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Minireview

Simian virus 40 infection in humans and association with human diseases: results and hypotheses

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Abstract

Simian virus 40 (SV40) is a monkey virus that was introduced in the human population by contaminated poliovaccines, produced in SV40-infected monkey cells, between 1955 and 1963. Epidemiological evidence now suggests that SV40 may be contagiously transmitted in humans by horizontal infection, independent of the earlier administration of SV40-contaminated poliovaccines. This evidence includes detection of SV40 DNA sequences in human tissues and of SV40 antibodies in human sera, as well as rescue of infectious SV40 from a human tumor. Detection of SV40 DNA sequences in blood and sperm and of SV40 virions in sewage points to the hematic, sexual, and orofecal routes as means of virus transmission in humans. The site of latent infection in humans is not known, but the presence of SV40 in urine suggests the kidney as a possible site of latency, as it occurs in the natural monkey host. SV40 in humans is associated with inflammatory kidney diseases and with specific tumor types: mesothelioma, lymphoma, brain, and bone. These human tumors correspond to the neoplasms that are induced by SV40 experimental inoculation in rodents and by generation of transgenic mice with the SV40 early region gene directed by its own early promoter–enhancer. The mechanisms of SV40 tumorigenesis in humans are related to the properties of the two viral oncoproteins, the large T antigen (Tag) and the small t antigen (tag). Tag acts mainly by blocking the functions of p53 and RB tumor suppressor proteins, as well as by inducing chromosomal aberrations in the host cell. These chromosome alterations may hit genes important in oncogenesis and generate genetic instability in tumor cells. The clastogenic activity of Tag, which fixes the chromosome damage in the infected cells, may explain the low viral load in SV40-positive human tumors and the observation that Tag is expressed only in a fraction of tumor cells. "Hit and run" seems the most plausible mechanism to support this situation. The small tag, like large Tag, displays several functions, but its principal role in transformation is to bind the protein phosphatase PP2A. This leads to constitutive activation of the Wnt pathway, resulting in continuous cell proliferation. The possibility that SV40 is implicated as a cofactor in the etiology of some human tumors has stimulated the preparation of a vaccine against the large Tag. Such a vaccine may represent in the future a useful immunoprophylactic and immunotherapeutic intervention against human tumors associated with SV40.
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The relationship of simian virus 40 (SV40) with the human species has focused on two main aspects: the circulation of the virus in humans by contagious transmission and its association, as a possible etiologic cofactor, with some human tumors. Contrasting reports have appeared on both these subjects and several reviews have analyzed and discussed the different contributions published in the literature (Barbanti-Brodano et al., 1998; Butel and Lednicky, 1999; Carroll-Pankhurst et al., 2001; Ferber, 2002a,b; Geissler, 1990; Jasani et al., 2001; Klein et al., 2002; Lednicky and Butel, 1999; Monini et al., 1995; Mortimer et al., 1981; Pennisi, 1997; Rollison and Shah, 2002; Shah, 2000; Strickler and Goedert, 1998; Strickler and The International SV40 Working Group, 2001; Strickler et al., 1996, 1998; Testa et al., 1998; Vilchez et al., 2003). As a consequence of these conflicting results, a considerable debate has developed in the scientific community. An excellent analysis has recently addressed the problems raised by this controversy, discussing and evaluating the pertinent literature on SV40 infection of humans and on its

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involvement in human tumors (Garcea and Imperiale, 2003). More than examining again in detail all the existing data, in the present review we consider the main results supporting SV40 infection of humans and its association with human tumors, and comment on the hypotheses arising from these results.

