THE RELEVANCE OF RNA-DIRECTED DNA POLYMERASE ACTIVITY TO HUMAN NEOPLASIA

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I have been asked to write a short article on some biological aspects of RNA-directed DNA polymerase activity that are relevant to the theme of this workshop. Because I was not able to attend the workshop, I shall write a general article without data or specific literature references. At the end of the article, I have listed some of my articles which give detailed references.

Why are RNA tumor viruses and RNA-directed DNA polymerase activity considered relevant to the etiology of human leukemia? In animals, especially in mice and chickens, much of the leukemia is caused by RNA tumor viruses. Furthermore, RNA tumor viruses and other viruses with apparent RNA-directed DNA polymerase activity are widely distributed in some normal animals and have been isolated from many animals, although not yet from man. It appears to be a reasonable working hypothesis that RNA tumor viruses have some relevance to the etiology of human leukemia.

RNA tumor viruses are characterized by a medium-sized, enveloped virion with a characteristic morphology and a density in sucrose of about 1.16 g/cm^3. Infectious RNA tumor virus virions contain a 60–70S RNA complex and a DNA polymerase. The genome of an infectious, strongly transforming RNA tumor virus, such as Rous sarcoma virus, contains genes for virion structural proteins, also sometimes called the virogene, which includes genes for two external glycoproteins, three or more internal proteins, and a DNA polymerase. The internal proteins and the DNA polymerase have group-specific antigenicity. The genes for neoplastic transformation are often called the oncogene and may consist of at least four complementation groups. Thus, the genome of an infectious, strongly transforming RNA tumor virus, whether as virion RNA or as DNA provirus, equals the virogene plus the oncogene. (There are also non-transforming RNA tumor viruses that do not have an oncogene.)

RNA tumor virus replication involves attachment of the infecting virus to receptors of a sensitive cell, entrance into the cell and uncoating, synthesis and integration of the DNA provirus, activation of RNA transcription by normal passage of the infected cell through the replicative cell cycle, synthesis of virus-specific RNA and protein, formation of the virion core, and formation of the virion by budding from the modified cell plasma membrane.

The major descriptive questions about RNA tumor viruses are what genes exist in DNA proviruses in normal and neoplastic cells and what products of these genes are

formed in normal and neoplastic cells. The major genetic questions are what is the origin of these genes and what determines which products are formed.

The virion RNA-directed DNA polymerase has provided a way to answer some of the descriptive questions. The DNA product of RNA-directed DNA polymerase activity has allowed synthesis of radioactive DNA products, which can be used in nucleic acid hybridization experiments to find DNA and RNA sequences related to RNA tumor virus RNA. (Similar experiments have been done with cellular messenger RNA's.) Viral RNA has also been used in nucleic acid hybridization experiments to find cellular DNA sequences related to RNA tumor virus RNA. Limitations of this approach are the necessity to start with RNA of a known RNA tumor virus and the apparent lack of nucleotide sequence homology between the RNA from different RNA tumor viruses, even among those from different groups growing in the same cells (for example, avian leukosis viruses and reticuloendotheliosis viruses) and among those from antigenically related viruses (for example, mouse and feline leukemia viruses).

A similar requirement for a known RNA tumor virus exists when looking for most of the virion structural proteins. Only known proteins or proteins related to known ones can be studied. However, RNA-directed DNA polymerase activity is characteristic of RNA tumor viruses and thus can be looked for without starting with a known RNA tumor virus.

A limitation in the last approach is that endogenous RNA-directed DNA polymerase activity with the biochemical characteristics of RNA tumor virus RNA-directed DNA polymerase activity has been found in normal, uninfected chicken embryos and in normal, uninfected chicken fibroblasts and amnion cells in culture. This activity is unrelated to known viruses and has no other properties of a virus. It was isolated from apparently uninfected cells, which are not producing virus.

Therefore, without an infectious human RNA tumor virus, it may be hard to answer the descriptive questions about possible proviruses and their expression in normal and neoplastic human cells.

While there are fairly complete answers to some of the descriptive questions about RNA tumor viruses, the genetic questions about RNA tumor viruses are still unanswered in animals where many RNA tumor viruses are known. The current hypotheses regarding the occurrence of oncogenes are that oncogenes exist a) only in neoplastic cells or b) in normal and neoplastic cells. The hypotheses as to the origin of oncogenes are that they arise a) from the provirus of an infectious, strongly transforming RNA tumor virus, b) from the vertically transmitted provirus of a strongly transforming RNA tumor virus, c) from variational processes involving normal cellular elements called protoviruses, or d) from mutation of cell genes.

Much more work will have to be done to clarify these questions in animals before we can hope to shed much light on the etiology of human neoplasia. A further sobering thought is that, although RNA tumor viruses have been known since the early 1900's to cause some chicken leukemia, effective means of prevention or treatment of this leukemia are still unknown.

Further Reading

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