1. Abstract

Although the first platinum drug cisplatin was initially described in 1845, its biological activity was discovered more than 100 years later. Since then are cisplatin and its clinically used analogues carboplatin and oxaliplatin in widespread use for the treatment of variety of human cancers, including ovarian, cervical, head and neck tumors, non-small cell lung, breast, colon, gastric and renal cell carcinoma, sarcoma and relapsed lymphoma. However, the treatment is often accompanied by severe side effects of which nephrotoxicity, peripheral neurotoxicity and myelosuppression are the most serious. Another important obstacle in their clinical use is drug resistance. This thesis evaluates possible mechanisms of the development of platinum drugs resistance. There is a variety of them and they include (i) diminished accumulation of platinum drugs affected by influx transporters (Aquaporin 9, CTR1, OCT1, OCT2) and by efflux transporters (ATP7A, ATP7B,ABCG2); (ii) increased detoxification of drug by thiols glutathione and metallothionein; (iii) improved repair of nuclear lesions affected by NER, MMR, Homologous recombination, and enhanced tolerance to nuclear lesions caused by Replicative bypass, inhibition of pro-apoptic factors (including caspase-3, -8, Fas and other), or by overexpression of apoptosis inhibitors (Xiap, Bcl-2, Bcl-xL). Some of them seem to be crucial in determining platinum drugs efficacy, but importance of most of them remains unclear. Therefore more work needs to be done to determine to which extent these mechanisms influence resistance to platinum drugs and influence their efficacy in the pharmacotherapy.