ABSTRACT

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Title of diploma thesis: Study of resistance in cancer therapy - protein kinase inhibitors influence on activity of selected human reductases II.

Nowadays cancerous diseases are significant problem, and the incidence is still increasing. Anthracycline antibiotics are important in therapy of cancerous diseases, unfortunately, they have serious side effects and drug resistance is often obstacle for the effective treatment. The origin of cardiotoxicity is still not clear, older theories were based on formation of reactive oxygen species (ROS). Nevertheless, newer theories confirm that anthracyclines or their metabolites influence complicated cell pathways. The enzymes, which metabolize anthracyclines, specifically daunorubicin, were the subject of this work.

The carbonyl reducing enzymes are NADP(H)-dependent oxidoreductases, which are able to catalyse reduction of aldehydes and ketones to primary and secondary metabolites, daunorubicin is transformed to daunorubicinol directly by this way. Therefore we are most interested in enzymes from aldo-keto reductase family and short-chain dehydrogenases (SDR), namely AKR1C3 and CBR1. Many enzymes of this family are involved in the pathogenesis of some metabolic, inflammatory and degenerative processes. These transformations are important for origin of resistance or side effects of anthracyclines. This is a reason for finding specific subtypes of enzymes which metabolize daunorubicin.

We deal with inhibition of these enzymes by inhibitors of cyclin-dependent kinases (CDK). CDK play an important role in the cell cycle and influence many cell processes and increase in their activity can lead to the start of tumor growth. If they inhibit AKR and CBR, they would apply another mechanism to lower the anthracycline resistance and enhances the efficiency of cancer treatment.