The second concept is the role of retroelements in chronic illnesses (3). Approximately 1% of the human genome is endogenous retroviruses, and another 5% of the genome are short, interspersed, nuclear retroelements known as Alu sequences. Alu retroelements are important because of the following: 1) they are expressed as a result of viral infection, cell stress, and toxic exposures; 2) they are actively involved in recombinatorial events leading to novel RNA generation; and 3) they are inextricably linked to primate evolution. SV40 T-antigen recognizes binding sites present within Alu family sequences (4).

The third concept is the detection of RNA in serum and plasma. Novel "rearranged" RNA, with chromosome 22q11.2 segments, has been detected in the serum of veterans who have Persian Gulf War-related illnesses (5). The presence of plasma RNA also has been described for several cancers (6). In studying active human multiple myeloma, we have noted the presence of an unique plasma RNA species (GenBank accession number AFO18254) that has 99% homology from four different patients (7). Sequencing of the amplicon from reverse transcription–polymerase chain reaction revealed a 713-nucleotide segment from the flanking region of the PPAR gene (GenBank accession number HSBSE3A) at chromosome 22q11.2. Interestingly, the PPAR gene is specifically triggered by pesticides and herbicides. Within the segment was an Alu retroelement containing two SV40 T-antigen binding sites.

Appreciating the concepts outlined above will further assist us in dissecting the molecular pathways by which cells respond to genotoxic events. Finding fingerprints of viruses (e.g., SV40) is just as meaningful as finding the entire viral genome for determining the factors leading to tumorigenesis. New techniques and procedures are needed to identify and measure the cumulative damage to the genome, cell, and body to fully understand the associations between SV40 and cancer.

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RESPONSE

Drs. Durie and Urnovitz make the important point that a combination of host and cellular responses must be considered when evaluating the possible involvement of viral exposure in human cancer development. The status of the host immune response is an important determinant, including not only antibody production but also cytotoxic T-cell responses. In addition to subtleties of the immune response, other undefined pertinent host factors include age effects on susceptibility to virus infection and tissue distribution of susceptible cells.

The authors point out that finding fingerprints of viruses is as meaningful as finding the entire viral genome for considering an etiologic involvement in tumorigenesis. This conclusion is substantiated by many studies of...
DNA virus carcinogenesis in model systems. Mounting evidence is now available that viral genes may be lost as tumor progression and accumulation of cellular genetic mutations make viral oncogene expression redundant (1–3). This process might reduce the number of genome copies of viral DNA to less than one per cell in a tumor sample.

Viral factors are also relevant to an evaluation of whether simian virus 40 (SV40) is a human tumor virus. Factors still to be examined include possible virus variants differing in oncogenic potential, modes of transmission among hosts, and possible restricted distribution of viral infections within geographic regions or human subpopulations. The detection of SV40 DNA in hospitalized children raises important questions about infection rates and sources of viral exposure in the population (4). Another ill-defined variable is the possible involvement of environmental carcinogens that might act synergistically with virus infection to induce cancer.

Rodent animal models, although invaluable in establishing that SV40 is a potent tumor virus, have limitations as predictors of the expected state of SV40 in human cancer. One major difference is that SV40 does not establish productive infections in rodents, as it does in many human cells. A recent report described the presence of episomal SV40 genomes in human transformed cells (5); although episomal gene copies have been detected in transformed rodent cells (6), the SV40 genome is usually integrated in the chromosomal DNA of those cells.

The biologic complexities pointed out by the correspondents remind us to be cautious in attempts to extrapolate directly from one viral system in humans to another. For example, although the human papillomaviruses are related to SV40, the biologies of the two groups of viruses are quite different, and the human papillomavirus–cervical cancer association cannot predict details of SV40 interactions with human tumors.

The complexities itemized above illustrate why different studies may draw conflicting conclusions regarding a viral association with a particular cancer, depending on the sources of samples analyzed, the procedures followed during sample preparation, and the specificity and sensitivity of test assays.

The possible role of SV40 in human cancer remains an intriguing and challenging question. The answers to this emerging public health puzzle will come gradually as different studies address host, cellular, and viral issues such as those highlighted above.

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