Combination of proteasome and Hsp90 inhibitors induces autophagic cell death in HIV-1-infected macrophages and CD4+ T cells: approaches to elimination of the virus reservoirs

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Background: CD4+ T cells and macrophages are major in vivo HIV-1 reservoirs where the virus replicates and persists. Development of approaches to better pharmacological targeting these reservoirs is of importance for anti-AIDS therapy. In our previous studies, we have revealed the sensitivity of the HIV-1-infected cells to various inhibitors of proteasomes or heat shock protein 90 (Hsp90). The present research work was aimed at examining effects of two pharmacological inhibitors of proteasomes (bortezomib) and Hsp90 (17AAG) on HIV-1-infected and non-infected CD4+ T cells and macrophages from AIDS patients.

Methods: The pools of CD4+ T cells and monocytes were isolated from 14 HIV-1-seropositive patients with established AIDS. Sorting of the HIV-1-infected and non-infected cells was performed on a FACS using labels to cell surface markers. The harvested monocytes were in vitro developed into adherent macrophages. The separated subpopulations of CD4+ T cells and macrophages were treated with bortezomib (a proteasome inhibitor) and/or 17AAG (an Hsp90 inhibitor). Apoptosis/necrosis was determined with FITC-annexinV/propidium iodide staining. The autophagic cell death was monitored on lethal autofagosome-autolysosome transition.

Results: It was found that co-treatment with 100-400 nM bortezomib and 10-250 nM 17AAG induces autophagy in both the HIV-1-infected macrophages and CD4+ T cells what was manifested in massive formation of autophagosomes and subsequent appearance of large autolysosomes. Afterwards 60-75% of those cells underwent autophagic death (i.e. lethal autolysis) with total elimination of the infectious matter. The observed effect on HIV-1-infected macrophages was similar to what is exerted by vitamin D. The minor fraction (25-30%) of the infected and drug-treated macrophages and CD4+ T cells died via necrosis or apoptosis without clear signs of autophagy. Importantly, non-infected macrophages and CD4+ T cells exhibited no autophagy and only low (15-20%) apoptosis following the same drug co-treatment, while 80-85% of them remained viable.

Conclusion: We conclude that HIV-1-infected macrophages and CD4+ T cells are much more sensitive to the co-treatment with inhibitors of proteasomal and Hsp90 activities as compared with the non-infected cells. Simultaneous administration of such inhibitors (e.g. bortezomib + 17AAG) may be used for beneficial clearance of the AIDS-patients' organism from the HIV-1 reservoirs.