancet*, vol. 2, no. 8601, pp. 1–4, 1988.
- [110] R. Zivadinov, D. Nasuelli, M. A. Tommasi et al., "Positivity of cytomegalovirus antibodies predicts a better clinical and radiological outcome in multiple sclerosis patients," *Neurological Research*, vol. 28, no. 3, pp. 262–269, 2006.
- [111] I. Pirko, R. Cardin, Y. Chen et al., "CMV infection attenuates the disease course in a murine model of multiple sclerosis," *PLoS ONE*, vol. 7, no. 2, Article ID e32767, 2012.
- [112] E. J. Shillitoe, T. E. Daniels, and J. P. Whitcher, "Antibody to cytomegalovirus in patients with Sjogren's syndrome. As determined by an enzyme-linked immunosorbent assay," *Arthritis & Rheumatism*, vol. 25, no. 3, pp. 260–265, 1982.
- [113] C. Ferri, M. Cazzato, D. Giuggioli, M. Sebastiani, and C. Magro, "Systemic sclerosis following human cytomegalovirus infection," *Annals of the Rheumatic Diseases*, vol. 61, no. 10, pp. 937–938, 2002.
- [114] T. Hayashi, S. Lee, H. Ogasawara et al., "Exacerbation of systemic lupus erythematosus related to cytomegalovirus infection," *Lupus*, vol. 7, no. 8, pp. 561–564, 1998.
- [115] M. Nawata, N. Seta, M. Yamada, I. Sekigawa, N. Iida, and H. Hashimoto, "Possible triggering effect of cytomegalovirus infection on systemic lupus erythematosus," *Scandinavian Journal of Rheumatology*, vol. 30, no. 6, pp. 360–362, 2001.
- [116] A. E. Pérez-Mercado and S. Vilá-Pérez, "Cytomegalovirus as a trigger for systemic lupus erythematosus," *Journal of Clinical Rheumatology*, vol. 16, no. 7, pp. 335–337, 2010.
- [117] M. F. Cusick, J. E. Libbey, and R. S. Fujinami, "Molecular mimicry as a mechanism of autoimmune disease," *Clinical Reviews in Allergy and Immunology*, vol. 42, no. 1, pp. 102–111, 2012.
- [118] Z.-S. Zhao, F. Granucci, L. Yeh, P. A. Schaffer, and H. Cantor, "Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection," *Science*, vol. 279, no. 5355, pp. 1344–1347, 1998.
- [119] S. Deshpande, M. Zheng, S. Lee et al., "Bystander activation involving T lymphocytes in herpetic stromal keratitis," *Journal of Immunology*, vol. 167, no. 5, pp. 2902–2910, 2001.
- [120] M. S. Horwitz, A. La Cava, C. Fine, E. Rodriguez, A. Ilic, and N. Sarvetnick, "Pancreatic expression of interferon- γ protects mice from lethal coxsackievirus B3 infection and subsequent myocarditis," *Nature Medicine*, vol. 6, no. 6, pp. 693–697, 2000.
- [121] C. Münz, J. D. Lünemann, M. T. Getts, and S. D. Miller, "Antiviral immune responses: Triggers of or triggered by autoimmunity?" *Nature Reviews Immunology*, vol. 9, no. 4, pp. 246–258, 2009.
- [122] E. Murphy, D. Yu, J. Grimwood et al., "Coding potential of laboratory and clinical strains of human cytomegalovirus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 25, pp. 14976–14981, 2003.
- [123] P. Q. Hu, N. Fertig, T. A. Medsger Jr., and T. M. Wright, "Correlation of serum anti-DNA topoisomerase I antibody levels with disease severity and activity in systemic sclerosis," *Arthritis & Rheumatism*, vol. 48, no. 5, pp. 1363–1373, 2003.
- [124] C. Lunardi, C. Bason, R. Navone et al., "Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells," *Nature Medicine*, vol. 6, no. 10, pp. 1183–1186, 2000.
