CORRESPONDENCE

Re: Lack of Serologic Evidence for Prevalent Simian Virus 40 Infection in Humans

We read with interest the article by Carter et al. (1) in which the authors performed a retrospective cross-sectional study using an enzyme-linked immunosorbent assay (ELISA) to determine the presence of simian virus 40 (SV40) antibodies in serum samples from three patient groups and from macaques. The results of their study indicated that the frequency of SV40 antibodies in human samples was 6.6%, that the ELISA detected cross-reactive antibodies for JCV, BKV (common human polyomaviruses), and SV40 in both human and macaque sera, and that the prevalence of authentic SV40 antibodies in human sera was unclear. These findings are similar to those of another retrospective analysis using enzyme immunoassays (2) in which serum samples from humans and macaques showed cross-reactivity to all three polyomaviruses. These demonstrations of cross-reactive antibodies are not surprising because ELISAs can detect non-neutralizing antibodies, and the assays used in the above-mentioned studies were based on the polyomavirus major capsid protein VP1, which shares some epitopes among the three viruses (3).

The dynamics of SV40 infections in humans and the immune response to those infections are not fully characterized. Some issues to consider in this regard are that human responses to SV40 may not be comparable to those against more common viral pathogens (e.g., adenovirus and herpesvirus) and that specific antibodies to SV40 may wane without re-infection. Interestingly, children receiving a known SV40-contaminated oral poliovirus vaccine were shown to excrete infectious SV40 in their stools for up to 5 weeks after vaccination but none showed a neutralizing antibody response to the viral infection (4).

It is agreed among those in the research community that prospective studies using sensitive and specific reagents for SV40 are needed to determine the prevalence of viral infections in the general population and to define groups of individuals at elevated risk for SV40-associated disease. However, for the reasons cited above, serologic tests alone may not be the most reliable way to conduct those studies (3). For example, serologic assays for identification of human infections with herpes B virus of macaques are limited by low sensitivity and specificity, similar to reports concerning SV40 assays (5). The herpes B virus system illustrates that the immune response in macaques to a given virus may not predict the human response to the same virus. Serologic assays may also be of minimal use for diagnosing or making therapeutic decisions in regard to SV40 infection because most overt polyomavirus infections presumably result from reactivation of latent infections (3). Cell culture for JCV, BKV, and SV40 infections is rarely helpful in diagnosing infection because of slow viral growth and the requirement for specialized cell lines (3). Therefore, modern molecular biology techniques, such as real-time polymerase chain reaction (PCR) and conventional PCR with sequence analysis, which are known to be highly sensitive and specific for SV40, are excellent alternatives for the analysis of SV40 infections and for studies of SV40 prevalence in humans. These techniques have been recognized as essential tools for providing insights into the possible infectious etiology of human malignancies (3).

In conclusion, future studies need to focus on how SV40 is transmitted among humans, how it is distributed throughout the infected host, and how the host responds immunologically. Indeed, the Institute of Medicine (6) recognized that those gaps in our understanding of the pathogenesis of SV40 infections in humans are important and recommended targeted biologic research of SV40 infection in humans.

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RESPONSE

We agree with Vilchez and Butel’s comments that serology is but one of several valid methods for examining the question of whether simian virus 40 (SV40) is circulating in the general population. The utility of polymerase chain reaction (PCR)-based methods for detecting SV40 DNA is indisputable; however, PCR results may be compromised by problems with specificity and/or contamination with plasmids containing SV40 sequences. Inter-laboratory comparisons of PCR methods have been equivocal (1). In addition, it will be important to determine the copy number of SV40 sequences in tumor tissues to determine whether SV40 sequences are present in every cell of the tumor. Serology must address similar issues of sensitivity and specificity, and we are currently validating our methods by
comparing them with those of another laboratory using blinded samples.

Vilchez and Butel point out that the dynamics of the SV40 antibody response in humans is not known. However, it is known that the human antibody response to other polyomaviruses and the macaque antibody response to infection by SV40 are vigorous and long-lasting. In our study (2), no human serum was found to have a vigorous antibody response specific for SV40 infection, whereas macaque sera had a pronounced response to SV40 infection. This finding suggested that SV40 antibody responses in humans were either extremely rare or, unlike other polyomavirus infections, of very low titer. Children who received oral SV40-contaminated poliovirus vaccine did not produce high-titer SV40 antibody responses; however, individuals who were injected with SV40-contaminated vaccines did have high-titer SV40 antibody responses (3). Together these findings suggest that, although SV40 is immunogenic, it is likely that there is not a sufficient quantity of virus to engender an antibody response when administered to humans in the oral form. Studies that have detected SV40 DNA in tumors in individuals who were not exposed to SV40-contaminated poliovirus vaccines would suggest that SV40 infection is widespread in the population (4). However, it is difficult to understand how SV40 could produce enough virus to be effectively transmitted without generating an antibody response in infected individuals.

Our results are consistent with several recent epidemiologic studies (5,6) that have failed to detect an association between exposure to SV40-contaminated poliovirus vaccines and human cancers and with the Viscidi laboratory (7), where no association between SV40 seropositivity and lymphoma was found. Although it is impossible to prove the absence of any SV40 infection in the population, the consistency of these findings, using different populations and methods, provides compelling evidence to suggest that SV40 is not a prevalent human pathogen.

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