Preparation and Use of Recombinant Molecules Involving Animal Virus Genomes

The construction and study of hybrid DNA molecules offer many potential scientific and social benefits. Because the possible biohazards associated with the work are difficult to assess and may be real, it is essential that investigations be re-initiated only under conditions designed to reduce the possible risks. Although the need for the development of new and safer vectors is clear, we believe that the study of these recombinant DNAs can proceed with the application of existing National Cancer Institute guidelines for work involving oncogenic viruses. We point out that is likely that cellular DNAs contain nucleotide sequences similar to those found in viral genes, including genes associated with oncogenic transformation. Therefore the following recommendations are made for the preparation and use of recombinant DNA molecules derived from animal viruses and mammalian cells.

Biohazard Classification and Guidelines

"The National Cancer Safety Standards for Research Involving Oncogenic Viruses" is divided into standards for control of (1) low risk, (2) moderate risk, and (3) high risk oncogenic viruses (see appendix). With the exceptions noted below, we recommend that self-replicating recombinant DNA molecules containing animal virus genomes or genome segments in biological vectors be handled according to guidelines for moderate risk oncogenic viruses. Experiments involving purified segments of viral genomes that are proven not to be associated with pathogenicity may be carried out according to the guidelines for low risk oncogenic viruses. On the other hand, genome segments from highly pathogenic viruses, e.g., smallpox, Lassa virus, hemorrhagic fever agents and others listed as class 4 in "Classification of etiologic agents on the basis of hazard" (Atlanta, Ga. CDC Publication) should be handled according to the guidelines for high risk oncogenic viruses. The vast majority of experiments, however, will fall into the moderate risk category.

Regulation

We recommend that facilities and practices in investigations involving recombinant DNAs be reviewed and approved by institutional committees which would both advise principal investigators and certify in writing to granting agencies that proposed studies would be done according to the specified guidelines.

We also recommend that a national and/or international body review the guidelines and classifications periodically. To facilitate this review, additional data should be acquired; for example, it is important to assess the biological activity of DNA injected into animals, the transfer of plasmids between bacterial strains in the gut, the persistence there of carrier DNAs, and the efficacy of the immune response in dealing with new plasmids introduced into the gut.

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I disagree with certain aspects of the written statement submitted by the working group considering problems associated with the development, propagation, and study of plasmids containing segments of DNA from animal viruses. The plasmid recombinant technology certainly appears to be a useful development for genetic studies on animal viruses; however, given the limited amount of information available at this time, I believe that the risks associated with the wide-spread, semi-contained use of this procedure exceed the rewards from the information to be obtained. Because of these risks, the diversity of opinions among individual scientists that these risks have provoked, and the moral and legal issues raised by the rising public concern about rapid advances in biomedical technology, I believe that application of this procedure to study animal virus genomes requires a methodical and carefully conceived attempt to reduce the risks to more acceptable levels.

The initial step in the reduction of these risks is the development and testing of new and theoretically safe vectors. After such vectors have been provided, laboratories with adequate containment facilities (equipped to handle moderate risk organisms as defined in the NCI "Guidelines for work with oncogenic viruses") could begin to study recombinants containing DNA from supposedly nonvirulent regions of the genome from low to moderate risk animal viruses while attempting to assess any hazards associated with such recombinants. As the problems associated with such agents become better understood, more detailed studies could be undertaken. By such a slow, step by step approach, I believe that useful data could be obtained, the risks posed by these recombinants could be adequately evaluated, and most importantly, any untoward problems could be quickly appreciated and contained.

Andrew M. Lewis Jr.

On the basis of further discussions and additional information obtained during the conference, we wish to append the statement on the preparation and use of recombinant DNA molecules involving animal virus genomes.

Two types of mechanisms for controlling potentially hazardous experiments are the use of physical and of biological barriers, i.e. containment and a safe vector. Their combined use provides a margin of safety against potential biohazards that is greater than either mechanism by itself.

We suggest that experiments involving animal virus genomes be divided into two categories:

(1) Animal viruses as vectors in animal cells.
Experiments in this category can be done with low risk viruses under the N.C.I. guidelines for moderate risk viruses. The use of physical barriers is considered adequate because (a) virus particles containing covalently-linked mammalian and viral DNAs are known to occur naturally, (b) the vectors are likely to require helper viruses in order to replicate, (c) the synthesis of viral capsid protein which occurs in infected cells would be expected to result in an immune response in any individuals who may become infected, and (d) the recommended level of containment is greater than that required for work with the unmodified viruses.

(2) Viral genomes, viral genome segments, or eukaryotic DNA recombined with prokaryotic vectors and introduced into prokaryotic cells.
These experiments involve host range extensions and therefore require the use of both biological and physical barriers. They should proceed only with vectors that are considered to be safe. Because the panel does not have the expertise to judge the safety of vectors, we suggest that an appropriate panel make this evaluation. Moderate risk containment procedures are recommended for all experiments in this category, except that should highly pathogenic viruses ever be used for such purposes, then high risk containment must be employed. However, we can see no justification for employing highly pathogenic viruses for experiments of this type at the present time.

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