Epidemiology of SV40 infection in humans

Natural infection by SV40 in humans was considered a rare event, restricted to people living in contact with monkeys, the natural hosts of the virus, such as inhabitants of Indian villages located close to the jungle, and persons attending to monkeys in zoos and animal facilities (Shah and Nathanson, 1976). This epidemiological evidence, however, did not consider that massive infection of the human population by SV40 occurred between 1955 and 1963, when hundreds of millions of persons in the United States, Canada, Europe, Asia and Africa were vaccinated with both inactivated and live polio vaccines contaminated with infectious SV40 (Carbone et al., 1997b). Soon it was shown that people vaccinated with contaminated polio vaccines shed infectious SV40 in stools for at least 5 weeks after vaccination (Melnick and Stinebaugh, 1962). This observation suggested that SV40 could be transmitted by recipients of contaminated polio vaccines to contacts by the orofecal route, raising the possibility that, although human cells are less susceptible to SV40 replication compared to monkey cells (O'Neill and Carroll, 1981; Shein and Enders, 1962), SV40 would spread in humans by horizontal infection.

This hypothesis is now supported by several observations, in agreement with the indications of a scientific panel that recently established the importance of assessing the ways of contagion by SV40 and the mechanisms of SV40 transmission in humans (Ferber, 2002b). First, SV40 DNA sequences were detected in normal and neoplastic tissues of persons too young (1 to 30 years) or too old (60 to 85 years) to have been vaccinated with SV40-contaminated polio vaccines (Barbanti-Brodano et al., 1998; Bergsagel et al., 1992; Carbone et al., 1994, 1996; Lednicky et al., 1997; Martini et al., 1996, 2002). This finding may also explain the lack of difference in cancer incidence between individuals vaccinated with SV40-contaminated and SV40-free polio vaccines (Strickler and Goedert, 1998). Second, SV40 sequences were detected in blood and sperm specimens of neoplastic and normal individuals (David et al., 2001; Li et al., 2002a,b; Martini et al., 1995, 1996, 1998, 2002; Yamamoto et al., 2000) and SV40 virions were found in urine and sewage samples (Li et al., 2002b; Vastag, 2002), indicating that the hematic, sexual and orofecal routes of transmission are likely to be responsible for SV40 horizontal infection in humans. Third, infectious SV40 was rescued by transfection of CV-1 monkey cells with the DNA of an SV40-positive human choroid plexus carcinoma (Lednicky et al., 1995). Finally, antibodies to SV40 capsid antigens were found in human sera. One study reported the presence of SV40 antibodies in human sera before the introduction of poliovirus vaccination (Geissler et al., 1985), raising the possibility that SV40 or an SV40-like virus was circulating in humans before the use of contaminated vaccines. This investigation, however, was conducted before the discovery of the two ubiquitous human polyomaviruses BK (BKV) and JC (JCV) (Imperiale, 2000, 2001) which cross-react antigenically with SV40. Therefore, the specificity of the antibodies detected in this study may be questioned. The antigenic cross-reaction between the two human polyomaviruses and SV40 has been so far the most difficult problem to study the real diffusion of SV40 infection in humans. The tests used in serological surveys were a plaque reduction assay and an ELISA test based either on SV40 virions or on the SV40 recombinant VP1 capsid protein produced in a baculovirus system. By these assays, a limited number (1.3% to 15.6%) of normal human sera showed antibodies to SV40 (Basetse et al., 2002; Butel et al., 1999, 2003; De Sanjose et al., 2003; Jafar et al., 1998; Rollison et al., 2003; Shah, 1966; Shah et al., 1971; Viscidi et al., 2003), suggesting a low virus circulation in the human population. All these serological tests, however, do not exclude cross-reaction with BKV and JCV capsid proteins. Preliminary analyses in our laboratory indicate that SV40-specific antibodies could be present in a fraction of the human population larger than previously reported. On the whole, these observations support the notion that infectious SV40 is present in human tissues and may be contagiously transmitted in the human population either directly by person-to-person contacts or indirectly by the orofecal route, independently from the earlier administration of SV40-contaminated polio vaccines.

