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Mixing It Up: New Insights Into Interspecies Recombination Between Herpes Simplex Virus Type 1 and 2

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Abstract

Herpes simplex viruses (HSV-1 and HSV-2) are closely related alphaherpesviruses, with more than 80% identity at the deoxyribonucleic acid (DNA) sequence level [1]. More than two thirds of the world's population is estimated to have been infected with one or both viruses. The divergence of the common ancestor to these viruses is thought to have coincided with the separation of the human and chimpanzee lineages approximately 6 million years ago, leading to separate evolution of HSV-1 and HSV-2, respectively. Zoonotic transmission of HSV-2 to an extinct early hominid occurred approximately one and a half million years ago [2]. No other primate species are known to serve as common hosts for 2 distinct herpes simplex species.

Recombination events between isolates of the same species have now been documented for all 9 herpesviruses for which humans are the natural host. This activity is currently understood to be one of the principal drivers of herpesvirus evolution and diversity [3]. For example, all of the circulating clades of varicella-zoster virus (VZV) are evidently mosaics of each other, arising from the recombinant interaction of distant ancestral viruses. Many VZV clinical samples have now been completely sequenced, and various stable clades display distinctive geographic distributions, with only a few genuinely single clade-specific sequences observed [4–6].

Knowledge that intertypic HSV-1 X HSV-2 recombinant viruses could be generated during in vitro coculture was established more than 40 years ago [7, 8]. However, the identification of naturally occurring intertypic recombinants was reported only in the past few years [9, 10]. The common presence of these recombinant events in several specific open reading frames led to the conclusion that they were generated at some remote period in the past, and it seemed possible that such recombination events were no longer occurring. Such interspecies recombination has also been observed in 2 closely related betaherpesvirus species, human herpesvirus (HHV)-6A and HHV-6B, which can also coinfect humans [11].

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In this issue of *the Journal of Infectious Diseases*, Casto et al evaluated approximately 500 complete HSV genome sequences, 255 of which were newly sequenced by the authors. In addition to the previously identified recombinants in UL29, UL30, and UL39, it was determined that both the sizes and locations of the recombination events were much more variable than previously appreciated. Two more remarkable events, each larger than 5 kilobase pairs and encompassing more than 1 open reading frame, were also identified. One of these occurred in a person with documented coinfection with HSV-1 and HSV-2; analysis of DNA sequence data from the 2 viruses indicated that the actual recombination event occurred in this study participant.

These results led the authors to reasonably conclude that interspecific HSV-1 × HSV-2 recombination is still occurring in dually infected persons. Moreover, as the authors note, the study likely underestimates the frequency of recombination events, because many of the viruses evaluated for the study were collected locally.

We were surprised to find that this phenomenon was unidirectional in nature; that is, no HSV-1 isolates were found to contain elements of HSV-2 DNA. There is no immediately apparent reason why this should be so, given that the 2 viruses share sufficient sequence identity to form HSV-2 viruses bearing HSV-1 sequence elements. This unidirectionality might be explained in several ways. For example, it has been shown that rates of genital shedding of HSV-1 are lower than for HSV-2 [12]. In addition, dual oral infection with HSV-1 and HSV-2 occurs less commonly than genital coinfection. It may also be a reflection of the relative history of HSV-1 versus HSV-2 in humans. Specifically, HSV-1 has coevolved with the human lineage for an estimated 6 million years. In contrast, HSV-2 is thought to have been first transmitted to humans only approximately 1.6 million years ago [2]. As such, HSV-1 strains may possess a higher degree of host-specific selective fitness than HSV-1X HSV-2 recombinants.

This phenomenon raises concerns that the use of a live-attenuated HSV-2 vaccine in areas where HSV-1 prevalence is high could result in interspecific recombinant viruses with enhanced pathogenicity. Genital infections with HSV-1 are increasing in prevalence, which could result in an increased frequency of HSV-1 × HSV-2 recombination [13, 14].

These fascinating new insights into the dynamic interaction between 2 common HHV infections provide fresh concepts into how these complex viruses can maximize variation and thus continue their eons-old balance of power with their hosts. The larger scale, more geographically encompassing studies proposed by the authors promise to greatly expand our current knowledge about the evolution and generation of diversity in these viruses.

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