Abstract

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Title of diploma thesis: The effects of topoisomerase II beta on the sensitivity of the cancer cells to the antineoplastics

Topoisomerase II (TOP II) is a cellular enzyme responsible for solving topological problems of double-stranded DNA. Alpha and beta isoforms of TOP II are different gene products having similar catalytic activities. The expression of TOP IIα is cell-cycle dependent, peaking in G_2/M phase, while TOP IIβ isoform is expressed constitutively throughout the cell cycle. It is therefore present also in non-proliferating differentiated cells. Anthracycline antibiotics are an old class of anticancer drugs, belonging to TOP II poisons. Although their clinical usefulness is high, the incidence of side effects (especially myelotoxicity and cardiotoxicity) may limit the therapy. The key role of TOP IIβ inhibition, which is present also in cardiomyocytes, has been increasingly discussed. Dexrazoxane, the only clinically used cardioprotective, leads to depletion of TOP IIβ in cardiomyocytes, which may explain its cardioprotection. Although TOP IIβ was previously shown to be dispensable for cellular proliferation, its possible effects on the sensitivity to various antineoplastic agents is not known.

Therefore, practical aim of this thesis was to describe the properties of a HL-60 human promyelocytic leukaemia cell lines mutated for TOP IIβ. The cells with both, one, or no functional copies of TOP IIβ gene were previously developed by the CRISPR-Cas9 technology. First, we studied these cell lines regarding the TOP IIα and TOP IIβ mRNA and protein expression (by RT-qPCR and immunoblotting, respectively), and then regarding their sensitivity to daunorubicin and dexrazoxane.