

Simian virus 40, poliovirus vaccines, and human cancer: research progress versus media and public interests

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From 1955 through early 1963, millions of people were inadvertently exposed to simian virus 40 (SV40) as a contaminant of poliovirus vaccines; the virus had been present in the monkey kidney cultures used to prepare the vaccines and had escaped detection. SV40 was discovered in 1960 and subsequently eliminated from poliovirus vaccines. This article reviews current knowledge about SV40 and considers public responses to reports in the media. SV40 is a potent tumour virus with broad tissue tropism that induces tumours in rodents and transforms cultured cells from many species. It is also an important laboratory model for basic studies of molecular processes in eukaryotic cells and mechanisms of neoplastic transformation. SV40 neutralizing antibodies have been detected in individuals not exposed to contaminated poliovirus vaccines. There have been many reports of detection of SV40 DNA in human tumours, especially mesotheliomas, brain tumours and osteosarcomas; and DNA sequence analyses have ruled out the possibility that the viral DNA in tumours was due to laboratory contamination or that the virus had been misidentified. However, additional studies are necessary to prove that SV40 is the cause of certain human cancers. A recently published review article evaluated the status of the field and received much media attention. The public response emphasized that there is great interest in the possibility of health risks today from vaccinations received in the past.

Keywords: drug contamination; mass media; poliovirus vaccine, adverse effects; *Polyomavirus maccacae*; public opinion.

Voir page 197 le résumé en français. En la página 197 figura un resumen en español.

Simian virus 40 (SV40) is a polyomavirus of rhesus macaque origin (1–3). It was present but unrecognized in the monkey kidney cell cultures used to prepare both the inactivated and live attenuated poliovirus vaccines, as well as several other viral vaccines (4). Consequently, between 1955 and the early part of 1963, millions of people were inadvertently exposed to live SV40 when they were administered SV40-contaminated vaccines (5–8). The major sources of exposure were poliovirus vaccines; not only was SV40 present in early lots of live poliovirus vaccine, but some infectious SV40 survived the inactivation treatments used to prepare the killed vaccine. As far as is known, no contaminated poliovirus vaccine has been used since early 1963.

Following its discovery in 1960, SV40 became the object of intense investigation. It was found to possess potent oncogenic potential, having the ability to induce tumours in rodents, to transform cells in tissue culture (1–3, 9), and to promote tumour formation in transgenic mice (10). The major transforming protein of SV40 was identified as large

T-antigen (T-ag), a nonstructural protein essential for viral replication (1, 2, 11). Fundamental to its driving effects on the cell cycle, T-ag complexes with and functionally inactivates cellular tumour suppressor proteins (p53 and pRb), as well as other members of the pRb family (p107 and p130) (1, 12, 13). SV40 has also provided a facile and rewarding model for molecular biology studies of eukaryotic cell processes (1, 2); its genome was the first eukaryotic viral genome to be sequenced in its entirety.

Although it was assumed for many years that there was a single strain of SV40 and that all isolates were identical, recent observations have refuted this (2). Although available evidence indicates that there is a single serotype, sequence analyses have revealed that multiple genetic strains exist. The viral regulatory region differs among isolates, with most laboratory-adapted strains containing a duplication in the enhancer that is usually lacking in fresh isolates from monkeys and in DNA associated with human tumours (14–20). There is also a variable domain at the extreme C-terminus of T-ag that differs among viral isolates (14, 18–20). These sequence differences provide a means of identifying viral strains and helped allay concerns that human tumour-associated sequences might have been due to laboratory contamination.

SV40 infections in monkeys are generally asymptomatic. However, if the host's immune

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system is compromised, SV40 disease may develop (2). In macaques infected with simian immunodeficiency virus, SV40 lesions have been observed in many tissues, including brain, lung, kidney, lymph node and spleen (14–16, 21). Some animals developed SV40 meningoencephalitis and others the demyelinating disease, progressive multifocal leukoencephalopathy. These observations indicate that SV40 can be neurotropic and produce infections that involve the central nervous system.

