Herpesviruses and the microbiome

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The focus of this article will be to examine the role of common herpesviruses as a component of the microbiome of atopic patients and to review clinical observations suggesting that atopic patients might be predisposed to more severe and atypical herpes-related illness because their immune response is biased toward a T_H2 cytokine profile. Human populations are infected with 8 herpesviruses, including herpes simplex virus HSV1 and HSV2 (also termed HHV1 and HHV2), varicella zoster virus (VZV or HHV3), EBV (HHV4), cytomegalovirus (HHV5), HHV6, HHV7, and Kaposi sarcoma–associated herpesvirus (termed KSV or HHV8). Herpesviruses are highly adapted to lifelong infection of their human hosts and thus can be considered a component of the human "microbiome" in addition to their role in illness triggered by primary infection. HSV1 and HSV2 infection and reactivation can present with more severe cutaneous symptoms termed eczema herpeticum in the atopic population, similar to the more severe eczema vaccinatum, and drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is associated with reactivation of HSV6 and possibly other herpesviruses in both atopic and nonatopic patients. In this review evidence is reviewed that primary infection with herpesviruses may have an atypical presentation in the atopic patient and conversely that childhood infection might alter the atopic phenotype. Reactivation of latent herpesviruses can directly alter host cytokine profiles through viral expression of cytokine-like proteins, such as IL-10 (EBV) or IL-6 (cytomegalovirus and HHV8), viral encoded and secreted siRNA and microRNAs, and modulation of expression of host transcription pathways, such as nuclear factor κB. Physicians caring for allergic and atopic populations should be aware of common and uncommon presentations of herpes-related disease in atopic patients to provide accurate diagnosis and avoid unnecessary laboratory testing or incorrect diagnosis of other conditions, such as drug allergy or autoimmune disease. Antiviral therapy and vaccines should be administered promptly when indicated clinically. (J Allergy Clin Immunol 2013;132:1278-86.)

Key words: *Hygiene hypothesis, genomics, microbiome, herpes, therapy, vaccines*

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Abbreviations used

CMV:	Cytomegalovirus
DRESS:	Drug reaction with eosinophilia and systemic symptoms
EBNA:	Epstein-Barr nuclear antigen
HSV:	Herpes simplex virus
HSV1:	Herpes simplex virus type 1, also known as HHV1 (human herpes virus type 1)
HSV2:	Herpes simplex virus type 2, also known as HHV2 (human herpes virus type 2)
KSV:	Kaposi sarcoma virus
vIL-10:	Viral IL-10–like protein encoded by EBV
VZV (or HHV3):	Varicella zoster virus

Increasing evidence suggests that the human genome is only one component of allergic and atopic disease and that the complex "human biome," including bacteria and fungi, interacts with the genome in complex pathways influencing allergic and atopic disease.[1,2] The human microbiome can also include herpesviruses because these infectious agents establish lifelong infection of the human host, although unlike bacteria and fungi, this persistent state is maintained through latent genomic persistence within the host cell nucleus. Herpesviruses are ubiquitous, large, double-stranded DNA viruses categorized into 3 families. α Herpesviruses, such as human herpes simplex virus (HSV) 1 and HSV and varicella zoster virus (VZV or HHV3), establish latency in neurons; β herpesviruses, such as cytomegalovirus (CMV or HHV5) and human herpesvirus (HHV) 6 and HHV7, establish latency in macrophages and lymphocytes; and γ herpesviruses, such as EBV (HHV4) and HHV8, establish latency only in lymphocytes. The ability of herpesviruses to establish a latent state of infection with low levels of viral gene expression for the life of the host is a defining feature of these pathogens and requires that the virus establish means of evading or neutralizing the host's immune system.

Soon after the discovery of human cytokines and the differentiation of these cytokines into type 1 and type 2 cytokines, which direct responses against intracellular and extracellular pathogens, respectively, it was observed that EBV (HHV4) encodes a protein resembling human IL-10, a cytokine with actions in the T_H2 family.[3-5] The ability of a virus to encode a copy of a human cytokine supported the hypothesis that EBV and related herpesviruses might in some way exploit the host immune system for their own purposes.[6-8] Clinical observations had also previously suggested that patients with atopic disease, such as severe eczema, reflecting a T_H2 cytokine bias, were at risk for more severe reactions (termed eczema herpeticum or eczema vaccinatum) to other non-herpes DNA viruses, such as smallpox.[9-11]

Epidemiologic studies suggest that age of infection with EBV and related herpesviruses can affect the subsequent development of atopic disease, possibly related to viral modulation of T_H2 cytokines.[12-17] Subsequent study of EBV

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suggested herpesviruses can encode or trigger the expression of superantigens that nonspecifically activate T-lymphocyte subsets, possibility resulting in increased allergic cytokine expression and inflammation.[18,19] Because of the possibility that atopic patients might be at increased risk of atypical or severe presentations of herpesvirus-related disease both during primary infection and viral reactivation, common and uncommon presentations of herpesvirus infection, as well as therapy options, should be familiar to physicians caring for the atopic patient, and therapy, such as antiviral drugs and vaccines, should be administered promptly when indicated. This review will examine evidence that human herpesviruses are a component of the human microbiome and important in modulating allergic and atopic disease and summarize existing evidence that atopic patients are at increased risk of severe and atypical responses to herpes pathogens.

