VIRUS SPECIFIED ENZYMES IN HERPES SIMPLEX VIRUS INFECTED CELLS

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The genome of Herpes simplex virus (HSV) is a molecule of double-stranded DNA with molecular weight of about 100 x 10^6 and consequently the polypeptide-specifying potential of herpesviruses is considerable. Although over fifty polypeptides induced following herpes virus infection of cells in tissue culture - have been recognised, the function of most of them is still unclear, but in a few cases induced enzyme activities have been identified and studied. The present discussion is concerned chiefly with the possible role of these enzymes in antiviral chemotherapy, and in this context only herpesvirus-induced (and coded) DNA polymerase and pyrimidine deoxynucleoside kinase activities can be related to current knowledge of antiviral reagents. However, the several other enzymes implicated as herpesvirus induced-DNA exonuclease (Morrison and Keir, 1968) ribonucleotide reductase (Cohen, 1972), dTMP kinase (Nohara and Kaplan, 1963), ATPase (Randall et al., 1972), dCMP deaminase (Keir, 1968) and protein kinase (Rubenstein et al., 1972) - may well include potential target molecules for chemotherapy.

In HSV infected cells, a new DNA polymerase activity can be detected which is quite distinct in biochemical, immunological and genetical properties from any of the DNA polymerase activities of the uninfected cell. The most striking biochemical difference is the stimulated activity of the viral enzyme in high monovalent cation concentrations, which enables the assay in vitro of virus-specific enzyme essentially free of inter-
ference from cell activities (Keir et al., 1966a; Keir et al., 1966b). The HSV type 1 DNA polymerase has been extensively purified (Weissbach et al., 1973) and may be associated operationally with a virus-induced exonuclease activity. The native molecular weight of the enzyme has been estimated to be 150-200,000 daltons and recent estimates of its polypeptide molecular weight suggest, that this may be a single molecular. The DNA polymerase has been shown to be a DNA binding protein (Bayliss et al., 1975). Other members of the herpesvirus group are known to induce a salt-stimulated DNA polymerase activity after infection e.g. Pseudorabies virus (Hay and Moss, unpublished observations); Marek's disease virus (Boezi et al., 1974). This may be a characteristic feature of the group.

Using HSV specific antiserum it has been demonstrated with HSV infected cells of different species that the DNA polymerase is not only virus induced but virus specified (Keir et al., 1966b).

Genetic studies with herpes simplex virus types 1 and 2 have shown that over 50% of randomly-selected temperature-sensitive mutants are defective in viral DNA synthesis (Halliburton and Timbury, 1973; Brown et al., 1973; Schaffer et al., 1973). Two of these mutants, ts 6 from HSV type 2 and ts H from HSV type 1, appear to be in the structural gene for DNA polymerase, which constitutes direct evidence for the essential nature of viral DNA polymerase for herpes virus growth and DNA synthesis (Hay et al., 1975; Crombie, 1975). In addition, mutants in three separate cistrons of HSV type 2: ts 1, 9 and 11; and in two cistrons - ts K and J - of HSV type 1 possess lesions which affect DNA polymerase synthesis, but not its function: these must constitute failure of essential control mechanisms normally operating during virus replication.

In terms of DNA polymerase induction and viral DNA synthesis complementation and recombination have been demonstrated between two mutants of HSV type 2: ts 6 and ts 9. Although the complementation is surprisingly inefficient, a correlation between DNA polymerase activity and DNA synthesis can be seen (Timbury and Hay, 1975).

Phosphonoacetic acid (PPAA), a potent anti-herpesvirus agent in animals (Overby et al., 1974) has been shown in vitro to be a specific inhibitor of the salt-stimulated viral DNA poly-