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MINIREVIEW

Simian Virus 40 Infection of Humans

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Since its discovery, simian virus 40 (SV40) has been one of the most intensely studied animal viruses. The molecular biology of SV40 has led to seminal discoveries in the fields of transcription, DNA replication, and oncogenic transformation (19). Over the last decade, provocative evidence has accumulated that suggests that SV40 may be a human pathogen. Does SV40 infect humans? If so, when did this monkey polyomavirus enter the human population and where is the reservoir? What is the behavior of SV40 in human cells? Does it cause or contribute to acute or chronic disease? Other comprehensive reviews have also addressed these issues, with a variety of emphases (8, 10, 52, 57, 107).

In 1960, Sweet and Hilleman first described an agent, which they named SV40, that induced cytopathic effects and vacuole formation in monkey cells (117). SV40 was isolated from normal monkey kidney cells, stocks of the Sabin poliovirus vaccine, and an adenovirus vaccine. The last two reagents were prepared in primary kidney cell cultures derived from rhesus monkeys. Subsequent analyses found that the Salk poliovirus vaccine administered from 1955 to 1963 in the United States was also contaminated with SV40, potentially exposing an estimated 100 million people (106). Although poliovirus in the Salk vaccine was inactivated by formalin treatment, the conditions were insufficient to completely inactivate SV40. Soon thereafter, it was demonstrated that SV40 could infect humans and also induce tumors in experimental animals (26, 28, 29, 42, 43). These observations raised concerns that vaccinated people worldwide may have been inadvertently exposed to an oncogenic virus. Early epidemiological studies allayed these fears, revealing no increased incidence of cancers directly related to immunization status (34, 35, 83, 106). However, these initial analyses were necessarily limited in that it was unknown whether (i) the virus could be transmitted, either horizontally or vertically; (ii) vaccinated, immunocompetent individuals would be at equal risk for development of cancer with others having defective immunity or a cancer predisposition; (iii) the power of the analysis was sufficient to detect increases in rare cancers; and (iv) SV40 normally circulated in humans before development of the poliovirus vaccine. A recent review of all epidemiological data by the Institute of Medicine concluded that evidence to date was "inadequate to accept or reject a causal relationship between SV40-containing poliovirus vaccines and cancer" (115). Criticisms included misclassification bias, lack of confidence intervals for the data, and "ecological" study design, which are unlikely to be remedied by further follow-up of the study populations.

A brief overview of the biology of SV40 is relevant to understand the concerns raised by these initial analyses (101). When SV40 infects its natural host, it initially undergoes a lytic replication cycle. The early viral genes encode the tumor (T) antigens: large T antigen (LT), small t antigen (ST), and 17K T antigen (also tiny T or T′). LT plays a dominant role in infection, repressing early viral gene transcription and stimulating late viral gene transcription (1, 54, 98, 121). LT is also an initiation factor for viral DNA replication (16, 97, 120, 123), recruiting the DNA polymerase α-primase complex to the origin of replication and acting as a helicase (21, 112, 114). Following the strategy of other DNA viruses, the SV40 early proteins dysregulate the cell cycle and impede cell apoptosis in order to maximize virus production. LT binds the members of the retinoblastoma protein family, pRb, p107, and p130, resulting in release and activation of E2F transcription factors, which stimulate expression of genes involved in S-phase progression and DNA synthesis (22, 27, 45). LT also binds p53 and inactivates its function, preventing the infected cell from undergoing apoptotic cell death (65, 71, 75). After viral DNA replication is under way, the infection enters the late phase, when viral structural proteins are synthesized and new virions are produced. Ultimately, the infected cell releases progeny virions, frequently but not always by cell lysis (18). The immune system is critical for controlling the initial lytic phase in vivo, quenching the initial infection to a state of persistent low-level or nonreplicating genomes (i.e., in the proximal renal tubular epithelium for SV40), with detectable lytic viral reactivation coincident only with host immunosuppression (48).

Some data on the infectivity of SV40 in humans were obtained from volunteers and individuals receiving contaminated vaccines. However, antibody data from many surveys must be viewed with the knowledge that the human BK virus (BKV) and JC virus (JCV) (closely related human polyomavirus family members) might give an indistinguishable response in these assays due to the high degree of cross-reactivity between capsid protein antigens. Melnick and Stinebaugh found SV40 (by cytopathic effects in monkey cells) in the stools of children 3 to 4 weeks after ingestion of 100 to 1,000 PFU of SV40 with oral poliovirus vaccine (77). Morris et al. gave SV40 intranasally to volunteers and found subclinical infections (82). They were able to isolate virus 7 to 11 days after administration from 3 of 8 subjects, and they detected antibody responses of various

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amplitudes. Horváth and Fornosi found SV40 excreted in the stools of 10 of 35 children 1 to 2 weeks after being given contaminated oral poliovirus vaccines (47). Thus, SV40 may replicate in humans after oral administration, but the efficiency and duration of the replication may be low in these immunocompetent subjects who were given small inocula.