- [125] C. Lunardi, M. Dolcino, D. Peterlana et al., "Antibodies against human cytomegalovirus in the pathogenesis of systemic sclerosis: a gene array approach," *PLoS Medicine*, vol. 3, no. 1, p. e2, 2006.
- [126] A. M. Namboodiri, K. M. Rocca, and J. P. Pandey, "IgG antibodies to human cytomegalovirus late protein UL94 in patients with systemic sclerosis," *Autoimmunity*, vol. 37, no. 3, pp. 241–244, 2004.
- [127] T. Murayoi, K. N. Kasturi, M. J. Kafina et al., "Antitopoisomerase I monoclonal autoantibodies from scleroderma patients and tight skin mouse interact with similar epitopes," *Journal of Experimental Medicine*, vol. 175, no. 4, pp. 1103–1109, 1992.

- [128] J. P. Pandey and E. C. LeRoy, "Human cytomegalovirus and the vasculopathies of autoimmune diseases (especially scleroderma), allograft rejection, and coronary restenosis," *Arthritis & Rheumatism*, vol. 41, pp. 10–15, 1998.
- [129] D. Hamamdžić, R. A. Harley, D. Hazen-Martin, and E. C. LeRoy, "MCMV induces neointima in IFN- γ R^{-/-} mice: Intimal cell apoptosis and persistent proliferation of myofibroblasts," *BMC Musculoskeletal Disorders*, vol. 2, article 3, 2001.
- [130] M. R. Arbuckle, M. T. McClain, M. V. Rubertone et al., "Development of autoantibodies before the clinical onset of systemic lupus erythematosus," *The New England Journal of Medicine*, vol. 349, no. 16, pp. 1526–1533, 2003.
- [131] M. Ramos-Casals, M. J. Cuadrado, P. Alba et al., "Acute viral infections in patients with systemic lupus erythematosus: Description of 23 cases and review of the literature," *Medicine*, vol. 87, no. 6, pp. 311–318, 2008.
- [132] M. Chang, M.-R. Pan, D.-Y. Chen, and J.-L. Lan, "Human cytomegalovirus pp65 lower matrix protein: A humoral immunogen for systemic lupus erythematosus patients and autoantibody accelerator for NZB/W F1 mice," *Clinical and Experimental Immunology*, vol. 143, no. 1, pp. 167–179, 2006.
- [133] A.-H. Hsieh, Y.-J. Zhou, C.-T. Liang, M. Chang, and S.-L. Wang, "Fragment of tegument protein pp65 of human cytomegalovirus induces autoantibodies in BALB/c mice," *Arthritis Research & Therapy*, vol. 13, p. R162, 2011.
- [134] H. A. Curtis, T. Singh, and M. M. Newkirk, "Recombinant cytomegalovirus glycoprotein gB (UL55) induces an autoantibody response to the U1-70 kDa small nuclear ribonucleoprotein," *European Journal of Immunology*, vol. 29, pp. 3643–3653, 1999.
- [135] M. M. Newkirk, W. J. van Venrooij, and G. S. Marshall, "Autoimmune response to U1 small nuclear ribonucleoprotein (U1 snRNP) associated with cytomegalovirus infection," *Arthritis Research*, vol. 3, no. 4, pp. 253–258, 2001.
- [136] B. C. Marshall, R. A. McPherson, E. Greidinger, R. Hoffman, and S. P. Adler, "Lack of autoantibody production associated with cytomegalovirus infection," *Arthritis Research*, vol. 4, article R6, 2002.
- [137] M. R. Schleiss, D. I. Bernstein, M. Passo et al., "Lack of induction of autoantibody responses following immunization with cytomegalovirus (CMV) glycoprotein B (gB) in healthy CMV-seronegative subjects," *Vaccine*, vol. 23, no. 5, pp. 687–692, 2004.
