

# Human parvovirus B19, autoimmunity and systemic lupus erythematosus

Tsai-Ching Hsu, Bor-Show Tzang

## INTRODUCTION

Imbalance of autoimmunity is a significant issue worldwide, which results in autoimmune disorders. To date, more than eighty autoimmune diseases are identified [1]. An autoimmune disorder may cause diverse impacts such as destruction of body tissue, abnormal growth of an organ, and organ dysfunction [2]. Various factors are strongly associated with the development of autoimmunity such as genetics, age and environment. Among environmental factors, viruses, bacteria and other infectious pathogens are the major postulated triggers of autoimmune diseases including systemic lupus erythematosus (SLE) [3, 4], which is known as a prototypic autoimmune disease with unknown etiology [5]. Notably, human parvovirus B19 has been suspected as contributors to human autoimmune diseases, especially SLE [6].

## B19 virus induces autoimmunity and mimics SLE manifestations

Human parvovirus B19 (B19) is known as the cause of fifth disease in childhood, and the possible trigger in the spectrum of autoimmune diseases in adults [7]. B19 is

a linear, non-segmented single-stranded DNA virus that belongs to the large *Parvoviridae* family. B19 consists a nonstructural protein (NS1) and two capsid proteins, VP1 (83 kDa) and VP2 (58 kDa) [8]. These two capsid proteins of B19 are identical except for 227 amino acids at the amino-terminal end of the VP1-protein, the so called VP1-unique region (VP1u) [9]. Notably, B19 VP1u has been linked to the phospholipase A2 (PLA2)-like activity, which is essential for parvovirus B19 infectivity [10].

B19 infection has been recognized as a cause or trigger of autoimmune diseases [11, 12] and associated with the production of various autoantibodies against beta2-glycoprotein I ( $\beta$ 2GPI), and cardiolipin (aCL) [13, 14]. Accumulating evidences have indicated that human parvovirus B19 infection is highly associated with the onset and exacerbations of SLE [15]. B19 infection may present a clinical and serological tableau like the episode of SLE such as cytopenia, hypocomplementemia and generation of autoantibodies [16, 17]. An in vitro study has indicated that B19-NS1 proteins enhanced the expression of cleavage of 70 kDa U1-snRNP autoantigen, suggesting a role of B19-NS1 on autoantibody induction [18]. In addition, a previous study has also demonstrated the induction of autoimmunity by antibodies against B19-VP1u in naïve mice. In BALB/c mice infused with recombinant B19-VP1u proteins through tail vein, thrombocytopenia, prolongation of aPTT, and autoantibody against  $\beta$ 2GPI and PhL were detected [19].

B19 infection and anti-phospholipid syndrome (APS) have been reported to show similar symptoms leading to the hypothesis of a common pathogenetic background [13]. Remarkable similarity exists in the specificity of anti-phospholipid antibody (APhL) between patients with B19 infection or SLE [13, 14, 20]. The APS is an autoimmune disease characterized by the persistent presence of APhL and by the occurrence of thrombosis, fetal loss and thrombocytopenia [21]. An APhL is a pathogenic antibody mainly directed against the phospholipid-binding protein  $\beta$ 2GPI [22–24]. The  $\beta$ 2GPI is an abundant plasma phospholipid-binding protein and has been demonstrated binding to human endothelial cells via annexin II, resulting in activation of human endothelial cells [25]. The activated endothelial cells induce the pro-coagulant

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and pro-inflammatory phenotype with adhesion molecule such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin [26, 27] and pro-inflammatory cytokines and chemokines [28, 29], which is regarded to be involved in the generation of autoimmunity. Notably, autoantibodies against CL,  $\beta$ 2GPI, and phospholipid (PhL) in sera from patients with B19 infection were cross-reactive with B19-VP1u [19]. In animal experiments, sera from rabbits immunized with recombinant B19-VP1u protein displayed raised detectable immunoglobulins against B19-VP1u, CL,  $\beta$ 2GPI and PhL. Moreover, the mice immunized with anti-B19-VP1u IgG developed thrombocytopenia, prolongation of aPTT, and autoantibody against  $\beta$ 2GPI and PhL [30]. These experiments provided rational evidences of B19 on inducing autoimmunity.

## **B19 infection aggravated liver injuries in SLE**

B19 infection has been associated with liver abnormality in SLE [31]. The liver is such an important organ that plays important role in the metabolism of various substances. It is also involved in the induction of immune tolerance and recognized as a target for immune-mediated injuries [32]. Notably, the liver involvement in SLE, recently gained extensive attention worldwide. Although further hepatic inspection is not a routinely diagnostic criterion [33], accumulating studies have indicated that more than 50% of SLE patients reveal various liver abnormalities during the course of their illness [34–36]. To investigate whether B19 infection induces liver injury and contributes to induction of autoimmunity, experiments of passive transfer of B19 viral proteins or antibodies against B19 viral proteins were performed. Likewise, significantly aggravated liver inflammation was observed in liver of the lupus-prone mice receiving antibodies against B19-VP1u [37]. Additionally, significantly aggravated liver damage indices, including elevated MMP-9 activity and expressions of iNOS, COX-2 and TNF- $\alpha$  were detected in lupus-prone mice that were treated with B19-NS1 proteins [38] as well as liver fibrosis through TGF- $\beta$ /Smad signaling [39].

Numerous studies have recognized that virus-induced liver damage is involved in generation of autoimmunity. For instance, chronic viral hepatitis induced by HCV or HDV is usually accompanied by production of autoantibodies, particularly liver/kidney microsomal (LKM) antibodies [40]. Although direct evidence of B19 infection for the development of SLE is lacking, these studies indicated that B19 aggravated liver injury in SLE could be a potential impact for autoimmunity. Whether B19-aggravated liver injuries induce autoimmunity in SLE needs further investigations to clarify the precise mechanism.

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**Keywords:** Autoimmunity, Fetal loss, Thrombocytopenia, Liver injury, Infection

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Tsai-Ching Hsu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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### **Guarantor**

The corresponding author is the guarantor of submission.

### **Conflict of Interest**

Authors declare no conflict of interest.

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