The biology of SV40 in human cells was first studied in the 1960s with fibroblast cell lines or primary human fibroblast cell cultures (108). Whereas uninfected primary human fibroblasts can only be passaged a finite number of times before ceasing to divide and undergoing senescence, cell cultures infected with SV40 undergo a "crisis" at this same stage, followed by the outgrowth of a small number of cells that are phenotypically transformed (58). During the initial phase of the infection, generally the first 4 weeks, approximately 0.1% of the cells produce 500 to 1,000 virions per cell. Virus output from the culture then remains at a constant, very low level but with 100% of the cells producing virus at a rate of approximately 1 to 2 virions/cell (41, 42, 108). Once the cell culture progresses through crisis, virus production generally decreases, accompanied by a concomitant decrease in production of viral capsid proteins and an increase in the production of LT. One interpretation of these data is that the cells producing large amounts of virus are killed, but the cells that produce low levels of virus (as assayed by infectious center assays) survive. Finally, as the culture reaches its passage limit, most cells die, but those expressing a threshold level of LT overgrow the culture. Interestingly, the onset of transformation varies quite significantly in cells isolated from different individuals, ranging from 20 to almost 50 weeks in culture (91). Based on these early studies, human cells were termed semipermissive for SV40 growth (109). This nomenclature is confusing since the virus can clearly replicate in some human cell types more efficiently than in others, although the development of cytopathic effect is more rapid in African green monkey kidney cells.

More recent data have shown that while LT alone can immortalize human cells, ST is also necessary for eliciting a fully transformed phenotype (53, 93). For example, infection of cultured human mesothelial cells with SV40 establishes an apparently persistent infection in which little or no progeny virus is produced and the cells become transformed, a process requiring both LT and ST (4, 130). As described above, however, infected primary human fibroblasts can support robust lytic replication. The steady-state level of p53 in normal mesothelial cells is fourfold higher than that in fibroblasts, suggesting that the elevated p53 level interferes with the effect of LT upon DNA replication (4). Indeed, inhibition of p53 expression in mesothelial cells with an antisense oligonucleotide allows increased SV40 replication. Mesothelial cells therefore resemble infected late-passage primary fibroblasts with respect to virus production and growth characteristics.

SV40 is highly oncogenic in experimental animals and readily transforms rodent cells in culture (58). Hamsters inoculated with SV40 develop lymphomas, brain tumors, osteosarcomas, and mesotheliomas (25, 26, 28, 40, 56, 95). SV40 is likely oncogenic in rodents because LT is unable to interact functionally with the rodent DNA polymerase α-primase complex (84). In this setting, the oncogenic functions of the T antigens are engaged but the productive cycle is not completed, resulting in uncontrolled cell division rather than cell lysis. LT is both necessary and sufficient for initiation and maintenance of transformation of rodent cells in tissue culture in most instances (7). Under certain conditions, however, usually involving primary cells in the absence of growth factors, ST is also required. ST functions by inhibiting the activity of the cellular phosphatase PP2A, resulting in activation of cell growth signal transduction pathways (90, 100). Mice that are transgenic for LT transcriptionally regulated by tissue-specific promoters develop tumors in those tissues (for an example, see reference 105). Transgenic mice in which LT expression is regulated by the native viral promoter elements specifically develop tumors of the choroid plexus (6), the specialized epithelial structure of the brain ependymal lining that produces cerebrospinal fluid. This finding is interesting in view of the discovery of SV40 DNA in certain brain tumors, as discussed below.

After the discovery of SV40's tumorigenic and cell transformation properties, a wave of studies in the 1960s and 1970s pursued the identification of viral oncogenic agents in humans (9). SV40 DNA was detected on rare occasions, usually in brain tumors, using relatively low-sensitivity Southern hybridization techniques, immunostaining for LT, and electron microscopy (2, 61, 62, 76, 104, 118). Also during this period, the distinctly human polyomaviruses BKV and JCV were identified, and the destructive brain white matter disease progressive multifocal leukoencephalopathy was attributed to JCV infection (39, 86, 88). These human viruses were also shown to induce tumors in animals and to transform rodent and human cells in culture (20, 33, 94, 113, 127, 132). However, virtually all investigations failed to reveal any significant associations between human malignancy and these suspected oncogenic viruses. With the discovery of oncogenes, the emphasis in cancer research shifted from viruses to genomic mutations.