- [138] A. B. Jenson, H. S. Rosenberg, and A. L. Notkins, "Pancreatic islet-cell damage in children with fatal viral infections," *The Lancet*, vol. 2, no. 8190, pp. 354–358, 1980.
- [139] A. K. Foulis, M. McGill, M. A. Farquharson, and D. A. Hilton, "A search for evidence of viral infection in pancreases of newly diagnosed patients with IDDM," *Diabetologia*, vol. 40, no. 1, pp. 53–61, 1997.
- [140] M. J. Smelt, M. M. Faas, B. J. de Haan et al., "Susceptibility of human pancreatic β cells for cytomegalovirus infection and the effects on cellular immunogenicity," *Pancreas*, vol. 41, no. 1, pp. 39–49, 2012.
- [141] C. Y. Pak, C. Y. Cha, R. V. Rajotte, R. G. McArthur, and J. W. Yoon, "Human pancreatic islet cell specific 38 kilodalton autoantigen identified by cytomegalovirus-induced monoclonal islet cell autoantibody," *Diabetologia*, vol. 33, no. 9, pp. 569–572, 1990.
- [142] B. O. Roep, "The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure," *Diabetologia*, vol. 46, no. 3, pp. 305–321, 2003.
- [143] J. A. Todd, N. M. Walker, J. D. Cooper et al., "Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes," *Nature Genetics*, vol. 39, no. 7, pp. 857–864, 2007.
- [144] H. S. Hiemstra, N. C. Schloot, P. A. van Veelen et al., "Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 7, pp. 3988–3991, 2001.
- [145] S. Walton, S. Mandaric, and A. Oxenius, "CD4 T cell responses in latent and chronic viral infections," *Frontiers in Immunology*, vol. 4, article 105, 2013.
- [146] E. M. M. van Leeuwen, E. B. M. Remmerswaal, M. H. M. Heemsker, I. J. M. ten Berge, and R. A. W. van Lier, "Strong selection of virus-specific cytotoxic CD4⁺ T-cell clones during primary human cytomegalovirus infection," *Blood*, vol. 108, no. 9, pp. 3121–3127, 2006.
- [147] A. E. R. Fasth, D. Cao, R. van Vollenhoven, C. Trollmo, and V. Malmström, "CD28nullCD4⁺ T cells - Characterization of an effector memory T-cell population in patients with rheumatoid arthritis," *Scandinavian Journal of Immunology*, vol. 60, no. 1, pp. 199–208, 2004.
- [148] M. Thewissen, V. Somers, N. Hellings, J. Fraussen, J. Damoiseaux, and P. Stinissen, "CD4⁺CD28null T cells in autoimmune disease: Pathogenic features and decreased susceptibility to immunoregulation," *Journal of Immunology*, vol. 179, no. 10, pp. 6514–6523, 2007.
- [149] S. Markovic-Plese, I. Cortese, K.-P. Wandinger, H. F. McFarland, and R. Martin, "CD4⁺CD28⁻ costimulation-independent T cells in multiple sclerosis," *Journal of Clinical Investigation*, vol. 108, no. 8, pp. 1185–1194, 2001.
- [150] A. Komocsi, P. Lamprecht, E. Csernok et al., "Peripheral blood and granuloma CD4⁺CD28⁻ T cells are a major source of interferon- γ and tumor necrosis factor- α in Wegener's granulomatosis," *American Journal of Pathology*, vol. 160, no. 5, pp. 1717–1724, 2002.
- [151] P. Eriksson, C. Sandell, K. Backteman, and J. Ernerudh, "Expansions of CD4⁺CD28⁻ and CD8⁺CD28⁻ T cells in granulomatosis with polyangiitis and microscopic polyangiitis are associated with cytomegalovirus infection but not with disease activity," *The Journal of Rheumatology*, vol. 39, pp. 1840–1843, 2012.
