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Homology modeling and molecular dynamics simulation studies of a hypothetical HIV-1 DNA binding protein and potential E2-like target site in the HIV-1 LTR. Chandra S. Ramanathan, David E. Stewart and E. Will Taylor, Computational Center for Molecular Structure and Design and Department of Medicinal Chemistry, University of Georgia, Athens, GA 30602-2352.

Based on an analysis of the genomic RNA structure of HIV-1 and its relation to novel open reading frames, Taylor *et al.* recently reported that several previously unnoticed potential genes in HIV-1 could be expressed by a combination of ribosomal frameshifting and termination suppression (*J. Med. Chem.* **37**: 2637-54, 1994). Due to the existence of several well conserved UGA codons in two of these open reading frames, and the presence of potential selenocysteine (SeC) insertion sequences, these potential genes may encode selenoproteins. One such hypothetical protein, obtained by a -1 frameshift from the protease gene, is likely to be a nuclear protein due to its high content of basic amino acids (computed pI ≈ 11). Searches against the entire PIR protein database using the complete sequence of this hypothetical protein revealed its similarity to various DNA binding proteins, at significance levels of 4-8 SD relative to the database average. The hypothetical HIV-1 selenoprotein has significant similarites to papillomavirus E2 proteins, which can be positive or negative transcriptional regulators, depending on splicing. There are two UGA codons in this hypothetical gene; the first is highly conserved in primate retroviruses. This potential SeC falls precisely at a point which can be aligned with the highly conserved Cys of the papillomavirus E2 DNA binding domain. This Cys is in the DNA recognition helix, at the heart of the interaction of this protein with its DNA target, which has been resolved by X-ray crystallography. The hypothetical HIV-1 DNA binding protein conforms well to an alignment of various E2 protein DNA-binding domain sequences and contains the most essential elements in correct positions, assuming SeC can substitute for cysteine. The essential tryptophan that is critical for the dimerization of this protein is correctly placed. HIV-1 has a palindromic DNA sequence, thematically similar to the E2 DNA recognition site. This palindrome is located immediately downstream of the TATA box and proposed initiator protein binding site, at the +9 to +19 positions in the LTR, which is a perfect position to block an initiation complex. This and other evidence suggests that our novel protein may be a virally-encoded repressor of HIV transcription. Homology modeling and molecular dynamics simulation studies of this protein will be discussed.

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Do some viruses encode selenoproteins? - Assessment of the theory in the light of current theoretical, experimental and clinical data. E. Will Taylor, C. S. Ramanathan, R. G. Nadimpalli & R. F. Schinazi*, Dept. of Medicinal Chemistry, The University of Georgia, Athens, GA 30602, and *Dept. of Pediatrics, Emory University and Veterans Administration Medical Center, 1670 Clairmont Road, Decatur, GA .

Various researchers have pointed out the need for supplementation with the essential antioxidant mineral selenium (Se) in HIV infections, because of the well documented progressive depletion of Se in the plasma of ARC and AIDS patients, which has been widely assumed to be merely a consequence of the AIDS wasting syndrome. We recently reported the discovery of potential novel genes in HIV that may cast a new light on this phenomenon (*J. Med. Chem.* 1994; 37:2637-54). These novel genes potentially encode Se-containing proteins, suggesting a role for Se in the biochemistry and regulation of HIV. Thus, Se depletion may not only be a correlate of AIDS progression: it may be directly involved in the mechanism by which HIV causes AIDS. Se is required for the enzyme glutathione peroxidase, which breaks down harmful peroxides using reduced glutathione. Thus, depletion of Se in HIV-infected cells, and the potential existence of virally-encoded regulatory selenoproteins, could help explain the increased susceptibility to oxidative stress characteristic of AIDS. Various observations are consistent with this theory, e.g., an HIV-associated depletion of glutathione peroxidase was observed in an infected cell line, and suggested to be an important mechanism for T-cell loss in HIV disease (*J. Biol. Chem.* 1994; 269:798-801). Inorganic Se compounds have been previously reported to inhibit other retroviruses both *in vitro* (BLV) and *in vivo* (MMTV). We have found that certain simple Se compounds inhibit HIV-1 in acutely infected primary human lymphocytes, with EC_{50} below 5 μM, and selectivity index >30. The theory can also potentially help explain the role of various cofactors that stimulate HIV infection, since many infectious disease states stimulate free radical formation, producing oxidative stress. Finally, Keshan disease, a classical Se-deficiency disease that was also found to involve an RNA virus, may be a precedent for the ability of dietary Se to modulate the virulence of viral strains, because the coxsackievirus involved has genes analogous to those we recently described in HIV.