Evidence for the association of SV40 with human diseases

SV40 sequences were detected in kidney and cells of urine sediments from patients with focal segmental glomerulosclerosis and SV40 was isolated by cocultivation of cells from urine sediments of such patients with CV-1 monkey cells (Li et al., 2002b). Several strains of SV40 were rescued in this study, including strain 776 and other strains bearing mutations in the early and late regions. In addition, SV40 sequences were detected, in association with BKV sequences, in kidneys of patients with post-transplantation interstitial nephritis (Li et al., 2002a). Since the two SV40-like human polyomaviruses BK and JC are implicated in human nephropathy in renal allograft recipients (Baksh et al., 2001; Drachenberg et al., 1999; Hogan et al., 1980; Howell et al., 1999; Nickeleit et al., 1999, 2000a,b; Randhawa et al., 1999), these results suggest that SV40 too may be etiologically related to these two syndromes and may cooperate, by co-infection with BKV, to the etiopathogenesis of chronic interstitial nephritis (Li et al., 2002a). In addition, the

presence of SV40 in kidney and urine points to the kidney as a site of virus latency, like in the natural monkey host (Sweet and Hilleman, 1960).

In spite of its possible involvement in these inflammatory diseases, the main role postulated for SV40 in human pathology derives from its association with some human cancers: mesothelioma, lymphoma, brain and bone tumors as well as thyroid, pituitary and parotid gland tumors (Bergsagel et al., 1992; Carbone et al., 1994, 1996; Cristaudo et al., 1995; Galateau-Salle et al., 1998; Geissler, 1990; Griffiths et al., 1998; Huang et al., 1999; Jasani et al., 2001; Klein et al., 2002; Lednicky et al., 1997; Martinelli et al., 2002; Martini et al., 1996, 1998, 2002; Mendoza et al., 1998; Monini et al., 1995; Pacini et al., 1998; Pepper et al., 1996; Rizzo et al., 2001; Shivapurkar et al., 2002; Strickler et al., 1996; Suzuki et al., 1997; Testa et al., 1998; Vivaldi et al., 2003; Vilchez et al., 2002; Woloschak et al., 1995). These human tumors correspond to the neoplasms that are induced by SV40 experimental inoculation in rodents (Barbanti-Brodano et al., 1998) or by generation of transgenic mice with the SV40 early region gene directed by its own early promoter–enhancer (Brinster et al., 1984; Palmiter et al., 1985; Van Dyke et al., 1987). It is notable that mice transgenic for the SV40 Tag gene directed by the JCV regulatory region develop choroid plexus carcinomas (Feigenbaum et al., 1992) like mice transgenic for the SV40 Tag gene controlled by its own natural promoter, indicating that polyomavirus transforming sequences per se play a critical role, independently from the control region that directs their expression, in the determination of tissue targeting and pathogenicity. The association of SV40 with human tumors is proved by the presence of SV40 sequences in tumor tissues and by the expression of the virus-specific RNA and proteins. The SV40 sequences were generally detected in an episomal state and rarely integrated in tumor DNA (Mendoza et al., 1998; Pacini et al., 1998). In addition, infectious SV40 was isolated from a choroid plexus carcinoma (Lednicky et al., 1995). Human brain tumors, like kidneys affected by post-transplantation nephritis (Li et al., 2002a), are often co-infected by SV40 and BKV (Martini et al., 1996), suggesting a possible co-operation between the two polyomaviruses in the oncogenic effect or a helper function of BKV for SV40 replication in human cells. Negative results were also reported on the association of SV40 with human tumors (Capello et al., 2003; De Sanjose et al., 2003; Engels et al., 2002; Gordon et al., 2002; Shah, 2000; Strickler and The International SV40 Working Group, 2001; Volter et al., 1997). However, Capello et al. (2003), while failing to detect SV40 sequences in lymphomas, reproducibly found them in mesotheliomas, and Volter et al. (1997) investigated human tumor samples for the presence of SV40 late gene sequences which are unlikely to be involved in the process of SV40-induced transformation and tumorigenesis. The contribution by Engels et al. (2002) raised a controversy because the assay used in this study was estimated to be affected by low sensitivity (Carbone et al., 2003; Engels et al., 2003). To settle the dispute among different results on SV40 in human tumors, two multi-institutional studies were performed to examine the presence of SV40 in human malignant mesotheliomas (Strickler and The International SV40 Working Group, 2001; Testa et al., 1998). Unfortunately, the two investigations reached opposite conclusions, leaving the question unresolved. Recently, a serological survey for antibodies to capsid proteins of BKV, JCV and SV40 indicated no association of the three viruses with human astrocytic brain tumors (Rollison et al., 2003). Search for antibodies to polyomavirus structural proteins (De Sanjose et al., 2003; Rollison et al., 2003) may not be the best assay to evaluate polyomavirus association with human tumors. Indeed, antibodies to polyomavirus large T and small t oncoproteins may better reflect immunization against polyomavirus tumor-specific antigens.

