[CANCER RESEARCH 57, 3319-3320, August 1, 1997]

Letters to the Editor

Correspondence re: F. Martini *et al.*, SV40 Early Region and Large T Antigen in Human Brain Tumors, Peripheral Blood Cells, and Sperm Fluids from Healthy Individuals. Cancer Res., *56:* 4820–4825, 1996

Letter

The data suggesting that SV40 DNA is present in human tissues continue to accumulate (1–4), although not all studies have shown this (5, 6). Recently, Martini *et al.* (7) presented interesting PCR results showing that SV40 large Tag[1] DNA was detected in a high percentage of choroid plexus tumors (5 of 6) and ependymomas (8 of 11), consistent with a previous study (1). Notably, they also detected SV40 DNA in many normal tissue specimens, including 24% (24 of 100) of circulating blood cells and 45% (9 of 20) of seminal fluid samples from healthy donors. Similarly, Woloschak *et al.* (8) found SV40 in the vast majority of pituitary tumors and also detected SV40 in the vast majority of normal pituitary tissue samples obtained postmortem. Taken at face value, the results in these two studies suggest that SV40 is a common human polyomavirus, detectable in a large number of normal human tissues, and prevalent in the general community. They also remind us that it would be a mistake to suggest a causal relationship between SV40 and human tumors based primarily on the detection of the virus in human cancers.

The biological plausibility of SV40 as a tumorigenic agent has been extensively demonstrated. SV40 is tumorigenic in rodents and can immortalize human epithelial cell lines *in vitro*. It is also understood that SV40 large Tag interferes with *p53* and *Rb* gene functions, and it may induce chromosomal instability.

However, before a causal relationship can be reasonably inferred between human cancers and SV40, a number of questions must be answered. Among other points: *(a)* What is the strength of association? Is SV40 more common in human cancers than in normal healthy tissue? In this connection, Bergsagel *et al.* (1) detected SV40 in most choroid plexus tumors and ependymomas but in none of 100 normal blood specimens taken from children (Martini *et al.* tested adults; Ref. 7); Carbone *et al.* (2) showed that SV40 was in 60% of pleural mesotheliomas and not in lung samples; and, Carbone *et al.* (3) showed that SV40 was present in 32% of tissues from osteosarcoma patients, but much less frequently in tissue samples from patients who had other Li-Fraumeni-related tumors, and not at all in lung cancers (suggesting that SV40 is not naturally in these tissues). However, based on the high prevalence of SV40 in normal tissues reported in Martini *et al.* (7) and in Woloschak *et al.* (8) it is unclear whether the virus is at least as common in some normal tissues as it is in some cancers.

(b) Is SV40 DNA detected in essentially all cells in each SV40-positive cancer? Because tumors are of clonal origin, all cancer cells in a SV40-related tumor should contain the virus. Certainly that is the case with cervical cancer, caused by HPV (9).

(c) Is SV40 infection more common in individuals who later develop SV40-positive tumors? A prospective study of temporality probably could be conducted using stored blood cells (again, assuming that SV40 is indeed a natural infection of peripheral blood cells in humans) obtained from individuals who later did or did not develop cancer enrolled in any of several large population-based cohort studies; *e.g.*, as a nested case-control investigation.

(d) Is there low prevalence of *p53* and *Rb* mutations in SV40-positive cancers? Because it is believed that large Tag immortalizes cell lines by interfering with the function of the *p53* and *Rb* tumor suppressor genes, it can be inferred that the presence of the virus should substitute for mutations in these genes. Indeed, *p53* and *Rb* mutations are rare in HPV-positive tumors, possibly for this very reason, because the E6 and E7 proteins of HPV act analogously to large Tag in detrimentally affecting the function of tumor suppressor genes (9). Alternatively, however, SV40 may be tumorigenic through other mechanisms, such as inducing chromosome instability. Therefore, this point is not absolute in making the connection between SV40 and human cancers.

