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Cytomegalovirus (CMV) Infection: A Role in the Pathogenesis of Systemic Lupus Erythematosis (SLE)

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Abstract

Autoimmune Diseases and in particular Systemic Lupus Erythematosis (SLE) are associated with responses to viral antigenemia. The mechanisms by which the virus and autoimmune disease are related include disease activation, mitigation and susceptibility of the host to the viral infection during exacerbations of autoimmune disease. This paper will review the cellular, molecular and disease associations between SLE and Cytomegalovirus infection.

Keywords: Systemic lupus erythematosis; Autoimmune disease; Viral infection

Introduction

Viruses, like other microbial agents may be integral triggering factors in the development of autoimmune disease. Many specific viruses have been implicated in the modulation of local and systemic environmental factors that lead to the formulation of organ specific and circulating auto-antibodies. Direct infection may activate an immune response by cross reaction between carbohydrate, proteins, peptides or nucleic acids of the pathogen and the host's molecular structural receptors [1,2].

Viruses with pathogen specific epitopes with similarity to the host might activate auto reactive lymphocytes, which is termed molecular mimicry. Transfer of viral specific epitopes to the host then initiates the process of disease pathogenesis [3].

Mitigation of the autoimmune process by viral infections can also occur, particularly if there is repeated infection by the same viral strain. Viruses can attract potentially injurious T cells towards the infection by release of chemokines, which decreases the likelihood of autoantibody production. T regulatory cells (TREG cells) when activated, may help to lessen the autoimmune processes [4].

Genetic Predisposition

Other lines of evidence suggest that genetic haplotype influences initiation of autoimmunity following a viral infection. The HLA D3 haplotype and multiple genes, such as the STAT4 and APOA2 gene, have been implicated as susceptibility factors [5,6]. The response to viral disease and the host's genetic susceptibility to disease are both important regulatory factors. The timing, cumulative viral disease burden, degree of inflammation, type of virus and its particular strain are bidirectional factors which can either induce or lessen the course of autoimmune disease.

Specific epitope targeted expansion of CD8+ T cells, in response to CMV is not typical of other viral infections. CMV has been associated with many autoimmune diseases, and there has been a higher prevalence of autoimmune disease among patients with CMV infection described

[7]. The immune profile among seropositive CMV autoimmune disease patients includes the proliferation of CD4+/CD28 null T cells. CD4+ CD28 null population is three fold higher among CMV positive rheumatoid arthritis patients compared with healthy CMV positive patients [8]. This increase may be a marker for disease pathogenesis and progression. A previous study has shown that CMV specific CD4+CD 28 null cells are regulatory T cells [9].

Cytomegalovirus and Human Disease

Human cytomegalovirus (CMV) is a member of the *Herpesviridae* family. Compared to other members of the same viral family, CMV has the most genomic potential to modify the innate and adaptive immunity of the host. CMV is able to infect a multitude of cell types, including endothelial, epithelial, fibroblast cells and immune effector cells such as dendritic cells and monocytes/macrophages [10]. CMV infection may take many forms including primary infection, endogenous infection, or exogenous reinfection. Latent infection and persistent infection of the host may occur and causes activation of the immune system.

CMV Clinical Infection

The manifestations of CMV vary from an asymptomatic state or mild respiratory infection to a potentially fatal multi-organ system infection. CMV infection most often will initially present in childhood as a mild illness. In neonates, of the infection may be acquired in utero, and results in a multi-system disease with liver involvement, purpura, hepatosplenomegaly, microcephaly and sensorineural hearing loss. In older children and adults, CMV may be more prolonged and presents with fever and mild hepatitis [10].

Autoimmunity and CMV Infection

Multiple pathways in pathogenesis

Autoimmune responses are one result of defective tolerance. The factors involved in triggering autoimmune responses are infection, genetic predisposition, immunologic, hormonal, psychological, emotional and external environmental conditions [10,11].

In general, there are multiple molecular mechanisms linking infections to the development of autoimmune disease. Among these are that infections can trigger or exacerbate autoimmune disease. The lifelong cumulative effects of multiple infections and immune dysregulation may also be responsible for subsequent disease. Genetic predisposition to autoimmune disease and its influence on host responses leading to autoimmune disease is a key differentiating factor in determining which infected patients develop autoimmune responses. One example of genetic determination of response to pathogens and susceptibility to autoimmune disease are genetic variations in toll like receptors such as TLR3,7 and 9 which may predispose to autoimmune disease [12].

Induction of the production of autoantibodies during CMV infection may be based on a number of possible mechanisms. Autoantigens present on the surface of cells following CMV infection. One described mechanism is that there is an induction of autoantigens on the surface of cells following CMV infection, and similar cell surface epitopes then induce autoantibodies [13].

