Abstract

Ovarian cancer is serious and one of the most common gynecologic cancers. Carboplatin is the therapeutic agent of the first choice in the ovarian cancer therapy. However, after the primary therapeutic response to carboplatin, the relapse of the disease may occur with developed resistance to carboplatin. Chemoresistance and insufficient therapy response are considered to be the reason of the high mortality rate of ovarian cancer.

The DNA damage response pathways play an important role in the therapeutic response and chemoresistance development. Restoration of homologous recombination function in cancers is the key mechanism of resistance development to platinum agents. Based on this knowledge, we formed our hypothesis, that the inhibition of homologous recombination could increase the sensibility to carboplatin. The main goal of this thesis was to define the role of double-strand breaks repair in response to chemotherapy of ovarian cancer. Protein MRE11 is part of the MRN complex, that participates in double-strand breaks repair. Using mirin as a pharmaceutic inhibitor of MRE11 we were aiming to determine the impact of homologous recombination on the effect of carboplatin and its role in resistant development to carboplatin.

In the practical part of the thesis, we described the association between increased expression of MRE11 and worse overall survival of ovarian cancer patients, using biostatistical analysis. The *in vitro* functional assays tested the individual and combined effect of carboplatin and mirin on the OVCAR3 cell line, and the resistant cell line created by the Department of Molecular Biology of Cancer (IEM CAS, Prague). Our results have shown that combined application of carboplatin and mirin results in the decreased cell proliferation and cell growth, and in the increased accumulation of DNA damage in comparison with a single application of carboplatin. After our experiments on the resistant cell line, we found out that the combined application of carboplatin and mirin results in decreased cell growth. According to our results, the inhibition of homologous recombination using MRE11 inhibitor results in increase sensibility of ovarian cancer cells to carboplatin in the sensitive and resistant cell lines.

Keywords: ovarian cancer, mirin, carboplatin, chemoresistance, homologous recombination, DNA damage response