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Drug-Resistant HIV-1 Mutants May Undergo Further Mutations in their Reverse Transcriptase (RT) under Continuous Pressure of HIV-1-Specific RT Inhibitors

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A mutant human immunodeficiency virus type 1 (HIV-1) strain selected for resistance against nevirapine and containing Cys in stead of Tyr at position 181 (Y181C) of its reverse transcriptase (RT) was kept under the continuous pressure of high concentrations (2.5-10 μg/ml) of the HIV-1-specific RT inhibitors TIBO R82913, pyridinone L697661, nevirapine and BHAP U88204E. Treatment of the HIV-1 (Y181C)-infected CEM cell cultures with BHAP at 10 μg/ml did not prevent a productive virus infection, although it markedly delayed virus breakthrough. The BHAP-resistant HIV-1 strain that originated under these conditions contained a novel mutation at RT position 181, where Cys (codon: TGT) appeared to be replaced by Ile (codon: ATT), which represents a double mutation of the 181th codon. The virus mutant containing Ile at position 181 proved exquisitely resistant to all HIV-1-specific RT inhibitors (i.e. BHAP, nevirapine, TIBO, pyridinone), and the reverse transcriptase containing the Y181I mutation was also found to be highly resistant to the HIV-1-specific RT inhibitors. In one of the mutant HIV-1 (Y181I) populations traces of a 181 Phe-containing HIV-1 strain were detected. Therefore, we postulate that the HIV-1 (Y181I) strain was derived from the HIV-1 (Y181C) strain through the intermediate HIV-1 (Y181F) strain. At the molecular level, codon 181-Cys (TGT) may have mutated to codon 181-Phe (TTT) and subsequently to codon 181-Ile (ATT).

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DRUG-INDUCED CELL MEDIATED MECHANISM LEADING TO RESISTANCE OF HIV TO AZT.

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Resistance of HIV to antiviral drugs is thought to be one of the factors responsible for therapeutic failure in AIDS patients. Some of the mutations of the viral genome which confer drug resistance have been identified. This study is focused on the possibility that cellular factors, other than viral mutations, could impair the antiviral action of AZT against HIV.

First, it has been demonstrated that a cellular line, namely CEM VBL100, resistant to Vinblastine and expressing the multi-drug resistance (MDR) protein gp-170 is less susceptible to the antiviral action of AZT (Antonelli et al. AIDS and Human Retrovir. 8, 1839, 1992). Other experiments have indicated that AZT itself can induce cellular factors conferring drug resistance. Cell line, preliminarly called CEMazt , resistant to the antiviral and cytostatic activity of AZT has been obtained simply by propagating the cells in the presence of AZT. These cells became resistant to the antigrowth activity of AZT (IC50 for CEM = 50 uM; IC50 for CEMazt > 1000 uM). More importantly, these cells support HIV-1 replication in the presence of inhibitory concentrations of AZT (ID50 for HIV: CEM= 8 nM; CEMazt 200 nM). Furthermore, intracellular accumulation of AZT was diminished in CEMazt as compared to the parental cell line. Intriguing results however have been obtained when these cells were examined for the expression of gp 170. In fact only a transient expression of the MDR protein induced by AZT was observed, while during and at the end of the selection process CEMazt, although displaying a high degree of resistance to AZT, do not show any significant expression of gp 170 on the cell membrane. These findings indicate that other mechanism of cell resistance, active on the cell membrane or intracellularly, may be responsible for decreased activity of antiviral drugs. Preliminar evidence indicate that this by hypothesis is real. In conclusion this study suggests that cell-mediated AZT-induced mechanism(s) of acquired resistance to AZT may also exist. The role of these mechanisms in the clinical pathobiology of long-treatment with AZT is still to be ascertained.

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