Transformation of rodent and human cells by SV40 is induced by the two oncoproteins encoded in the early region of the viral genome, the large tumor antigen (Tag) (Simmons, 2000) and the small tumor antigen (tag) (Rundell and Parakati, 2001). Both these proteins display multiple functions. However, the main activity of Tag for cell transformation and tumorigenesis is to target key cellular proteins, such as the tumor suppressor p53 and pRB family proteins, inactivating their functions (Pipas and Levine, 2001; Sáenz-Robles et al., 2001). The principal role of tag in transformation is to bind the serine–threonine protein phosphatase PP2A (Beck et al., 1998; Pallas et al., 1990). This interaction leads to inhibition of PP2A with consequent constitutive activation of the Wnt pathway (Cadigan and Nusse, 1997), lack of inactivation of β-catenin, its translocation to the nucleus and stimulation of cell proliferation (Ikeda et al., 2000; Willert and Nusse, 1998). The block of PP2A functions by tag induces an alteration of the actin cytoskeleton and tight junctions, resulting in loss of cell polarity and tumor invasiveness (Nunbhakdi-Craig et al., 2003). Small tag interacts with the centrosome and blocks mitosis in human cells (Gaillard et al., 2001), suggesting that it may disrupt cell cycle progression. Recently, it was shown that tag activates, in human mammary epithelial cells, phosphatidylinositol 3-kinase (Zhao et al., 2003), an enzyme involved in pathways crucial for cell proliferation and transformation. The functions of SV40 Tag must be continuously expressed in SV40-transformed cells to establish and maintain transformation, since rodent and human cells transformed by temperature-sensitive mutants of Tag lose the transformed phenotype at the non-permissive temperature (Brugge and Butel, 1975; Martin and Chou, 1975; Osborn and Weber, 1975; Tegtmeyer, 1975).

This condition is in contrast with the evidence that the viral load in SV40-positive human tumors is generally low (less than one genome equivalent per cell) and Tag is expressed only in a fraction of tumor cells (Barbanti-Brodano et al., 1998; Garcea and Imperiale, 2003; Martini et al., 1998). The situation, however, may be more complex