In summary, an increasing amount of data suggest that SV40, or a virus very similar to it, is a human polyomavirus. If this observation alone is indeed confirmed, it will be a major discovery. Furthermore, there is a substantial biological basis for considering a role for SV40 in cancer development, and because of the wide distribution of SV40-contaminated polio vaccines between 1955 and 1963, there is also no question that there has been extensive human exposure to this virus. Thus, SV40 could some day be shown to be an important cause of certain human cancers. It is still premature to come to that conclusion, however, and it will require additional evidence before it is reasonable to suggest that SV40 contamination of the polio vaccine is at all connected with the occurrence of any tumors in humans. Given the potential volatility of these issues, researchers should continue to be particularly conservative in the interpretation of their data.

Howard Strickler
Viral Epidemiology Branch
National Cancer Institute, NIH
Bethesda, Maryland

Received 10/30/96; accepted 6/17/97.

[1] The abbreviations used are: Tag, T antigen; HPV, human papillomavirus.

References

1. Bergsagel, D. J., Finegold, M. J., Butel, J. S., Kupsky, W. J., and Garcea, R. L. DNA sequences similar to those of simian virus 40 in ependymomas and choroid plexus tumors of childhood. NEJM, *326:* 998–993, 1992.
2. Carbone, M., Pass, H. I., Rizzo, P., Marinetti, M., Di Muzio, M., Mew, D. J., Levine, A. S., and Procopio, A. Simian virus 40-like DNA sequences in human pleural mesothelioma. Oncogene, *9:* 1781–1790, 1994.
3. Carbone, M., Rizzo, P., Procopio, A., Giuliano, M., Pass, H. I., Gebhardt, M. C., Mangham, C., Hansen, M., Malkin, D. F., Bushart, G., Pompetti, F., Picci, P., Levine, A. S., Bergsagel, J. D., and Garcea, R. L. SV40-like sequences in human bone tumors. Oncogene, *13:* 527–535, 1996.
4. Lednicky, J. A., Garcea, R. L., Bergsagel, D. J., and Butel, J. S. Natural simian virus 40 strains are present in human choroid plexus and ependymoma tumors. Virology, *212:* 710–717, 1995.
5. Strickler, H. D., Goedert, J. J., Fleming, M., Travis, W. D., Williams, A. E., Rabkin, C. S., Daniel, R. W., and Shah, K. V. Simian virus 40 and pleural mesothelioma in humans. Cancer Epidemiol., Biomarkers & Prev., *5:* 473–475, 1996.
6. De Mattei, M., Martini, F., Tognon, M., Serra, M., Baldini, N., and Barbanti-Brodano, G. Polyomavirus latency and human tumors. J. Infect. Dis., *169:* 1175–1176, 1994.
7. Martini, F., Iaccheri, L., Lazzarin, L., Carinci, P., Corallini, A., Gerosa, M., Iuzzolino, P., Barbanti-Brodano, G., and Tognon, M. SV40 early region and large T antigen in human brain tumors, peripheral blood cells, and sperm fluids from healthy individuals. Cancer Research, *56:* 4820–4825, 1996.
8. Woloschak, M., Yu, A., and Post, K. D. Detection of polyomaviral DNA sequences

in normal and adenomatous human pituitary tissues using the polymerase chain reaction. Cancer (Phila.), *76:* 490–496, 1995.
9. IARC Working Group. Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 64: Human Papillomaviruses. Lyon, France: IARC, 1996.

Reply

I agree with most of Dr. Strickler's comments concerning the article by Martini *et al.* (1) and the problem of SV40 as a putative human virus. I find reasonable his warning to consider the presence of SV40 sequences in human tissues as an association and not as proof of an etiologic role of the virus in human tumors. However, if it would be a mistake to suggest a causal relationship between SV40 and human tumors based on the detection of the virus in human cancers, I feel it would be an equal mistake to ignore the presence of a highly oncogenic virus in humans.

Mauro Tognon
Institute of Histology and General Embryology
School of Medicine
University of Ferrara
Via Fossato di Mortara 64/B
44100 Ferrara, Italy

Received 5/12/97; accepted 6/17/97.

Reference

1. Martini, F., Iaccheri, L., Lazzarin, L., Carinci, P., Corallini, A., Gerosa, M., Iuzzolino, P., Barbanti-Brodano, G., and Tognon, M. SV40 early region and large T antigen in human brain tumors, peripheral blood cells, and sperm fluids from healthy individuals. Cancer Res., *56:* 4820–4825, 1996.