EFFECTS OF COMBINATION TREATMENT WITH AZIDOTHYMIDINE AND PHARMACOLOGICAL INHIBITORS OF NF-KB ON APOPTOTIC CELL DEATH IN UNINFECTED OR VIRUS-INFECTED TRANSFORMED CELL LINES

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Recently it has been shown that the nucleoside analogue azidothymidine (AZT) induced apoptosis in EBV-positive lymphoma cell lines by means of mechanisms involving NF-kB regulation. Thus, we wanted to investigate the relationship between NF-kB activation and apoptosis modulation by AZT in uninfected or virus-infected, transformed cell lines. The uninfected U937 monocytoid cell line was found quite susceptible to AZT-induced cell death. Nevertheless, even U937 cells showed a limited capability to undergo AZT-induced cell death in comparison with death caused by other chemotherapeutic agents. U937 cells in which NF-kB activation was inhibited either through transfection with a DN-IkBα or through an NF-kB pharmacological inhibitor resulted more susceptible to AZT-induced cell death. In order to investigate mechanisms underlying this response, apoptosis-related gene expression was investigated by a commercial gene-array system. The results showed that AZT induced, at the same time, pro-apoptotic and anti-apoptotic gene expression. AZT-induced anti-apoptotic genes belonged to the NF-kB-dependent gene family. We then focused our attention on the relationships between NF-kB activation and induction of apoptosis by AZT in virus infected cells. To this purpose, we first assayed the susceptibility to apoptosis induced by AZT, with or without the addition of NF-kB inhibitors, in HTLV-1 chronically infected MT-2 cells or in different IL-2-dependent, HTLV-1-infected cell lines transformed or immortalized in our laboratory. MT-2 and other HTLV-1-infected cell lines were found variably, but in any case poorly, susceptible to AZT-induced cell death. However, combination treatment with AZT and an NF-kB inhibiting compound highly increased cell death of HTLV-1-infected cells. To understand mechanisms involved in this effect, apoptosis-related gene expression by means of a gene-array was assayed also in these cells. We observed that combination treatment remarkably modulated apoptosis-related genes in comparison with single treatments. Results of our experiments suggest that a combination treatment with AZT plus a NF-kB inhibitor could be a new interesting pharmacological approach to simultaneously control both HTLV-1 infection and HTLV-1-induced dysfunction of cell growth.