- [152] M. Hooper, E. G. Kallas, D. Coffin, D. Campbell, T. G. Evans, and R. J. Looney, "Cytomegalovirus seropositivity is associated with the expansion of CD4⁺CD28⁻ and CD8⁺CD28⁻ T cells in rheumatoid arthritis," *Journal of Rheumatology*, vol. 26, no. 7, pp. 1452–1457, 1999.
- [153] M. Thewissen, V. Somers, K. Venken et al., "Analyses of immunosenescent markers in patients with autoimmune disease," *Clinical Immunology*, vol. 123, no. 2, pp. 209–218, 2007.
- [154] R. Gerli, G. Schillaci, A. Giordano et al., "CD4⁺CD28⁻ T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients," *Circulation*, vol. 109, no. 22, pp. 2744–2748, 2004.
- [155] A. Pawlik, L. Ostanek, I. Brzosko et al., "The expansion of CD4⁺CD28⁻ T cells in patients with rheumatoid arthritis," *Arthritis Research & Therapy*, vol. 5, no. 4, pp. R210–213, 2003.
- [156] D. Schmidt, J. J. Goronzy, and C. M. Weyand, "CD4⁺ CD7⁻CD28⁻ T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity," *Journal of Clinical Investigation*, vol. 97, no. 9, pp. 2027–2037, 1996.
- [157] A. Tovar-Salazar, J. Patterson-Bartlett, R. Jessor, and A. Weinberg, "Regulatory function of cytomegalovirus-specific

- CD4+CD27-CD28- T cells," *Virology*, vol. 398, no. 2, pp. 158–167, 2010.
- [158] J. J. Goronzy, E. L. Matteson, J. W. Fulbright et al., "Prognostic markers of radiographic progression in early rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 50, no. 1, pp. 43–54, 2004.
- [159] P. B. Martens, J. J. Goronzy, D. Schaid, and C. M. Weyand, "Expansion of unusual CD4+ T cells in severe rheumatoid arthritis," *Arthritis & Rheumatism*, vol. 40, no. 6, pp. 1106–1114, 1997.
- [160] J. van Bergen, F. A. van Gaalen, H. van Dongen et al., "Anticytomegalovirus seropositivity in rheumatoid arthritis is not associated with the presence of severe extraarticular complications," *Arthritis & Rheumatism*, vol. 64, pp. 2803–2805, 2012.
- [161] E. Scotet, M.-A. Peyrat, X. Saulquin et al., "Frequent enrichment for CD8 T cells reactive against common herpes viruses in chronic inflammatory lesions: Towards a reassessment of the physiopathological significance of T cell clonal expansions found in autoimmune inflammatory processes," *European Journal of Immunology*, vol. 29, no. 3, pp. 973–985, 1999.
- [162] S. J. Griffiths, N. E. Riddell, J. Masters et al., "Age-associated increase of low-avidity cytomegalovirus-specific CD8+ T cells that re-express CD45RA," *The Journal of Immunology*, vol. 190, pp. 5363–5372, 2013.
- [163] H.-R. Kim, K.-A. Hwang, S.-H. Park, and I. Kang, "IL-7 and IL-15: biology and roles in T-cell immunity in health and disease," *Critical Reviews in Immunology*, vol. 28, no. 4, pp. 325–339, 2008.
- [164] M. Rist, C. Smith, M. J. Bell, S. R. Burrows, and R. Khanna, "Cross-recognition of HLADR4 alloantigen by virus-specific CD8+ T cells: a new paradigm for self-/nonself-recognition," *Blood*, vol. 114, no. 11, pp. 2244–2253, 2009.
- [165] S. G. Hansen, J. B. Sacha, C. M. Hughes et al., "Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms," *Science*, vol. 340, Article ID 123787, 2013.
- [166] S. Michelson, J. Alcamí, S.-J. Kim et al., "Human cytomegalovirus infection induces transcription and secretion of transforming growth factor β 1," *Journal of Virology*, vol. 68, no. 9, pp. 5730–5737, 1994.