Abstract

Application of cytotoxic chemotherapy still remains the essential treatment strategy in advanced colorectal cancer. The intrinsic and acquired drug resistance represents one of the reasons that may even lead to failure of cancer therapy. The DNA damage response pathways have been shown to play an important role in the development of chemoresistance. There is sufficient evidence showing the high-frequency deregulated expression of many DNA repair genes across multiple cancer types. An example of such gene in colorectal cancer is *MRE11*, which encodes protein known as a sensor of DNA double-strand breaks.

In year 2016, there was a substantial study published by our group at The Department of Molecular Biology of Cancer (IEM CAS, Prague), the study analysed the association of polymorphisms in predicted microRNA target sites of double-strand breaks (DSBs) repair genes, including *MRE11*, and clinical outcome and efficacy of chemotherapy in colorectal cancer. Our hypothesis, based on the mentioned study, is that specifically and exactly defined microRNAs with ability to regulate certain DNA repair proteins may not only affect the survival of colorectal cancer cells, but also the sensitivity to chemotherapy.

In practical part of the submitted thesis we have identified miR-140 as a potential regulator of MRE11 protein. The *in vitro* functional assays tested the effect of miR-140 on the behavior of chemosensitive and chemoresistant colorectal cancer cell lines before and after treatment with oxaliplatin, the standard chemotherapeutic agent for colorectal cancer. The obtained observations were finally validated in 33 patients with colorectal cancer.

According to our results, there is a possible association between level of miR-140 and the activity of MRE11 protein in colorectal cancer. We also found a significant effect of miR-140 on the behavior of chemosensitive colorectal cancer cells after treatment with oxaliplatin. Furthermore, the ectopic expression of miR-140 suppressed proliferation, increased cytotoxicity in colorectal cancer cells and at the same time the elevated level of miR-140 was associated with decreasing in *MRE11* expression. Finally, the same results were also confirmed on tumor samples obtained from patients with colorectal cancer.

Keywords: colorectal cancer, oxaliplatin, cancer therapeutic resistance, DNA damage and repair, Mre11, short non-coding RNAs, miR-140