Following the discovery of SV40, the conventional wisdom was that it was unable to establish human infections and was, therefore, harmless. However, in studies dating back to the 1970s, SV40 neutralizing antibodies have been detected in sera from individuals born after the use of contaminated vaccines, as well as in sera collected before vaccines were available (2). The low prevalence of serum antibodies (2–13%) suggested that there were sources of exposure to SV40, or a cross-reacting virus, other than the vaccines. In a recent study of hospitalized children born from 1980 through 1995, SV40 neutralizing antibodies were detected in about 6% of unselected sera (22). Tests were done on archival kidney tissue samples from 13 antibody-positive patients and SV40 DNA was amplified by polymerase chain reaction (PCR) from specimens taken from four individuals, confirming that SV40 is present in children today (23). The source(s) of contemporary SV40 infections is (are) unknown, but it is presumed that the virus is being transmitted among humans. These serological and molecular findings, coupled with numerous tissue culture studies that have demonstrated that SV40 can replicate in human cells (2), prove that SV40 is able to infect humans. These data suggest, additionally, that SV40 should be considered infectious for both monkeys and humans.

SV40 DNA has been detected in human tumours in numerous independent studies (2, 24), with the most commonly involved cancers being paediatric and adult brain tumours, mesotheliomas and osteosarcomas. Expression of T-ag, the SV40 oncoprotein, has been observed in some tumours. Recent studies using PCR and DNA sequence technologies have substantiated earlier reports dating from the mid-1970s of the presence of SV40 in human cancer tissue. Importantly, many of the SV40-positive tumours in recent studies have been from patients too young to have been exposed to SV40-contaminated poliovirus vaccines. Evidence that authentic SV40 was detected includes the following types of observations: four separated regions of the viral genome have been PCR-amplified from tumours; sequence analyses of PCR products have confirmed matches with the SV40 DNA sequence; and viable SV40 has been isolated from one paediatric brain tumour. Tumour-associated viral sequences have been distinguished from laboratory strains of SV40 by variation in the sequence at the

C-terminus of the T-ag gene and by the presence of a simple, nonduplicated enhancer in the regulatory region. Limitations of sample availability have generally precluded studies of the integration state of viral DNA in the tumours and quantification of genome copies of the viral DNA present.

A recently published review article evaluated the status of knowledge about the cell and molecular biology of SV40 and the implications for human infections and disease (2). Although the data suggest that SV40 DNA is present in some human tumours and that the virus probably has a causative role in some cancers, more studies are necessary to build definitive proof of etiology. The association of SV40 with human disease, if proven, would provide the opportunity for new approaches to the diagnosis, treatment, and prevention of human cancer. That, I believe, is the significance of this research, rather than the historical linkage of SV40 to the poliovirus vaccines. However, media reports focused on the possible connection between the contaminated vaccines and human cancer development. There was clear public interest in whether people who have received the contaminated poliovirus vaccines are at higher risk of getting cancer and whether current poliovirus vaccines are safe to give to children. The explanations that SV40 was once a contaminant of poliovirus vaccines and was now being detected in human tumours, but that we cannot say whether the virus came from the old vaccines or that the virus positively caused the cancers, are subtle distinctions that failed to be included in most reports.

This experience clearly shows that the public has concerns about possible delayed side-effects from vaccines and has great interest in related health reports (Table 1). It has been estimated that there are now about 15 000 health sites on the Internet, providing new means for rapid dissemination of both accurate and inaccurate information. It is fair to assume that events similar to the poliovirus vaccine/cancer scare could occur with respect to other vaccines at some future time. It would therefore be advisable for researchers and public health officials to be prepared for such an occurrence. ■

Table 1. Reports about vaccine side-effects: public concerns

- The public has great interest in possible delayed health risks due to vaccination
- Modern communications allow rapid and widespread dissemination of media reports
- Some public suspicion exists about vaccine safety
- Experts should present accurate information and interpretations in response to media reports
- Science may not be the main message in media reports; scientific subtleties get lost
- Reporters have a responsibility to convey health-related stories accurately