EBV AS A PROTOTYPE OF IMMUNOMODULATION BY HUMAN HERPESVIRUSES

As noted above, the discovery that a human herpesvirus EBV encodes a copy of a cytokine related to IL-10 (encoded by the BCRF1 open reading frame) was a seminal observation, suggesting that common and ubiquitous herpesvirus pathogens could have immunomodulatory properties.[6-8] Remarkably, the viral IL-10–like protein encoded by EBV (vIL-10) is different than cellular IL-10. vIL-10 has effects primarily on B lymphocytes; this is in contrast to the human cytokine, which targets both B and T lymphocytes.[20] In several experimental systems, an inflammatory effect of vIL-10 is evident because the inflammatory and proliferative effects of IL-10 on B lymphocytes are not opposed by the suppressive effects of IL-10 on T lymphocytes.[3,20] In addition, EBV infection also triggers expression of cellular IL-10 and other host cytokines because EBV activates host transcription factors.[21-24]

A virus-encoded protein (termed BZLF-1 or ZEBRA) activates the EBV replication cycle and is also a homolog of proteins in the activator protein 1 Fos/Jun family and nuclear factor κB transcription proteins, potentially activating multiple host inflammatory proteins regulated by these pathways.[25] EBV and other herpesviruses encode microRNAs that can be released into the cytoplasm in endosomes causing immunomodulation of distant cells.[26-29] Although many EBV-encoded proteins, noncoding RNAs, and cellular transcription factors are required for the viral lifecycle *in vitro*, it has been more challenging to demonstrate that EBV infection modulates the human immune system *in vivo*[30] because response to the virus might be an effect rather than a cause of T_H2 bias in patients with common autoimmune disease[31] and cancer.[32,33]

EARLY (INFANCY OR EARLY CHILDHOOD) VERSUS LATE (ADOLESCENCE OR ADULTHOOD) INFECTION WITH EBV AND OTHER HERPESVIRUSES AS A MODULATING FACTOR IN PATIENTS WITH ATOPIC DISEASE

Because of the immunomodulatory properties of EBV, population-based studies of EBV as a prototypical and ubiquitous herpesvirus suggest that early infection (infancy or early childhood) might have protective effects while later infection predisposes to atopic disease.[12-17] These studies do not distinguish between effects of primary infection versus effects of subsequent viral persistence with episodes of reactivation. In infancy maternal antibodies against EBV might limit the severity of primary infection and modulate the immune response, whereas in early childhood the immune system can respond differently to viral infections relative to the response in later childhood, adolescence, or adulthood.

These studies must all be controlled for the fact that patients with early childhood EBV infection might have other environmental exposures differing from those of patients with late infection. Thus it is difficult to prove with observational studies that increasing atopy and allergy with increasing age of EBV infection are causally related rather than common effects of different childhood hygiene, such as exposure to other components of the microbiome through exchange of body fluids or exposure to environmental antigens. Prospective studies of herpesvirus seroconversion in healthy infants followed through childhood would be required to determine to what extent age of infection with EBV and related viruses is correlated with allergy and atopy independent of other variables.

CLINICAL EVALUATION OF EBV AND RELATED CUTANEOUS SYNDROMES

Patients with nonspecific maculopapular rashes can be referred to allergists for evaluation of allergy, urticaria, immune deficiency, or autoimmune disease, often after extensive and unnecessary laboratory evaluation. EBV and related herpes pathogens often present with a maculopapular or urticarial rash that can persist for prolonged periods after primary infection (Fig 1). Maculopapular rashes are not specific for EBV and can also be associated with other herpesviruses, as well as acute infection with HIV, which should be considered depending on the clinical setting. Concurrent use of antibiotics during suspected primary infection with EBV or related viruses should be avoided because drug rash might be more common and lead to misdiagnosis of drug allergy.

If recent EBV infection is suspected, focused testing for virus-specific antigens, such as IgG and IgM to the viral capsid antigen, IgG to early antigen, and Epstein-Barr nuclear antigen (EBNA), can determine the presence or absence of primary infection, whereas the monospot test is less sensitive and specific for acute EBV infection but also less expensive. During viral latency, the virus expresses a very limited set of proteins, primarily EBNA-1, and thus past but not current or recent viral infection with EBV can be confirmed by expression of IgG against EBNA to distinguish between recent and past infection with viral reactivation. Because of the potential for atypical or prolonged primary infection or viral reactivation, clinicians caring for atopic patients should have a high index of suspicion to avoid misdiagnosis of EBV for other infectious diseases or allergic conditions (Figs 1 and 2).

Primary infection with other herpesviruses, such as CMV, can also present with a nonspecific rash. Serologic tests for IgG and IgM to virus-specific antigens for EBV and CMV are available from most clinical laboratories, with virus-specific IgM confirming recent primary infection and virus-specific IgG confirming past infection. After acute infection, virus-specific IgM values should gradually decrease to undetectable levels after infection, whereas virus-specific IgG levels will remain positive for the life of the host. PCR for EBV or CMV is also available at most academic centers but is rarely required to make a diagnosis. In general, a focused history including evidence of recent symptoms, such as fever and pharyngitis, is sufficient to make a clinical diagnosis of a postviral rash or syndrome without any required laboratory testing, although laboratory testing can be very useful