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**MSc DEFENCE Monday, November 20th, 2017**

**Student:** Arash Samiei

**Title:** ROLE OF EEF2K IN DNA DAMAGE RESPONSE

**Time and location:** 9:30am PST; Gordon & Leslie Diamond Family Theatre, BC Cancer Research Centre, 675 W 10<sup>th</sup> Avenue, Vancouver, BC

**Supervisor:** Dr. Poul Sorensen

## **ABSTRACT**

Many of the DNA damage inducing chemotherapeutic drugs preferentially kill cancer cells but they also have a negative impact on normal cells in the body. Having a better understanding of how tumors respond to the DNA damage caused by chemotherapeutic agents can improve the chemotherapy regimen and reduce the harm done on the patient. Eukaryotic elongation factor 2 kinase (eEF2K) is a regulator of mRNA translation which is over-expressed in medulloblastoma, gliomas, and some breast cancer patients with poor prognosis. Under stress conditions, such as nutrient deprivation or DNA damage, eEF2K inhibits mRNA translation elongation by phosphorylating and inhibiting the activity of eukaryotic elongation factor 2 (eEF2). It was reported that eEF2K increases cellular sensitivity to inducers of DNA damage, including hydrogen peroxide and doxorubicin. The goal of this thesis work was to define the mechanistic role of eEF2K in DNA damage response (DDR) and its role in sensitizing cells to genotoxic agents. To this aim, we used cisplatin to study the DDR in the presence and absence of eEF2K expression. We found that eEF2K enhances the overall DDR in response to cisplatin treatment and the sensitivity phenotype depends on the level of cisplatin that the cells are exposed to. When cells are treated with high levels of cisplatin, eEF2K enhances the activity of the ATM and ATR DDR pathways that lead to higher apoptosis through p53 activity. However, when treated with low levels of cisplatin, eEF2K enhances the DNA repair pathways and prevents cell death. In summary, our findings show that eEF2K boosts the DNA damage response to help repair the damaged DNA, or helps to kill the cell if the damage cannot be repaired. Overall, these results reinforce the role of eEF2K as a stress response protein.