Résumé

SV40, vaccins antipoliomyélitiques et cancer : les progrès de la recherche et l'intérêt que leur portent les médias et le grand public

Entre 1955 et 1963, des millions de personnes ont été exposées par mégarde au SV40 (« simian virus 40 » des Anglo-Saxons) qui contaminait les vaccins antipoliomyélitiques – ce virus ayant été présent dans les cultures de reins de singes utilisées pour préparer le vaccin et ayant échappé à la détection. Le SV40 a été découvert en 1960 et a été éliminé par la suite des vaccins antipoliomyélitiques. Dans cet article, on fait le point des connaissances actuelles concernant le SV40 et on examine les réponses du grand public à l'écho qu'elles ont eu dans les médias. Le SV40 est un virus oncogène puissant ayant un important tropisme tissulaire qui induit des tumeurs chez les rongeurs et transforme les cultures cellulaires de nombreuses espèces. C'est également un modèle de laboratoire précieux pour l'étude fondamentale des processus moléculaires en jeu dans les cellules eucaryotes et les mécanismes de transformation néoplasique. On a détecté des anticorps neutralisants

dirigés contre le SV40 chez des sujets qui n'avaient pas été exposés à des vaccins antipoliomyélitiques contaminés. L'ADN du SV40 a été à de nombreuses reprises détecté dans des tumeurs chez l'homme, surtout dans des mésothéliomes, des tumeurs cérébrales et des ostéosarcomes ; et l'analyse des séquences de cet ADN a exclu la possibilité d'une contamination de laboratoire pour expliquer la présence de cet ADN viral dans les tumeurs, ou d'une erreur d'identification du virus. Toutefois, des études supplémentaires sont nécessaires pour prouver que le SV40 est bien à l'origine de certains cancers chez l'homme. Un article récemment publié a fait le point de la question et a beaucoup retenu l'attention des médias. La réponse du grand public a souligné le grand intérêt porté au fait que l'on puisse courir des risques aujourd'hui à cause de vaccinations reçues dans le passé.

Resumen

Virus símico 40, vacunas contra el poliovirus y cáncer humano: avances de las investigaciones e interés de los media y el público

Desde 1955 hasta principios de 1963, millones de personas se vieron expuestas accidentalmente al virus símico 40 (SV40), contaminante de las vacunas contra el poliovirus. El virus había pasado desapercibido en los cultivos de células renales de mono utilizados para elaborar las vacunas. El SV40 fue descubierto en 1960, tras lo cual fue eliminado de las vacunas contra el poliovirus. En este artículo se examinan los conocimientos actuales sobre el SV40 y se considera la respuesta pública a las noticias aparecidas en los medios de difusión. El SV40 es un potente virus tumoral con amplio tropismo tisular, que induce la aparición de tumores en roedores y transforma las células de cultivo de muchas especies. También es un importante modelo de laboratorio para realizar estudios básicos sobre procesos moleculares en células eucariotas y sobre los mecanismos de transformación neoplásica. Se han detectado

anticuerpos neutralizantes del SV40 en personas no expuestas a vacunas contra el poliovirus contaminadas. Se han referido casos de detección de ADN SV40 en tumores humanos, en particular en mesoteliomas, tumores cerebrales y osteosarcomas, y los análisis de la secuencia del ADN tumoral han descartado la posibilidad de que el ADN vírico de los tumores se deba a contaminación de laboratorio o a errores de identificación del virus. Sin embargo, es necesario realizar estudios adicionales para demostrar que el SV40 provoca determinados cánceres humanos. Se ha analizado el estado de la cuestión en un estudio crítico publicado recientemente que ha atraído la atención de los medios de comunicación. La respuesta pública ha puesto de relieve el gran interés que despierta la posibilidad de que algunos riesgos sanitarios de hoy estén asociados a vacunas administradas en el pasado.

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