We read with interest the recent article by Carter et al. (1), in which human sera were screened for antibodies to simian virus 40 (SV40). Sera were screened for SV40 antibodies by an enzyme-linked immunosorbent assay using SV40 VP1 virus-like particles (VLPs) as antigens. Although the fraction of SV40-positive human sera (6.6%) in the Carter et al. study (1) is in agreement with the results obtained in other investigations (2–6), Carter et al. report that SV40 reactivity in human sera disappeared after serum preadsorption with VLPs of BK virus (BKV) and JC virus.
suggested that specific SV40 antibodies can be produced by humans.

Fourth, although seroconversion to BKV and JCV is age dependent (5), there is no detectable age-dependent seroconversion to SV40 (1, 5, 6), suggesting that most of the SV40 antibodies detected in human sera are not generated by infection with BKV or JCV.

Fifth, in human sera from two immuno-suppressed renal transplant patients that were examined sequentially for antibodies to BKV, JCV, and SV40 over a period of 82 and 51 weeks, respectively, a substantial rise in SV40 antibody titers was detected after the kidney transplant (6), suggesting that a latent SV40 infection, similar to a latent BKV and JCV infection, can be reactivated in humans by immunosuppression. Moreover, during the follow-up, the curve of antibody titers to SV40 was different from that of antibody titers to either BKV or JCV (6), suggesting a specific immunologic response to SV40 in these two patients.

In conclusion, although antibody cross-reaction can occur during the immunologic response of humans to polyomavirus infection, unique SV40-specific antibodies can be detected in human sera. SV40-specific antigens, such as peptides that include SV40 structural epitopes that do not cross-react with BKV and JCV capsid antigens, should be used to detect the antibody-specific response to SV40 infection in the human population.

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REFERENCES


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DOI: 10.1093/jnci/djh151

RESPONSE

We thank Barbanti-Brodano et al. for their interest in our recent manuscript (1). We set out to examine the hypothesis that antibodies to simian virus 40 (SV40) would be prevalent in the population; given that so many tumor sites have been reported to harbor SV40 DNA, even in individuals too young to have been exposed to SV40, one prediction would be that SV40 is a commonly circulating virus in humans. There appears to be general agreement that, whereas antibodies to BK virus (BKV) and JC virus (JCV) are frequent, i.e., present in more than 50% of the population (1–3), only a small percentage of various populations examined have antibodies to SV40, and in these populations seropositivity to SV40 is highly correlated with seropositivity to BKV and JCV.

We disagree with Barbanti-Brodano et al.’s suggestion that this correlation is to be expected because of the high degree of sequence homology among the polyomavirus capsid proteins (VP1s). First, cross-reactivity between BKV and JCV has not been observed in several studies; in fact, very different patterns of seroreactivity to BKV and JCV have been observed that are related to age (1–3). Second, most human sera that are
positive for JCV or BKV antibodies do not cross-react with SV40; conversely, the majority of macaque sera that are seropositive for SV40 do not cross-react with BKV or JCV. Third, human papillomaviruses (HPVs) have a T=7 icosahedral virion that is similar to that of the polyomaviruses. The capsid proteins (L1s) of HPVs are closely related, yet HPV types elicit type-specific serologic responses (4,5). Structural studies of the HPV capsid (or virus-like particles [VLPs]) have shown that conserved residues of L1 form the internal core of the capsid, whereas residues that vary among HPV types are exposed on the surface (6). These type-specific residues form the immunoreactive epitopes that are seen in natural infections with HPV and in experimental infections with VLPs. Broadly cross-reactive antibodies to HPV can be generated only in response to denatured L1 protein. Thus, the fact that polyomavirus VP1 proteins share extensive homology reflects their conserved virion structure, not their shared antigenicity.

The authors cite one study (7) that examined more than 2000 sera from several geographic areas and found neutralizing antibodies to SV40 in 3–5% of the sera, although two small sets of sera showed greater variation (0% and 100%). The meaning of finding 100% seropositivity to SV40 in Moroccan children with poliomyelitis is unclear. Given the generally negative findings of SV40 seropositivity, this result would need to be confirmed before concluding that the sera had antibodies specific for SV40. We agree with the authors that there is no apparent relationship between SV40 seropositivity and age, unlike the distinct patterns seen for JCV and BKV (1,3), but we question what that result means. If the SV40 antibodies are the response to infection with SV40, when does the infection occur?

At this time, serological testing for antibodies to polyomaviruses is a young field. It is not clear why some people have antibodies that cross-react between SV40 and human polyomaviruses. However, certain findings about SV40 antibodies are consistent: 1) anti-SV40 antibodies in humans are infrequent and are of low titer, whereas BKV and JCV antibodies are frequent and of high titer, like anti-SV40 antibodies in macaques (1–3); 2) SV40 antibodies are not associated with poliovirus vaccination history or age; 3) SV40 antibodies are not associated with osteosarcoma in children in the United States (1) nor with non-Hodgkin lymphoma in patients from Spain (2). It has been suggested (3) that SV40 cross-reactive antibodies occur in individuals who have very high titers of BKV or JCV infection. Perhaps cross-reactive epitopes are seen in response to high viral loads or certain types of infection or occur in individuals with a particular immunogenetic background. Or perhaps they occur because a small number of people have been infected by SV40. All of these possibilities await further research.

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REFERENCES


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DOI: 10.1093/jnci/djh152