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MOLECULAR STUDIES OF RETROVIRAL REPLICATION

Potential targets for therapeutic intervention

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The RNA tumor viruses (Retroviruses) have long been of interest to cancer researchers because they are known to cause disease in various animal species. Recently, there has been an increased sense of urgency in efforts to understand the molecular biology of these viruses due to the realization that some are also important human pathogens, causing both cancer (adult T cell leukemia) and AIDS.

AIDS is a progressive disease of the immune and central nervous systems. The course of this illness is closely coupled to virus replication. Disease symptoms in the late phase are correlated with a *decrease* in the number of $CD4^+$ "helper" T lymphocytes (the host cell target of the virus), and an *increase* in concentration of viral proteins in the circulation. Thus, control or elimination of virus replication is a rational strategy for therapy in this disease.

Investigations of the retroviral replication cycle have focused not only on reactions and functions that are unique to the human viral strains, but also on steps that are common to all retroviruses. The latter studies profit from a substantial background of knowledge obtained through earlier work with the C-type retroviruses of rodent and avian species.

Two of the most promising areas of research aimed at the development of therapeutic agents are analysis of the virus-host cell attachment phenomenon, and studies of the mechanism of reactions catalyzed by the three essential viral enzymes. Understanding how the virus attaches to a sensitive cell is important to the design of potential vaccines and can suggest strategies for intervention *before* the virus enters a susceptible cell. The viral enzymes are particularly attractive targets for potential drugs that can block replication *after* the virus enters the cell.

The first wave of therapeutic agents that are available for clinical application includes inhibitors of the viral/enzyme reverse-transcriptase (RT),

which is responsible for the synthesis of viral DNA. The limited, but significant, efficacy of one inhibitor of RT, the drug AZT (3'Azido, 2' 3' dideoxythymidine) has encouraged additional efforts in this direction and more compounds of this type are in various stages of clinical testing. The two other viral enzyme targets are the integration protein (IN) and the viral protease (PR). IN is associated with an endonuclease activity that is required in the reaction which joins viral DNA to the host DNA. PR is responsible for cutting the long viral precursor proteins in newly formed particles into the smaller proteins and enzymes that are necessary for subsequent infection. PR has been under intensive study by many academic and industrial researchers. Recently, two retroviral PRs, from the avian Rous sarcoma virus (RSV) and the AIDS virus (HIV), have been crystallized. Molecular modeling and biochemical studies with these proteins suggest several approaches for the design of inhibitors which may soon be available for biological testing.

The situation today is significantly changed from that of only five years ago, when there were virtually no promising AIDS drugs. Now there is such a large number of potential candidates and diverse approaches that clinical testing programs will soon be saturated. Because of this, new yardsticks for establishing priorities for drug candidates and end points of efficacy, will have to be established. This hopeful note comes none to soon both for physicians and for AIDS victims who are predicted to number close to a million, worldwide, by 1991.