ically linked variable of neuraminidase inhibitors for influenza viruses.

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Sub-optimal Protease Inhibition of HIV-1: Effects on Virion Morphogenesis and RNA Maturation

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During or soon after release of HIV-1 from an infected cell the virion initiates the process of maturation. The viral protease becomes activated, leading to the subsequent cleavage of the viral polyproteins Gag and GagPol into their constituent parts. As a result, an internal conical core condenses surrounding the viral nucleic acid and the particle becomes infectious. Concomitant with this global alteration in virion morphogenesis is a conformational change in the viral genomic RNA from a loosely associated dimer into a more thermodynamically stable form. Protease defective viruses are capable of virus release and viral RNA encapsidation, but these particles are non-infectious and immature due to an inability to carry out proteolytic cleavage. Within these particles the viral RNA is also observed to be in an immature state, demonstrating a link between the proteinaseous maturation and that of the nucleic acid. We have used sub-optimal concentrations (IC50 and IC90) of two protease inhibitor drugs (Lopinavir and Atazanavir) to demonstrate their effect on the Gag polyprotein processing and RNA properties of the treated virions. The results were then correlated to their effects on virion morphogenesis as determined by EM. The results show that even with high levels of viral inhibition (IC90) most of the viral protein is processed. However, a slight but significant increase in processing intermediates was detected upon drug exposure and a small decrease (2–3 °C when 50% of dimers remained) in overall thermostability of the viral RNA dimer was also observed. These defects correlated with an increase in immature particles as observed by EM, but the numbers of immature particles did not adequately account for the level of viral inhibition. These data suggest that the presence of small quantities of residual processing intermediates, within the viral particles, is capable of disproportionately inhibiting the viral replication cycle, without having comparative effects on either RNA maturation or virion core condensation.

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Significance of 3b-dehydroxysterol-D24-reductase (DHCR24) in life cycle of Hepatitis C virus

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Hepatitis C virus (HCV) causes persistent infection often progressing to hepatocellular carcinoma (HCC). We previously reported that full HCV genome-expressing HepG2 cells enhanced their clonogenic capacity after 44 days of passage (M6 44 days cells). We established monoclonal antibodies (MoAbs) against surface antigens on these cells. One of the MoAbs specifically recognized the molecule which was overexpressed in the cancerous region of livers of all HCV-positive HCC patients. It was identified as 24-dehydrocholesterol reductase (DHCR24), which was reported to be involved in cholesterol biosynthesis and hydrogen peroxide-induced cytotoxicity. The full-length HCV upregulated the transcription of DHCR24 in human liver cells in the presence of p53. Expression of HCV induced the upregulation of DHCR24 and p53, and was sustained in M6 44 days cells. However, activity of $p21^{WAF1/CIP1}$ promoter in response to hydrogen peroxide was impaired in M6 44 days cells. This might be induced by the post-translational modification of p53, which was regulated by DHCR24. Thus, DHCR24 plays a critical role in the regulation of the response to HCV and hydrogen peroxide, and this pathway is a target of HCV during its persistent expression.

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Inhibition of Human T-Cell Lymphotropic Virus Type-1 Integrase by Dicaffeoylquinic Acids Extracted from Coffee (*Coffea arabica*) Seeds

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Human T-cell lymphotropic virus type-1 (HTLV-1) replication depends on the viral enzyme integrase (IN) that mediates integration of a DNA copy of the virus into the host cell genome. Integrase represents a novel target to which antiviral agents might be directed. The C-terminal part of the HTLV-1 pol gene is predicted to encode the HTLV-1 IN; however, this protein has not yet been detected in virions or infected cells. In order to evaluate compounds with anti-HTLV IN activity, we extracted dicaffeoylquinic acids (DCQAs) from coffee (*Coffea arabica*) seeds. Using a baculovirus system we expressed a 38-kDa IN