Teminism and cancer

The connection between RNA viruses and cancer genesis remains a mystery

by Joan Lynn Arehart

While a mammoth cancer conquest program is being mapped out on Capitol Hill, cancer scientists are continuing about their business of trying to understand the disease and to find a cure for it. Some of their latest efforts were detailed at the autumn meeting of the National Academy of Sciences in Washington last week.

A casual visitor to the symposium might have received the impression that the most promising route to understanding and managing cancer lies in RNA-tumor-virus research. This may well turn out to be the best approach; it also happens to be the currently most fashionable one and the symposium reflected that. Teminism, as it is called, came into vogue after May 1970 when Howard Temin of McArdle Laboratory in Madison, Wis., provided evidence that RNA tumor viruses have a special enzyme capable of transferring information from RNA into DNA (SN: 7/25/70, p. 54)—in contrast to the dogma due to Francis Crick: that information goes from DNA to RNA. Researchers then suggested that RNA tumor viruses might use this special enzyme to get their RNA genetic information incorporated into host cells and thus transform the cells into cancer cells. Investigators working to substantiate this theory during the past year have included Sol Spiegelman of Columbia University, Maurice Green of St. Louis University and George Todaro and Robert Huebner of the National Cancer Institute, among others. These players in the Teminism drama received top symposium billing.

These scientists expressed guarded optimism about whether their efforts would lead to a cancer conquest. Temin reported that while the RNA-tumor-virus enzyme called RNA-directed DNA polymerase (also known as reverse transcriptase) clearly exists in the virus, is needed for viral replication, and is capable of making DNA on an RNA template, there is still no definitive proof that the virus actually incorporates its genetic information into the host-cell genome (genetic package), nor that such incorporation would explain a cell turning into a cancer cell.

Green confirmed this state of affairs by reporting that he has found tumor-virus RNA in animal cells made cancerous by the virus, but does not know how the presence of viral RNA in the cell might lead the cell to become cancerous. However, he and Spiegelman reported that they have now separated out the polyribosomes (a sort of conveyor belt for manufacture of proteins by RNA) from animal cancer cells, and the RNA on these polyribosomes contains some of the genetic information found in the RNA-tumor-virus RNA molecule. Such evidence strongly suggests that tumor-virus RNA gets into the protein-production act in a host cell.

Meanwhile Temin has been separating out components of RNA tumor virus. He has found that 30 percent of virus protein (which is found in the core of the virus along with viral RNA and the reverse transcriptase enzyme) is antigen. Raymond Gilden of Flow Laboratories, Rockville, Md., reported that this antigen is now known to be a single polypeptide chain and several of its amino acids have been determined.

In addition to reverse transcriptase, several other enzymes have been found in the tumor virus. These enzymes, such as DNA ligase and DNA nuclease, are found in the normal cell as well and are used for its DNA synthesis. Temin doesn't know whether these enzymes help reverse transcriptase replicate the tumor virus or not.

Huebner and Todaro reported a concept they have backed for some time now, that tumor-virus information may be part of all normal cell genomes. In fact during the past year or two, tests have shown that RNA-virus information is found in the genetic material that the cells of most vertebrates pass to their offspring. For example, the antigen of mouse leukemia virus (an RNA virus) is present in both embryonic cells and tumor tissue of mice not only when the cells have been treated with known cancer-inducing agents, such as chemicals, but under normal conditions.

Huebner said strong evidence along these lines is being developed at NCI labs now. When a large number of inbred mice were crossbred they evolved into four lines—one with RNA virus antigen, two that are mixed breeds, and one with no antigen. The mice with antigen have come down "with every tumor in the book," Huebner says, whereas the mice with no antigen have been free of tumors for four to five months. (The mice are still under study.)

In their discussion the symposium participants raised more questions than they answered. Why, for example, of the 600 viruses known to strike animals and man, are only some 120 known to induce cancer in animals, and why have none so far been shown, for sure, to induce cancer in humans? Of these 120 tumor viruses, some 50 are DNA viruses, not RNA viruses. How do they work in comparison to the RNA viruses? Various experiments have shown that DNA viruses, tumor or otherwise, can incorporate their DNA into host cells, and every time the host cell divides, it copies its own DNA plus the virus DNA. These DNA viruses, however, are not species-specific, and they have been introduced into host cells under artificial lab conditions. What makes RNA tumor viruses especially attractive candidates as cancer-causing agents in the natural environment is that they are generally species-specific. Also, as Huebner and Todaro pointed out, they seem to be inherent to the genetic makeup of organisms, which is not the case for DNA viruses, tumor or otherwise. However as George Klein of the Royal Caroline Institute in Stockholm pointed out, both DNA and RNA non-tumor viruses can be turned into tumor viruses under the appropriate lab conditions. Also, Temin says, so-called tumor viruses do not always cause tumors when tested in cell cultures or in live animals. How these various discoveries hang together remains a mystery.

Another question raised but not answered was how environmental substances that have been shown to induce cancer in both animals and man might fit in with tumor-virus action in the cell. Wallace Rowe of the National Institute of Allergy and Infectious Diseases reported that cells treated with various chemical agents produced RNA tumor virus, so there must be a connection.

Regardless of whether RNA-tumor-virus research leads to a cancer cure, there is little doubt that such experimentation is opening new doors in molecular biology. Such work could have value in the cures of many diseases, not just of cancer. □