in human cells. Indeed, in human cells, SV40 Tag induces chromosome aberrations (Ray et al., 1990; Stewart and Bacchetti, 1991) which likely affect the functions of genes involved in tumorigenesis, such as oncogenes, tumor suppressor and DNA repair genes (Coleman and Tsongalis, 2002; Reinartz, 2002; Shimamoto and Ohyashiki, 2002). Once chromosomal damage has been triggered in tumors and chromosomal aberrations have reached a threshold, genomic instability ensues (Lengauer et al., 1998), due to the functional alteration of DNA repair genes, leading to more genetic lesions and tumor progression (Coleman and Tsongalis, 2002; Lengauer et al., 1998; Shimamoto and Ohyashiki, 2002). This process does not need the maintenance of the original injury that initiated tumorigenesis. The same course of events may occur in SV40-positive human tumors, where the clastogenic activity of Tag, like a chemical or physical carcinogen, initiates the tumorigenic process by hitting the cell genome, then becomes dispensable and is lost in the progression phase of the tumor, when the accumulation of genetic alterations renders the presence of viral transforming functions unnecessary. Immunoselection may even be exerted against persistently SV40-infected cells, while genetically mutated, uninfected cells may have a proliferative advantage and become the prevalent population in the tumor. This "hit and run" mechanism was originally proposed to explain transformation of human cells by the mutagenic herpesviruses (Galloway and McDougall, 1983; Schlehofer and zur Hausen, 1982), and has been recently suggested to be operative in colorectal carcinogenesis associated with JCV (Ricciardiello et al., 2003). Contrary to SV40-transformed human cells, in transformed rodent cells, where SV40 Tag is equally clastogenic, SV40 sequences are not lost during chromosomal rearrangements. This difference may depend on the fact that rodent cells are non-permissive to SV40 replication and therefore the incoming viral DNA is integrated and fixed into the cell genome (Barbanti-Brodano et al., 1998). Because human cells are semi-permissive to virus replication, most of the SV40 DNA molecules remain in an episomal state, even when cell transformation is established (Barbanti-Brodano et al., 1998), rendering them more prone to be lost.

Another observation explaining the low viral load in SV40-positive human tumors is that SV40 Tag induces a paracrine mechanism by which a growth factor, such as insulin-like growth factor type I (IGF-I), is secreted by SV40-positive cells (Porcu et al., 1992) and may stimulate proliferation of surrounding cells that do not contain SV40. More recently, it was shown that Tag activates in mesothelial cells an autocrine–paracrine loop, involving the hepatocyte growth factor (HGF) and its cellular receptor, the oncogene c-*met* (Cacciotti et al., 2001), as well as the vascular endothelial growth factor (VEGF) and its cellular receptor (Cacciotti et al., 2002; Catalano et al., 2002). HGF and VEGF, released from SV40-positive cells, bind their receptors in neighboring and distant SV40-positive and SV40-negative cells, driving them into proliferation and tumorigenesis. Thus, not every cell would need to express polyomavirus Tag in order to participate in tumor growth.

The role of SV40 Tag in the pathogenesis of human mesothelioma was shown by: (i) its ability to bind in vivo p53 and RB family proteins in human mesothelioma samples (Carbone et al., 1997a; De Luca et al., 1997); (ii) activation of Notch-1, a gene promoting cell cycle progression and cell proliferation, in primary human mesothelial cells (Bocchetta et al., 2003); (iii) induction of apoptosis in mesothelioma cells transfected with antisense DNA to the SV40 early region gene (Waheed et al., 1999); (iv) the presence of SV40 Tag specific antibodies in sera of mesothelioma patients (Bright et al., 2002); and (v) the poorer prognosis of mesotheliomas harboring SV40 early region sequences compared to SV40-negative mesotheliomas (Procopio et al., 2000). Moreover, mesothelial cells are particularly susceptible to infection and transformation by SV40 (Bocchetta et al., 2000; Cacciotti et al., 2001). Asbestos, which is the main cause of human mesothelioma, cooperates with SV40 in transformation of murine cells as well as of human fibroblasts and mesothelial cells (Bocchetta et al., 2000; Dubes, 1993), suggesting that SV40 and asbestos may be co-carcinogens in the pathogenesis of mesothelioma. Fluorescent in situ hybridization analysis indicated that the RB and cyclin E/CDK2 genes undergo the same type of deregulation during the cell cycle in asbestos-treated and SV40-transformed human mesothelial cells as well as in mesothelioma cells (Dopp et al., 2002). Recently, it was shown that SV40 tumor antigens induce telomerase activity in human mesothelial cells, but not in human fibroblasts (Foddis et al., 2002), suggesting that both SV40 oncoproteins specifically participate in the immortalization of mesothelial cells during mesothelioma development.

