ABSTRACT

Multiple myeloma and its aggressive variant, plasma cell leukemia, are still considered to be incurable diseases despite the progressive treatment approaches comprising novel drugs. This can be attributed to the presence of the bone marrow microenvironment which plays an important role in drug resistance of myeloma cells. Hematopoietic cell lines derived from hematologic malignancies are suitable models for the study of etiopathogenesis of these malignant diseases and for testing new potential drugs. Establishment of these cell lines is still considered to be coincidental and rare event.

The first part of the thesis is focused on establishment and characterization of the cell line UHKT-944 derived from a patient with primary plasma cell leukemia, and on completion of characterization of the cell line UHKT-893 derived from a patient with multiple myeloma. Additional analysis of UHKT-893 cell line were performed including sequence analysis of IgVH gene rearrangements and cytogenetic analysis which contributed to more detailed characterization of this cell line. During cultivation of UHKT-944 cells, we monitored the cell growth and confirmed dependence on interleukin-6 (IL-6). Immunophenotype analysis revealed the presence of surface markers characteristic of malignant plasma cells. UHKT-944 cells were found to produce monoclonal IgA1-kappa. According to cytogenetic analysis, these cells were classified as near tetraploid with several numerical and structural abnormalities.

The second part of the thesis is focused on the effect of selected histone deacetylase inhibitors, valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA), on the UHKT-944 cell line in the presence or absence of the bone marrow microenvironment, which was simulated by the presence of bone marrow stromal cells derived from patients diagnosed with multiple myeloma, by extracellular matrix components or by various concentrations of IL-6. We found that SAHA and VPA induced apoptosis, inhibited cell proliferation but had no effect on the cell cycle distribution of UHKT-944 cells. Our results suggest that inhibition of JAK/STAT pathway is one of the mechanisms of action of VPA in myeloma cells. We further revealed that the bone marrow microenvironment, especially stromal cells, influence the efficiency of the used inhibitors. In conclusion, VPA and SAHA might represent an additional therapeutic strategy in the treatment of this rare malignant disease.