In 1992, Bergsagel et al. reported finding SV40-like DNA sequences in two types of rare childhood brain tumors, choroid plexus neoplasms and ependymomas, by use of PCR detection (3). This study was prompted by previous transgenic mouse studies and sought to determine whether the human polyomaviruses BKV and JCV might be present in these tumors. The PCR primers were designed to amplify the pRb binding domain of LT, which is highly conserved among all polyomavirus LT proteins. Unexpectedly, DNA sequences consistent with SV40 rather than BKV or JCV LT were amplified. Immunohistochemical nuclear staining for LT was also positive in a fraction of tumors. Subsequently, DNAs isolated from these same tumor types were evaluated by Lednicky et al., who verified the previous amplification results (67). In addition, they (i) found an unduplicated enhancer element, i.e., a single 72-bp repeat, characteristic of direct primate SV40 isolates but not laboratory virus strains (50), (ii) detected sequence variability in the carboxy terminus of different LT genes, and (iii) rescued infectious SV40 from one choroid plexus tumor whose DNA was directly isolated from fresh tumor tissue instead of from paraffin-embedded sections. Observations of SV40-like sequences in brain tumors continue to be reported (49, 59, 74).

With the same primers used by Bergsagel, Carbone et al. then detected SV40 sequences in human mesotheliomas (12). A mesothelioma is an aggressive tumor of the lung pleura, pericardium, or peritoneum and has been linked to asbestos

exposure. Carbone et al. had previously found that SV40 could induce mesotheliomas when injected into the pleural cavities of experimental animals (17). In extracts prepared from human mesotheliomas, p53, pRb, p107, and p130 can be coimmunoprecipitated with LT (13, 23). Microdissection studies have shown that SV40 DNA is present in tumor tissue but not in the normal surrounding lung (111). Adenovirus vectors expressing antisense SV40 LT arrest the growth of SV40-positive mesothelioma tumor cells and cause them to undergo apoptosis (126). As is the case for brain tumors, however, LT expression is not detectable by immunohistochemistry in all mesothelioma tumor cells, and the calculated amount of SV40 DNA may be less than one copy per cell. The number of reports identifying SV40 DNA in mesotheliomas far outnumber that for any other tumor type.

Other human tumors frequently associated with SV40-like DNA sequences are osteosarcomas and related bone tumors (14, 37, 68, 78, 129). When PCR strategies similar to those described above are used, approximately 30 to 40% of analyzed bone tumors are positive for viral DNA. SV40 sequences have been detected by Southern blot analysis in osteosarcoma tumor DNA, but this finding is rare. Most recently, in studies using the same primers, adult large-cell non-Hodgkin's lymphomas (NHL) were reported to contain SV40-like sequences (110, 125). Interestingly, the incidence of NHL has risen dramatically in the past three decades, similar to the increased incidence of mesotheliomas. In addition, throughout the past 10 years a potpourri of other tumors and tissues have been reported positive for SV40 DNA, although occasionally the results have not been independently confirmed by other groups (73, 74, 85). The search has extended to an association of SV40 with human renal disease, JCV with medulloblastomas and colon cancer, and BKV with neuroblastomas and urinary tract tumors (24, 32, 63, 64, 70, 81). The literature citations have proliferated, suggesting that SV40 has become epidemic or at least has developed into a cottage industry for PCR detection.

So why is there skepticism and controversy about the role of SV40 in human cancer? The following confounding technical issues remain problematic: (i) detection of SV40 DNA requires a large number of PCR cycles, i.e., 40 to 60, raising the question of how many cells contain viral DNA and how many genomes there are per cell; (ii) the method of DNA isolation has been questioned (e.g., some commercial extraction kits may lose small quantities of episomal viral DNA) (66); (iii) amplification of smaller genomic segments seems more prone to yield nonspecific products than amplification of larger fragments and these are often judged positive (e.g., the 572-bp fragment spanning the LT intron versus the 105-bp pRb binding region); (iv) DNA sequence verification of amplified products has not always been complete; (v) reproducibility among laboratories studying similar tumor types has not been universal (31, 55, 60, 99, 116, 128); (vi) lab contamination may confound some results (e.g., cloning vectors containing SV40 sequences have been suggested as sources of contamination, although those sequences should not be amplified by commonly used primers); (vii) the same PCR primer pairs have been used in most studies without attempts to improve upon their design or optimize their use; and (viii) the antibodies used for LT detection are not specific for SV40 but also cross-react with LT from JCV and BKV. Although detection of SV40 DNA by PCR for particular cancers (e.g., mesotheliomas and NHL) may reach 30 to 40% of cases, the lack of detectable SV40 DNA or LT in every cell of these tumors distinguishes the association from the recognized etiologic connection of high-risk human papillomaviruses with cervical cancer or Epstein-Barr virus with lymphoproliferative lesions in immunocompromised individuals (89, 131). This lack of uniform presence of the viral DNA, coupled with concerns about PCR techniques, a past history of negative associations, the litigious cloud of contaminated poliovirus vaccines, a paucity of information on the SV40 life cycle in relevant human cell types, and a scientific culture now emphasizing oncogenes rather than oncoviruses, have made the existence of SV40 in humans, let alone its causality in disease, a "hard sell."

