Pathogenesis From the Reactivation of Chromosomally Integrated Human Herpesvirus Type 6: Facts Rather Than Fiction

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(See the Brief Report by Endo et al on pages 545–8.)

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Viral latency, defined by the ability of a virus to remain dormant, is a commonly used immune evasion strategy that enables the long-term persistence of viruses within the infected host. On occasion, these viruses come out of latency and initiate their replicative cycles, yielding a progeny of infectious virions favoring viral propagation and dissemination with possible pathogenic outcomes depending on the immunological competency of the host. Among the most successful viruses utilizing latency as a mean of persistence are herpesviruses. Typically, during latency, herpesviruses maintain their genome in the nucleus in the form of an episome (extrachromosomal circular DNA) and express only a handful of proteins (often 1 protein) that ensure episome maintenance and transmission to daughter cells upon cell division. Among the 100 or so herpesviruses infecting vertebrates, a few of them have evolved mechanisms allowing them to integrate their viral genome into the host chromosomes in manners analogous to retroviruses. Example of such viruses include Marek disease virus (an oncogenic chicken herpes virus) and human herpesvirus (HHV) 6A and 6B (reviewed in [1]). HHV-6A and HHV-6B were isolated in 1986 and 1988 [2, 3], respectively, and the first report on chromosomally integrated HHV-6 (ciHHV-6) made in 1993 [4]. Daibata et al were the first to demonstrate vertical transmission of HHV-6 DNA over 3 generations by showing identical HHV-6 integration sites between a patient with acute lymphoblastic leukemia, his son, and his granddaughter, who were otherwise healthy [5]. HHV-6A and HHV-6B integration can take place in several distinct chromosomes, but the integration site invariably takes place at the ends of chromosomes within the telomeric region [6]. Since then, several other cases of ciHHV-6 were reported (reviewed in [1]) and biological consequences of ciHHV-6 discussed [7]. Whether HHV-6 integration was a viral dead end or constitutes a new form of latency remained, for many years, an unanswered fundamental biological question. Using Epstein-Barr virus-immortalized B-cell lines from subjects with ciHHV-6 and various culture conditions, several investigators proved unsuccessful at rescuing infectious HHV-6, although viral gene expression could be demonstrated [5, 8–11]. Using human cell lines, Arbuckle et al provided the first evidence of de novo integration and successful rescue of infectious HHV-6 virions from ciHHV-6-infected cells [12], suggesting that HHV-6 can reactivate once integrated. The first in vivo evidence of reactivation of ciHHV-6 came from Gravel et al, who provided data consistent with transplacentally acquired HHV-6 originating from the transmission of reactivated ciHHV-6 from the mother [13].

The article by Endo et al in this issue of Clinical Infectious Diseases goes a step further by convincingly demonstrating in vivo evidence of ciHHV-6A reactivation and isolation of infectious HHV-6A. The patient, a young boy with X-linked severe combined immunodeficiency (X-SCID), inherited ciHHV-6A from his father. Medical complications led doctors to suspect an HHV-6 infection. Such infection was confirmed by reverse transcription polymerase chain
reaction (PCR), DNA load, and HHV-6 antigen detection by immunohistochemistry performed on bone marrow biopsies. Antiviral treatments proved effective at reducing HHV-6A viral burden, in support of ongoing active infection. The key result came when the researchers could successfully isolate infectious HHV-6A at different time points. Viral sequence analyses indicate that the isolated HHV-6A is identical to the DNA sequence of the integrated HHV-6 from the child and his father but different from other HHV-6A and HHV-6B isolates. These results provide compelling evidence that HHV-6 integration does not represent an evolutionary viral dead end but rather a genuine form of latency of which much remains to be learned.

The incidence of X-SCID is 0.001%, and the frequency of ciHHV-6 is approximately 1%, meaning that an X-SCID subject with ciHHV-6 represents only 1 of 10 million individuals. Whether ciHHV-6 reactivates only in patients with X-SCID is unknown but unlikely. Interestingly, the X-SCID infant demonstrated no signs of active HHV-6A infection for the first couple of months after birth, suggesting that maternal antibodies provided some protection during this time. One can assume that reactivation of ciHHV-6 occurs sporadically in any individual, but given the fact that patients with X-SCID display profound immunosuppression, viral growth and dissemination cannot be contained due to the lack of specific anti–HHV-6 immune effectors. It is also important to note that individuals who have inherited ciHHV-6 from a parent have 1 integrated HHV-6 genome per cell, magnifying several-folds the number of cells, and distinct tissues/organs capable of reactivating ciHHV-6.

Nearly 100% of the adult human population is seropositive for HHV-6. Following primary infection, in early childhood, the virus likely integrates its genome in a minority of cells and establishes latency, but this has been difficult to validate experimentally, in part due to the absence of animal models (HHV-6 infects humans and selected monkey species). HHV-6 reactivations from this restricted pool of infected cells are generally controlled by the immune system (B- and T-cell responses) of immunocompetent individuals and are usually clinically silent. However, in iatrogenically immunosuppressed individuals, such as bone marrow transplant recipients, HHV-6B reactivates in 50% of subjects receiving allogeneic transplant between days 20 and 30 postengraftment [14–17] and significantly more in subjects receiving cord blood as a source of stem cells [18,19], pointing to a crucial role for T cells in controlling HHV-6 infection.

Now that it has been documented that HHV-6 can reactivate once it has integrated the human genome, what should we do with this information? From a clinical and ethical point of view, whether solid organs and stem cells derived from persons with ciHHV-6 should be used for transplantation needs to be questioned. Stem cells by definition have unlimited lifespans, in part due to abundant telomerase activity that maintains adequate telomere lengths. At present, the biological consequence of HHV-6 integration within the telomeric region is an understudied research area, and the long-term proliferative potential of ciHHV-6 stem cells remains to be defined. As far as solid organ transplantation is concerned, knowing that, once integrated, HHV-6 can express some of its genes, organs from a ciHHV-6–positive donor could trigger immunologic attacks from the recipient’s immune system, even in the absence of detectable viral replication. Considering this, the ciHHV-6 status of the donors should be determined prior to organ transplant, and recipients should be carefully monitored for signs of active HHV-6 infection (viral loads) and/or signs of immunity (induced by HHV-6 antigens) organ rejection.

In summary, what was initially considered an oddity is now recognized as a bona fide viral life cycle whose latent state encompasses HHV-6 genome integration within host telomeres. The results presented by Endo et al clearly demonstrate, for the first time, in vivo reactivation and pathogenesis resulting in the excision and expansion of integrated HHV-6A. Testing for ciHHV-6 can be easily performed through noninvasive procedures such as quantitative PCR on DNA extracted from blood, nail clippings or hair follicles. Present in approximately 1% of the world population, ciHHV-6 needs to be considered a relevant condition likely to affect the outcome of several medical procedures.

**Note**

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

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**References**


