

Citation Classics

Temin H M. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* 226:1211-3, 1970.

The presence of a ribonuclease-sensitive endogenous DNA polymerase activity in particles of RNA tumor viruses was first reported in this paper and the accompanying paper by David Baltimore.¹ The enzyme responsible for this activity, now known as reverse transcriptase, is the key part of the mechanism for the transfer of information from RNA to DNA (the pro-virus) in the replication of RNA tumor viruses. Publication of these papers led to the immediate acceptance of the DNA provirus hypothesis, originally proposed in 1963 and 1964. [The SC[®] indicates that this paper was cited a total of 664 times in the period 1961-1975.]

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"Since 1963-1964, I had been proposing that the replication of RNA tumor viruses involved a DNA intermediate. This hypothesis, known as the DNA provirus hypothesis, apparently contradicted the so-called 'central dogma' of molecular biology and met with a generally hostile reception. The hypothesis was not generally accepted until the publication of this and the accompanying paper by David Baltimore. These papers demonstrated the existence of an enzyme associated with an RNA template in particles of RNA tumor viruses that could carry out information transfer from RNA to DNA. This result might have been predicted from the previous discovery of polymerases in virus particles and the DNA provirus hypothesis. That the discovery took so many years might indicate the resistance to this hypothesis.

"The actual proof that information transfer from RNA to DNA occurred in the replication of RNA tumor viruses involved assay of infectious

virus DNA and nucleic acid hybridization and was published in the next two or three years. However, discovery of an enzyme with the ability to copy RNA to give a DNA product in virions associated with a possible template RNA was already convincing to most scientists.

"These papers had their greatest and most permanent effect on the study of RNA tumor viruses. They also led to the recognition that there are other viruses related to the RNA tumor viruses that did not cause cancer. All of these viruses are now called retroviruses. The acceptance of the DNA provirus hypothesis provided a theoretical framework for the work with these viruses. The availability of specific DNA complementary to viral RNA and the specificity of the viral DNA polymerase provided sensitive assay techniques and markers for these viruses and their components.

"The later attributes were also important in the search for an RNA tumor virus involved in human cancer. Although there has been much excitement in this area, as yet there is no convincing proof of involvement of an infectious RNA tumor virus in the etiology of human cancer.

"Another consequence of the discovery was the use of reverse transcriptase, especially that purified from avian myeloblastosis virus, as a standard reagent in molecular biology to form complementary DNA to specific RNA. In this way, it has been used as the first step in forming recombinant DNA molecules starting with messenger RNA.

"Finally, these papers led to the proposal of the provirus hypothesis and a hypothesis for the etiology of cancers in the absence of overt virus infection. Although there is some evidence consistent with these hypotheses, especially the mechanism of transformation by weakly transforming RNA tumor viruses involving genetic changes in the course of extended viral replication in an infected animal, these hypotheses are not yet established."

REFERENCE

1. **Baltimore D.** Viral RNA-dependent DNA polymerase. *Nature* 226:1209-11, 1970.