Gradually, however, the case for SV40 infecting humans and contributing to cancer has become more compelling, supported by both experimental and circumstantial evidence: (i) microdissection identified amplifiable SV40 DNA in mesotheliomas but not in adjacent normal tissues (111), (ii) SV40 DNA has been detected in an osteosarcoma by Southern hybridization (78), (iii) Li-Fraumeni syndrome patients appear to have a unique susceptibility to polyomaviruses (see below) (72), (iv) a single 72-bp repeat identified in the viral enhancer of SV40 DNA isolated from choroid plexus tumors is characteristic of virus isolates from monkeys (50, 67), and (v) infectious SV40 was isolated from choroid plexus tumor tissue (67). In an attempt to address the variance in detection, two multilaboratory studies were undertaken to examine the presence of SV40 in mesothelioma samples (51, 122). Unfortunately, both studies had technical flaws and their conclusions were contradictory, leaving the question of why there are differences in detection unsettled. However, analysis of samples from geographically distinct populations has provided unique naturally occurring controls. Mesothelioma samples from Finland, where contaminated poliovirus vaccines were not administered, are negative for SV40 DNA (46). A recent study of a Turkish community with a very high frequency of mesothelioma linked to environmental asbestos exposure also found no evidence for SV40 DNA in the tumors from this unvaccinated population (30). Thus, SV40 DNA is only found in mesotheliomas in areas of the world where the contaminated vaccines were used, indirectly suggesting a link between SV40 and the cancer.

If present, how might SV40 be selectively oncogenic in some tissues and/or individuals? Factors may include the sensitivity of the particular tissue to pRb and p53 dysfunction, activity of the viral promoter, tropism or targeting of the virus to specific cell types, genetic predisposition, and immune status. As demonstrated with transgenic mice, choroid plexus cells are unusually sensitive to p53 and pRb mutations, leading to rapid malignant transformation (15, 124). The choroid plexus may be functionally related to proximal renal tubular epithelium (i.e., an ion pumping machine), and thus factors in these cells may be similarly permissive for viral gene expression. In pRb-deficient patients, osteosarcomas are the second most common neoplasm after retinoblastoma. Thus, osteoblasts may be very susceptible to pRb deficiencies (69). Li-Fraumeni syndrome patients, who are heterozygous for germ line p53 mutations, seem unusually susceptible to SV40 infection, possibly because inactivation of the remaining wild-type p53 allele can be accomplished with lower T-antigen expression levels. It may also

be possible that SV40 can establish an initial infection in these individuals more easily if there is less p53 present to interfere with viral replication. Li-Fraumeni syndrome patients have been described who develop choroid plexus tumors and osteosarcomas that contain SV40 DNA, but other tumor types within the same individual, such as muscle rhabdomyosarcomas, are not associated with SV40 DNA sequences (72). This tissue preference may occur because of cell type variations in viral promoter activity, virus receptors, or the relative importance of p53 and pRb for the initial oncogenic event.

More difficult to explain is the apparent lack of SV40 DNA (calculated) or protein (detected by immunohistochemistry) in all the cells of a tumor. Possible reasons include the following: (i) levels of LT protein expression below the limits of detection; (ii) a paracrine mechanism by which LT-expressing cells secrete a growth factor, e.g., insulin-like growth factor type I (IGF-I), affecting surrounding cells that do not contain SV40 (92); (iii) isolation of the tumor after most virus-containing cells have died (hit-and-run), leaving only tumor cells with additional mutations contributing to proliferation (i.e., LT and/or ST causes chromosomal instability [36, 96] and is then lost in the transformed cells); and (iv) SV40 not contributing to tumorigenesis but being present because the tumor growth state is permissive for virus replication or LT protein expression.

