Fishing for Viruses in Cancer Cells

Graham Chedd

It is still barely three months since Howard Temin of the University of Wisconsin finally convinced his peers, after six years of labouring in that wilderness to which science tends to confine the unpalatable, that in cells invaded by cancer-inducing RNA viruses, DNA is synthesized from the viral RNA template. Yet already his latest claim that RNA cancer viruses contain an enzyme able to effect this partial reversal of the central dogma has been confirmed by numerous groups, some of whom have already published, and some have papers waiting in press. Sol Spiegelman’s large team at Columbia University is among the former, Spiegelman himself breathlessly announcing its corroboration of Feminism at the Royal Society in June.

Now he has pulled off another coup. For at the recent Tenth International Congress of Microbiology in Mexico City, Spiegelman gave stop-press news of his team’s latest findings. Apparently not one enzyme is involved in the “backwards” transfer of information from RNA to DNA, but two. Furthermore, the Columbia group have devised a neat and simple technique for “fishing out” minute quantities of viral RNA from cells, meaning that large-scale screening of cells from human cancers can be begun to determine whether any of them can be ascribed to a virus. And if the answer turns out to be in the affirmative, Spiegelman argues, a clear research path lies ahead towards a drug or drugs which will be able to prevent the transformation of normal cells into the cancerous state.

The oncogenic RNA viruses—viruses containing RNA as their genetic material instead of the more standard DNA, and which can induce cancers in animals—have always been a puzzle. The main problem in recent years has been to account for the stability with which they can transform cells grown in culture. Although such cells occasionally revert to normal, they usually remain in the transformed state through numerous generations. This implies that the genetic information forced upon the cells by the viruses, and which brings about transformation, is reliably passed on to its daughters when a cell divides. In 1964, Howard Temin suggested that they achieve this stability by first synthesizing DNA, using their RNA as a template, and then integrating the DNA into the chromosomes of the host cell. The viral genetic material is thereafter replicated by the host, and passed on to its daughter cells, as if the DNA were its own.

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Reprinted from New Scientist 47: 464-465, 1970.
But this idea runs contrary to the "central dogma" of molecular biology, which states that the flow of genetic material is unidirectional, from DNA to RNA to protein. (At least, this is what everybody thought the central dogma meant, but Francis Crick—its progenitor—has recently claimed that the dogma was in fact not that dogmatic.) Accordingly, Temin's idea received little attention and the evidence he adduced in its favour was conveniently dismissed. Now, of course, all this has changed, and Temin's image has transformed from that of stubborn crank to persistent visionary.

The discovery, and confirmation, of an enzyme carried by oncogenic RNA viruses able to synthesize DNA upon the viral RNA was what effected this transformation. Spiegelman, however, saw that the manufacture of double-stranded DNA suitable for integration into a chromosome from a single-stranded RNA template should involve two steps: first, the synthesis of single-stranded DNA on the template to give a DNA-RNA hybrid; and second, the formation upon the DNA partner of the hybrid of a complementary DNA strand. He predicted, therefore, that two enzymes might be involved, one for each step. At Mexico City, he presented evidence proving that he was right. In addition to the so-called RNA dependent DNA polymerase which Temin, he and others had already found, and which synthesizes the DNA-RNA hybrid, there exists another enzyme which transcribes the DNA-RNA hybrid into a DNA-RNA duplex. This extra enzyme copies DNA-RNA hybrids with a very high specificity, much preferring them to single-stranded RNA or DNA or double-stranded DNA.

Spiegelman's large and flexible team have also devised a test tube system for synthesizing radioactively labelled DNA from the RNA of oncogenic viruses. This DNA, because it is complementary to the RNA upon which it was made, will hybridize with this RNA whenever it encounters it again. Furthermore, the Columbia group have also devised a technique for detecting such hybrids when they are formed, employing density gradient centrifugation. The DNA-RNA hybrids "float" in the centrifuge tubes at a different position from that of double-stranded DNA, forming an easily recognizable bank. The extreme sensitivity of the combined technique (as little as 10^-13 grammes of RNA can be detected) plus its simplicity means that it now becomes practicable to launch a large-scale screening programme of human cancers—such as leukaemia—which might well be caused by RNA viruses. If the ground-up cells from such cancers contain even
the merest telltale trace of RNA that matches with the RNA of a known oncogenic virus, then Spiegelman's new technique will enable it to be fished out.

Anticipating the outcome of such screening programmes, Spiegelman has already embarked upon a search for substances which can inhibit one of the two enzymes involved in making double-stranded DNA from viral RNA templates. He has shown, for instance, that actinomycin D—a drug known to block the transcription of RNA from DNA templates—also prevents the formation of the DNA duplex from the DNA-RNA hybrid. It is almost certain that if people look hard enough, a more specific inhibitor of the RNA to DNA reaction will be found. And people will certainly be looking; for so extraordinary is this reaction in the context of the body's normal metabolism that a substance which can block it would presumably prevent the transformation of cells from a normal to malignant state, while leaving the rest of the cells' chemistry unharmed.

As if all this were not exciting enough, an even more startling and far-reaching possibility now hangs tantalizingly near. One of the people to react with most warmth to Temin's admission inside the pale was Robert Huebner, chief of the viral carcinogenesis group at the National Cancer Institute at Bethesda, Maryland. Huebner was also among the first to confirm the presence of the RNA dependent DNA polymerase in oncogenic viruses, and has his paper in press. His welcome of Teminism stems from the fact that for the past year or so he and George Todaro have been working on an audacious theory of cancer which suggests that all cancers, in all animals capable of bearing them, are caused by an RNA virus.

The genetic information of these viruses, the Huebner-Todaro hypothesis continues, lies hidden within the chromosomes of its hosts, where it is passed on from cell to cell at division, and from parents to offspring via the egg and/or sperm. In fact, we probably all of us contain this genetic material all of the time, lurking among our own genes. Normally, our cells produce a substance which keeps the viral genes switched off. But occasionally, an "oncogene" of the virus becomes switched on, and the host cell is transformed into a cancer cell. Dramatic though this hypothesis may be, the evidence in its favour is presently slim. Its main drawback, however, was that it required some mechanism by which the genes could be insinuated into the host genome. Then along came Teminism, and this stumbling block was removed.

At the very least, the next few months will see an answer to the question of whether any human cancers are caused by RNA viruses. If they are then we can expect the search for a drug to block the RNA to DNA reaction to receive some hefty industrial recruits. And if Huebner and Todaro turn out to be right...