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Blockade of Function and Expression of Erythropoietin-Receptor (Ep-R) by Zidovudine (AZT). K.C. Agrawal, S.R. Gogu and J.S. Malter. Departments of Pharmacology and Pathology, Tulane Univ. School of Medicine, New Orleans, LA 70112, USA.

The clinical trials with Ep to overcome the AZT-induced anemia have not shown a beneficial response in patients whose endogenous serum Ep levels were >500 IU/L, suggesting a relative resistance to the action of Ep on bone marrow progenitor cells (BMPC). We have investigated the effect of AZT on Ep-R expression and function in BMPC. The quantitation of Ep-R was achieved with biotinylated-Ep (b-Ep) followed by detection with flow cytometry using streptavidin-R phycoerythrin. Treatment of BMPC with AZT for 24 hr caused a dose-dependent decrease in Ep-R expression with an IC_{50} of 7.5 μM. In contrast, ddI did not affect the Ep-R expression up to 20 μM. Ep-R mRNA levels were measured by slot blot analysis using a 39-mer oligonucleotide probe end labelled with ^{32}P. AZT caused a dose-dependent decrease in the mRNA levels within 60 min. This decrease in Ep-R was found to correlate with inhibition of formation of CFU-E. Simultaneous addition of Ep (1.0 U/ml) during exposure of BMPC to AZT, blocked the down regulation of Ep-R suggesting a stimulatory effect of Ep on its own receptor expression, however, it did not restore AZT-induced proliferative blockade indicating a secondary block of AZT at the level of Ep-Ep-R mediated signal transduction. Addition of IL-3 (100 U/ml) with Ep partially ameliorated the proliferative blockade suggesting that a combination therapy with Ep and and IL-3 may be more beneficial than Ep alone for AZT-induced anemia in patients with AIDS.