Cause and effect have been indirectly addressed by antisense LT expression in cultured cells, which implies that, at least in mesothelial cells, LT makes a significant contribution to the ability of these cells to grow in culture (126). One approach to explore a causal role of LT in malignancy might be to correlate the *p53* and *RB1* status of tumors with the presence of SV40 sequences. Inactivation of these pathways by mutation would not be necessary if LT was continuously produced and active. For example, the frequency of *p53* and *RB1* gene mutations is low in mesothelioma and thus LT may be functionally important (11). Osteosarcomas with wild-type p53 and those with defective p53 would be candidates for such a comparative analysis.

What is needed to enhance our understanding of SV40 infection in humans and the role of SV40 in human malignancies? Current data on SV40 replication and transmission in human populations are nearly uninterpretable and will not improve until a highly specific serological assay for SV40 is used to analyze clinical samples. Such an immunoassay has been difficult to devise because of extensive cross-reactivity of the SV40 capsid proteins with those of BKV and JCV. Virus neutralization assays are extremely labor-intensive and have not been directly compared among the viruses. Recently, however, recombinant VP1 capsid proteins for SV40, JCV, and BKV have been prepared as virus-like particle preparations for use in enzyme-linked immunosorbent assays (K. Shah and D. Galloway, personal communications). The initial serological studies using these reagents have not detected specific or robust SV40 immune responses in any samples tested. A small fraction (5 to 7%) of sera (K. Shah, personal communication) have low-level reactivity with SV40 VP1 that may be due to cross-reactivity with JCV or BKV VP1 or to a transient SV40 infection. These assays will now permit case-controlled studies, however, comparing individuals with SV40-associated malignancies to control populations.

Seroepidemiologic studies would permit an assessment of SV40 prevalence in the population, suggest its mode of transmission, and correlate seropositivity with disease or perhaps even predisposition to disease. From current PCR data it appears that individuals who were never exposed to contaminated vaccines have been infected with SV40, suggesting that the virus has established itself as a human pathogen. The mode of transmission may be extrapolated from that of BKV and JCV. Studies have shown that these two viruses infect virtually 100% of most human populations, BKV during early childhood and JCV peaking in early adolescence (38, 87, 119). While both viruses ultimately establish a persistent infection in the urinary tract and perhaps in the central nervous system, recent reports have found the presence of viral DNA in tonsillar tissue (44, 79, 80). The presence of virus in the upper respiratory tract, along with the young age of seroconversion, suggests that SV40 may spread through a respiratory or fomite, i.e., hand-to-mouth, route. From this initial portal of entry, the virus must have access to the circulatory and/or lymphatic system in order to reach its presumed site of persistence, the kidney, or the tissues and organs that give rise to the tumors associated with the virus. By analogy with other viruses, such systemic virus spread, or virus replication at sites of tumor induction, should elicit a detectable immune response.

More information is needed concerning the SV40 life cycle in human cells. Are there differences in permissiveness among human cell types? Is there a correlation of oncogenicity with levels of p53 in different cell types, e.g., as seen in mesothelial cells? Are there differences among cell types in viral genome persistence? Are secondary cellular mutations induced when LT is highly expressed, and do the mutations lead to stable populations of dominantly replicating clones that now lack viral DNA? Finally, the role of the immune system in all phases of the disease process is undoubtedly profoundly important. Unlike most putative tumor antigens, SV40 T antigens are not self antigens and therefore ought to be recognized by the immune system. Does the tumor provide an immunoprivileged site in which these antigens are not detected? In rodent SV40 tumor models, the immune response against LT is robust and usually results in clearance of the virus, making this possibility unlikely (102, 103). Moreover, humans can apparently mount a cytotoxic lymphocyte immune response to LT (5). However, there must be some coexistence of the immune system and the virus to achieve persistence. Thus, defects in the immune system might permit virus persistence to develop into an oncogenic state. In this regard, it would be useful to study SV40 infections in immunocompromised individuals. Based on the evolving SV40 story, it also seems prudent to look more carefully at a possible role of BKV and JCV in human neoplasms, as there is no doubt that these viruses are endemic in most human populations.

At this time, some members of the jury remain undecided about a role for SV40 in human disease. Seroepidemiology and a basic understanding of virus biology in humans are essential pieces missing from the puzzle. Perhaps we expect SV40 to follow the "rules" for other oncogenic viruses such as human papillomavirus and Epstein-Barr virus. Rather, SV40 may be generating novel rules, leading the way as it has before into new paradigms of virus biology and pathogenesis.

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