ABSTRACT

Despite the great effort, the main obstacle to cancer therapy represents low response towards common chemotherapeutics and/or resistance. Chemoresistance causes cancer relapse and formation of metastases, dramatically challenging the prognosis of patients. It is estimated, that about 90% of cancer mortality can be directly or indirectly attributed to chemoresistance. There are several intrinsic or acquired cellular mechanisms of tumor chemoresistance, with DNA repair being one of the key culprits affecting the response towards chemotherapeutics in cancer cells. This is based on the fundamental principle of their action, as the majority of chemotherapeutics are designed to increase DNA damage and to suppress DNA repair or DNA damage response, ultimately triggering the death of malignant cells. Consequently, understanding the complex mechanisms of DNA repair and its regulation is essential for more targeted and effective treatment of cancer patients.

In this dissertation Thesis, we attempted to elucidate some of the regulatory mechanisms of DNA repair and their effects on response to common chemotherapeutics. We confirmed that single nucleotide polymorphisms in microRNA binding sites of DNA repair genes may influence the patient's survival and response to cancer therapy. We investigated the role of miR-140 in colorectal cancer and proposed that miR-140 ameliorates oxaliplatin response through inhibition of MRE11, an important protein in the repair of DNA double-strand breaks. We also investigated the impact of MRE11 inhibition, using Mirin and observed an increase in the cytotoxic effects of carboplatin on ovarian cancer cells and even re-sensitized resistant cell line to carboplatin. We also established a 5-FU resistant colorectal cancer cell line and demonstrated the crucial role of DNA repair and damage response gene dysregulation in developing 5-FU chemoresistance. Additionally, we were also interested in combination therapies of conventional chemotherapeutics and natural compounds to increase their efficacy. We analyzed the effect of *Ganoderma Lucidum* extract and confirmed its enhancing effect on 5-FU efficacy in colorectal cancer both *in vitro* and *in vivo*.

We believe that our results may add to a better understanding of the molecular mechanisms of resistance and sensitivity to chemotherapeutics in different types of cancer which may ultimately lead to better response and outcome for cancer patients.