Oral Session I - Retrovirus Infections I

1

Interfering with HIV-1 Replication by Affecting Cellular Factors. HIV-1 Inhibition by Hydroxyurea.

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HIV-1 DNA synthesis is completed extremely slowly and inefficiently in quiescent PBL compared to that in stimulated PBL. This phenomenon is caused by the existence of lower levels of deoxynucleotides (dNTP) in quiescent compared to activated PBL impairing the HIV-1 reverse transcriptase activity. Hydroxyurea treatment of stimulated PBL decreases the levels of dNTP and reduces DNA synthesis rate as well as DNA elongation to levels comparable to quiescent PBL. At concentrations commonly used in human therapy ($\leq$100 μM) hydroxyurea inhibits HIV-1 replication in primary human PBL and macrophages and acts synergistically in combination with the nucleoside analogs AZT and ddI, without increase in toxicity. Our data, therefore, indicate that low levels of dNTP may explain why HIV-1 DNA is synthesized slowly and inefficiently in quiescent PBL and suggest that pharmacologic induction of low dNTP levels represents an approach for inhibition of HIV-1 replication. Analogs of hydroxyurea show in part the same mechanism of action, though possessing specific individual characteristics. Comparison of efficacy vs. toxicity of these analogs and hydroxyurea are evaluated. SIV is inhibited by hydroxyurea similar to HIV-1 in quiescent and stimulated lymphocytes, however, is significantly less sensitive to the same drug in macrophages. Targeting cellular proteins (which mutate at much lower rate than the viral ones) could reduce the onset of escape mutants.