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus or SLE is one of the more frequently CMV associated autoimmune diseases. In particular, non-renal vascular SLE may manifest after CMV infection. It therefore may be useful in the study of the complex relationship between infection and autoimmunity. SLE is characterized by production of specific autoantibodies directed against nuclear proteins. CMV infection has been shown to trigger the production of autoantibodies and the clinical symptoms of SLE. The relationship on a molecular level between CMV infection and the production of autoantibodies is thought to involve the closely linked antibodies of anti-Sm and anti-RNP (ribonucleoprotein), which are directed to a small family of RNPs that bind to the U series of snRNAs [14]. Evidence supportive of this mechanism is that among patients with SLE, latent CMV is more detectable among patients with anti-RNP antibodies, compared to those without anti-RNP antibodies. Anti-RNP antibodies were more frequent in patients with symptomatic CMV infection, than in patients without CMV infection. The primary immune response to CMV is directed to epitopes on the pp65 viral antigen. In normal subjects, anti-CMV antibodies are produced and the infection does not lead to autoimmune disease. Among patients with SLE, 60% of patients have been shown to have IgG anti-pp65 antibodies [14].

Clinical Manifestations of CMV in SLE

Initiation and exacerbation

The clinical presentation of CMV in SLE varies considerably. The most frequently involved systems included persistent fever, lymphopenias, anemia and nephrotic syndrome. Both a higher viral load and higher IgG CMV titers are found among SLE patients in comparison with non SLE autoimmune control patients. Among SLE patients (n=28) who tested positive for CMV pp65 viral antigen, multivariate analysis revealed an odds ratio of 6.71, $p=0.028$, of having lymphopenia (less than 700/cubic mm). The median SLEDAI score was 10, with a range of 3-27. This study demonstrated that among those patients with lymphopenia, CMV viral load was also observed. In addition, this study demonstrated a specific correlation between CMV antigenemia and the development of CMV disease among the SLE patients studied. It is also possible that the infection itself may initiate autoimmune disease in non-SLE autoimmune diseases such as rheumatoid arthritis [15]. One example of CMV as a trigger for SLE onset is described in a case report of a 43 year old individual with CMV and no prior history of systemic illness [16].

In the study by Su et al. [15] there were 87 SLE patients studied. There were positive levels of anti-CMV IgG (97.7%) and the prevalence of positive anti-CMV IgM in the SLE group was 10.3% (9/87) compared with

1.03% in the control group ($p<0.001$). The clinical disease activity score or SLEDAI was significantly higher in patients positive for both anti-CMV IGM and IgG compared to the patients with negative CMV IgM levels (11.4+/-6.77 compared with 3.87+/-3.36, $p=0.012$). In a multi-center retrospective survey of rheumatic diseases, there were 151 patients with CMV infection. SLE was the most commonly diagnosed ($n=74,50\%$), CMV associated rheumatic disease [15].

The mechanistic links between CMV reactivation and SLE flare up is still unclear. There are several proposed mechanisms including i) SLE can lead to CMV reactivation, ii) SLE immunosuppressive therapy predisposes to CMV, iii) CMV reactivation leads to an SLE flare. The support for the role of CMV reactivation in the regulation of auto antibody production was shown in a study of SLE patients with CMV IgG antibodies. The authors identified differential production of antibodies to U1 RNP/Sm and U1-70K based on the presence of CMV IgM.

Reactivation and immunosuppression

CMV infection has also occurred as part of treatment protocols for SLE and autoimmune disease. The risk of reactivation of CMV is found in approximately 20 % of patients during anti-CD 20 therapy. CMV infection among SLE patients may be severe and fatal. Some associated risk factors for CMV mortality include cytopenias, prior cyclophosphamide therapy, multisystem involvement and delayed initiation of antiviral therapy [17].

CMV infection among patients with combined variable immunodeficiency (CVID), may be associated with an increased risk for autoimmune disease. This lends further support that among immunocompromised patients, CMV is a risk factor for the development of autoimmune disease. Further support for this possible mechanism is that patients, such as organ transplant patients receiving immunosuppressive therapies, have an established risk for CMV reactivation [18].

The molecular mechanisms of CMV induction of autoimmunity

Post-infection autoimmunity may be induced by the following molecular mechanisms [10]:

Molecular mimicry: This is one of the most likely mechanisms of autoimmunity following CMV infection. As the name suggests, there is a crossreactivity between epitopes (i.e. protein, carbohydrate or DNA) shared by the pathogen and the host. In the host, to establish this mechanism, the pathogen must provoke an immune response that crossreacts with host antigen after preceding the development of autoimmune disease.

Epitope switching may occur following protein processing and antigen presentation, resulting in an autoimmune response to a novel transformed epitope.

Bystander activation occurs following viral infection of tissue and subsequent release of sequestered antigen, which activates autoreactive lymphocytes, not involved in the early reaction to viral infection.

Persistent infection may result in a combination of mono and polyclonal antibodies.

Conclusion

In conclusion, there are multiple mechanisms of SLE pathogenesis, and viral infection of host cells may lead to specific pathways of disease initiation and clinical worsening. SLE is a polygenic multifactorial disease in which there is heterogeneity in its phenotypic presentation. Viral infections may initiate and amplify autoimmune disease. Microbial peptides with limited sequences have also been shown to lead to the autoimmune response. Further studies are needed to elucidate the cellular and molecular pathways and their interactions with host susceptibility and genotype.

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