The SV40 sequences detected in Italian samples (Barbanti-Brodano et al., 1998; Carbone et al., 1996; Cristaudo et al., 1995; Martini et al., 1998; Pacini et al., 1998; Tognon et al., 2001) constantly showed two 72-bp repeats in the enhancer domain of the regulatory region. Duplication of the 72-bp regulatory sequence gives a growth advantage to SV40 for replication in permissive cells in culture (Butel and Lednicky, 1999). The SV40 strains which contaminated polio vaccines show a regulatory region which contains either one or two 72-bp repeats (Rizzo et al., 1999). SV40 strains with two 72-bp repeats detected in human tissues may therefore represent viruses circulating in the human population after poliovirus vaccination. As pointed out in a recent critical review (Vilchez et al., 2003), descriptive epidemiological surveys are unable to distinguish between exposure to and infection by SV40. Thus, the SV40 strains with two 72-bp repeats in the regulatory region, present as contaminants in poliovirus vaccines, may have a selective advantage for infection and replication in human cells and propagate more easily in humans. SV40 strain variability, found in the United States (Lednicky and Butel, 2001; Vilchez et al., 2003), could be due to the heterogeneous

human population of this country, although the SV40 wild-type strain 776, which has two 72-bp repeats in the enhancer domain of the regulatory region, was the main representative among the different SV40 strains detected in kidney, urine and blood samples of an American group consisting of normal persons and patients affected by focal segmental glomerulosclerosis (Li et al., 2002b). SV40 regulatory region sequences with two 72-bp repeats were detected in the United States also in human osteosarcomas and mesotheliomas (Lednicky et al., 1997; Pass et al., 1998) as well as in monkey tissues (Lednicky et al., 1998; Stewart et al., 1998). The SV40 strain homogeneity detected by different groups in Italian patients may reflect the more homogeneous population present in Italy. Indeed, JCV, which is closely related to SV40, has a geographical strain distribution (Agostini et al., 1997; Barbanti-Brodano et al., 1998).

The problems of the SV40 infection in human population and of SV40 contribution to human cancer may be summarized by considering a recent evaluation by the Immunization Safety Review Committee established by the Institute of Medicine of the National Academies (Stratton et al., 2002). The Committee stated that "the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer". In fact, the epidemiological studies conducted in the past are flawed by the difficulty to establish which individuals received contaminated vaccines, to determine the dosage of infections SV40 present in different lots of vaccine (due to formalin inactivation of poliovirus which may have variably affected SV40 infectivity), and finally to follow large cohorts of subjects for several decades after virus exposure to monitor for cancer development (Vilchez et al., 2003). The Committee concluded that "the biological evidence is strong that SV40 is a transforming virus, but it is of moderate strength that SV40 exposure from polio vaccine is related to SV40 infection in humans and that SV40 exposure could lead to cancer in humans under natural conditions". The Committee also recommended development of specific and sensitive serologic tests for SV40 and use of standardized techniques that should be accepted and shared by all laboratories involved in SV40 detection.

Although it may seem somehow a premature effort, the conviction that SV40 is implicated as a cofactor in the etiology of some human tumors has prompted programs to prepare a vaccine against the main viral oncoprotein, the SV40 Tag (Imperiale et al., 2001). A recombinant vaccinia vector containing a safety-modified SV40 Tag sequence was constructed (Xie et al., 1999). Such modified Tag excludes the p53 and RB protein binding sites as well as the amino-terminal oncogenic CRI and J domains (Sáenz-Robles et al., 2001), but preserves the immunogenic regions. Tumorigenesis studies carried out in vivo indicated that this vector can efficiently prime the immune response to provide effective, antigen-specific prophylactic and therapeutic protection against SV40 Tag-expressing lethal tumors (Xie et al., 1999). Although truncation of Tag at the carboxyl terminus, where the p53 binding sites are located, yields unstable products (Sáenz-Robles et al., 2001), such types of vaccines may represent in the future a useful immunoprophylactic and immunotherapeutic intervention against human tumors associated with SV40.

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