Hepatic inflammation resulting from localized, subcutaneous expression of Parvovirus VP1u capsid protein: Importance and implication

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This issue of Virulence features an article entitled “Human parvovirus B19 VP1u Protein as inflammatory mediators induces liver injury in naïve mice” which elucidated a relationship between expression of the Parvovirus B19 (B19) VP1 unique region (VP1u) and liver damage in a transgenic mouse model.1 The in vivo effects of VP1u were investigated by subcutaneous injection of COS-7 cells transfected with an infrared reportable marker into Balb/c mice. Expression of the VP1u fusion protein was detectable up to 28 d following cell transfer by IVIS fluorescence imaging. A significant increase in inflammatory marker expression, STAT1 phosphorylation, and lymphocyte infiltration was observed in mice receiving COS-7 cells containing the VP1u expression plasmid. This study is the first to demonstrate a VP1u specific increase in liver inflammation from protein expression in non-hepatic cells.

Parvovirus B19 is a small, non-enveloped DNA virus whose main site of replication is in erythroid progenitor cells.2 Transmission occurs through contaminated respiratory or blood droplets, but fetal transmission can also occur from infected mothers. Principal diseases associated with acute B19 infection include erythema infectiosum, transient aplastic crisis, and hydrops fetalis, but an association between B19 infection and other inflammatory or autoimmune diseases has been reported.3-4 B19 produces 3 main proteins: a nonstructural protein, NS1, and 2 capsid proteins, VP1 and VP2, and 2 small proteins called the 7.5 and 11 kDa protein whose function has yet to be determined.5 The capsid proteins are identical except for an N-terminus region on the VP1 protein called the VP1 unique (VP1u) region.6

In vitro, expression of B19 proteins has been shown to upregulate multiple inflammatory proteins including IL-6, TNF-α, and STAT3 phosphorylation.7-10 Many of these studies have focused on NS1 expression, although VP1u has been shown to have phospholipase activity and can increase expression from the TNF-α and NF-κB promoters.11-12 In vivo, a correlation between B19 infection and activations of inflammatory genes or pathways has also been reported both in intra-cellular expression and circulating cytokine detection.12-14 Due to the strict specificity of B19 to human cells, there is no reliable animal model for wild type B19 infection to better explore these relationship between B19 infection and inflammatory disease.15

Current animal models to study the impact of B19 on disease including transgenic expression of B19 proteins, ex vivo transfection or transduction of cells injected into animals, or direct injection of B19 proteins or antibodies. Other animal models from this group have shown a correlation between B19 proteins or antibodies and liver inflammation. In one study, NZB/W F1 mice, a model of human systemic lupus erythematosus, were injected intravenously with an anti-VP1u antibody.16 Liver tissue from these mice showed an increase in matrix metalloproteinase-9 activity and increase expression in the PI3K and ERK pathways. In a similar study, injection of VP1u antibodies were also shown to result in increased inflammation and lymphocyte infiltration in cardiac tissue, further demonstrating the potential immune impact of B19 VP1u antibodies.17 In a subsequent study, B19 NS1, VP1u, VP2 were injected subcutaneously in NZB/W F1 mice.18 Increased fibrosis and collagen deposition was observed in mice injected with the NS1 protein, but no marked changes were observed in those receiving the VP1u or VP2 protein. These data indicate that the results seen in the current study are a result of cellular expression of the VP1u protein and a potentially immune response against the viral protein.

Analysis of circulating cytokine profiles of human patients acutely infected with B19 and at 2-37 months following initial infection has demonstrated prolonged upregulation of inflammatory cytokines IFN-γ and TNF-α.19 This increase was
also associated with development of chronic fatigue. Interestingly, in this work, Hsu et al. also reported an increase in IFN-γ in liver cells from mice injected subcutaneously with COS-7 cells expressing B19 VP1u protein. These data suggest B19 protein expression can elicit an indirect effect on other non-infected tissues. Further analysis of liver tissues from the VP1u expressing mice also demonstrated a significant increase in other inflammatory cytokines including MMP9/MMP2 ratios, CRP, IL-1β and IL-6 protein levels, and a marked increase in infiltrating lymphocytes, which may contribute to hepatic injury. Sasaki T. Regulation of tumor necrosis factor alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. J Gen Virol 2001; 82: 3011-9; PMID:11714978; http://dx.doi.org/10.1099/0022-1317-82-12-3011

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.