Abstract

In humans, multi enzymatic processes are involved in maintaining DNA stability and cellular homeostasis. Cells undergo several episodes to survive and protect itself in daily basis. Accumulation of DNA errors and breaks are repaired by dynamic machinery, such as mismatch repair (MMR), replication-related process.

In presented diploma thesis, we report the studied MMR pathway and its involvement in malignancy of epithelial ovarian cancer (EOC). Our working hypothesis postulated that core genes of MMR, such as *MLH1* and *MSH2* are down-regulated in malignant cells. Cells therefore become incapable to repair accumulating DNA damage, undergo apoptosis or most likely uncontrolled proliferation. Above mentioned genes may also be silenced in cancer patients at transcription, translation or epigenetic levels.

Our aims were to clarify and to investigate the importance of MMR based on mRNA transcription, protein stability and promoter hypermethylation on a set of major MMR genes, particularly *MLH1, MSH2, PMS1, MLH3, MSH6, MSH3,* and *PMS2*.

In our study, we analysed samples from 63 epithelial ovarian cancer patients and 12 non-malignant reference tissues using RT-qPCR, MS-HRM, and Western Blotting methods. Consequently, our results show down-regulation of all MMR genes except for *MSH2* (up-regulated) in tumor tissues as compared to reference tissues. By comparing clinical data (stages I+II vs. III+IV), *MLH1* and *PMS1* were significantly up -regulated in stages III+IV (*MLH1* $P \leq 0, 017$; *PMS1* $P \leq 0{,}042$), *MSH2* in stages I+II ($P \leq 0.033$). The regulatory link between promoter methylation and mRNA down-regulation was not observed, since none of the tested tumor tissue sample exhibited enhanced methylation status. The *in vitro* studies showed significant G_2 arrest in *MLH1* deficient cell line after neocarzinostatin mediated DNA damage.

Taking together, these results suggest that regulation of MMR pathway in ovarian tumors might be correlated with microsatellite instability (MSI), miRNA regulation, or other endo-exogenous stress induced pathways.