Project summary

Deoxyribonucleic acid (DNA) is the central store of genetic information in living organisms. DNA molecules constantly incur damage from intracellular metabolic processes as well as external stressors affecting cells. DNA double strand breaks are the most significant DNA lesions. Unrepaired double-strand breaks result in genomic instability, tumorigenesis, or cell death. Thus, eukaryotic cells respond to DNA damage by activating a comprehensive network of proteins and signaling pathways, which enable precise repair of DNA lesions.

On the other hand, increased activation of the DNA damage response signaling has been linked to cancer chemoresistance, as multiple chemotherapeutics act primarily by inducing DNA damage in rapidly dividing cancer cells. The recent studies indicate that specific inhibition of DNA damage response pathways in malignant cells might be an effective strategy to overcome cancer chemoresistance and improve survival of cancer patients.

Mixed-lineage kinase 4 (MLK4) is a protein kinase with a relatively poorly understood functions. We have recently found that MLK4 is highly expressed in breast cancer cells. Moreover, we discovered that this kinase promotes breast cancer chemoresistance and might regulate the repair of the DNA lesions induced by chemotherapeutics. These results suggest that MLK4 acts as a regulator of DNA damage response signaling, which is a noncanonical and yet undescribed function of this kinase.

Within this project, we aim to further investigate the role of MLK4 in DNA repair mechanisms. For this purpose, the activation of DNA repair machinery will be evaluated in MLK4-deficient and MLK4-competent cells. Furthermore, we will examine if MLK4 downregulation leads to the accumulation of DNA damage in both normal epithelial and cancer cells. We will also assess whether MLK4 is required for the repair of DNA damage induced by external stimuli (i.e., chemotherapeutics, hydrogen peroxide). Finally, we will evaluate if MLK4 inhibition can effectively sensitize cancer cells to drugs targeting different components of DNA repair pathways.

The project will provide further insights into the role of MLK4 in cancer cell signaling and can reveal novel mechanisms regulating DNA repair in human cells. Because DNA damage response pathways play a crucial role in the pathogenesis of multiple types of cancer and contribute to therapy resistance, the results of this project will have a significant scientific and translational relevance.