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PROTEOLYTIC PROCESSING OF THE CONSERVED V3 REGION OF HIV GP120 BY T-CELL LYSATES. IMPLICATIONS FOR HIV INFECTIVITY.

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The conserved V3 loop of HIV GP120 has been the focus of significant attention in the development of possible vaccines for HIV, since many HIV neutralizing antibodies bind to peptides from this region. Although much of the V3 loop sequence varies greatly from one isolate of HIV to the next, residues 311-315 (HIV_{IIIB} isolate), consisting of the sequence Gly-Pro-Gly-Arg are conserved in more than 90% of the HIV isolates that have been sequenced.

In this paper, we describe the proteolytic processing of peptides from this conserved region by a T-cell associated protease (or proteases) in a variety of T-cell lines. We employed specially tailored fluorogenic peptide substrates based on resonance energy transfer mediated-fluorescence quenching to measure the proteolytic activity.

Results from inhibition studies of this proteolytic activity by a variety of protease inhibitors will be presented, and the implications of these data for vaccine studies and infectivity studies will be discussed.

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Inhibition of Poly (ADP-ribose) polymerase by Various Antiviral and Anticancer Nucleoside Analogs. Arman D. Pivazyan, Tai-shun Lin and William H. Prusoff, Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

Poly (ADP)-ribosylation of proteins has been reported to be involved in the regulation of DNA replication, chromatin condensation, cell proliferation and DNA repair. ADP-ribosylation of adenovirus core proteins may play a role in decapsidation, and hence essential for viral infectivity (Déry, C.V. et al., Virus Res., 4, 313, 1986). Because ADP-ribosylation may have a role in viral propagation, we have investigated the effect of various antiviral and anticancer nucleosides on the activity of poly (ADP-ribose)-polymerase. All of the compounds were evaluated using [^{14}C]NAD^+ as the substrate, and non-competitive inhibition kinetics was observed. The most potent inhibitors of this enzyme, of those evaluated, with K_i in the range of 1 to 20uM, are 5'-azido-5-I-2'-deoxyuridine, 5-bromovinyl-2'-deoxyuridine, 5-propyl-2'-deoxyuridine, 5'-amino-5'-deoxythymidine, 5-iodo-2'-deoxyuridine, 5-Butyl-2'-deoxyuridine, 3'-azido-3'-deoxythymidine. Less potent inhibitors, with K_i in the range of 20 to 200uM, are 5-pentyl-2'-deoxyuridine, 3'-deoxy-thymidine (d2T), 5-bromo-2'-deoxyuridine, thymidine, 3',5'-diamino-3',5'-dideoxythymidine, 5-chloro-2'-deoxyuridine and 3'-deoxy2',3'-didehydrothymidine (d4T). Compounds with very little potency (K_i = > 1mM) include 5-methylamino-2'-deoxyuridine, 5-fluoro-2'-deoxyuridine and 2'-deoxyuridine. The finding that several nucleoside analogs have K_i's that are similar to the most potent inhibitors of this enzyme (3'-aminobenzamide, diadenosine-tetraphosphate, 2'-,5'-oligoadenylates) may be useful for investigation of a possible role of ADP-ribosylation of proteins in virus propagation, as well as in tumor growth, and may afford another target for drug design.