SUMMARY OF THE PROJECT

Project: Targeting Mitochondrial Dynamics and Mitophagy in Gastrointestinal Carcinomas: Unraveling the Therapeutic Potential of Drp1, Opa1, and PINK1 Pathways with NSAIDs and Conventional Anti-Cancer Drugs

Despite being the third leading cause of cancer-related death, there yet remain limited non-hazardous therapeutic strategies against gastric adenocarcinoma. This study delves into an innovative combinatorial drug treatment that positively manipulates mitochondrial dynamics in addition to also promoting mitochondrial pathology-mediated cell death. Mitochondria are a dynamic cell organelle that is capable of self-rejuvenation via multiple cycles of fusion and fissions. The involvement of multiple proteins plays an instrumental role to make happen such a dynamic process.

PTEN-induced kinase 1 (Pink1)/ Parkin-mediated mitophagy has always been considered a key mediator in the development of several diseases. One such characteristic of Pink1 was observed is insufficient expression levels in gastric cancer. Indomethacin, a well-known drug is not only used against inflammation by blocking the production of prostaglandins but has also been proven to inhibit the mitochondrial electron transport chain (ETC) complex I function, promoting mitochondrial oxidative stress which when unchecked results in cell death. When gastric cancer cells were treated with indomethacin, they failed to induce more Pink1 expression in addition to the already lacking Pink1 expression. Withholding this concept, upon investigating pink1-associated mitochondrial dynamics proteins, we identified the co-involvement and expression of Drp1, the key modulator in promoting mitochondrial fission. Bioinformatical studies also backed our claim of Drp1 being overexpressed in gastric adenocarcinoma. Inducing indomethacin treatment on gastric cancer cells, upregulated Drp1 expression suggesting enhanced mitochondrial fragmentation upon onset of mitopathology.

Following the identification of such a role of Drp1, we introduced mitochondrial division inhibitor-1 (Mdivi-1) as the combinatorial drug along with indomethacin, which is known for its inhibitory action on mitochondrial fission by directly inhibiting Drp1 expression. Employing the sub-optimal dose of indomethacin and Mdivi-1 we observed selective induction of cell death in gastric cancer cells with the assistance of pro-apoptotic proteins.

As a noncanonical chemotherapeutic method in highly resistant gastric cancer cells, our work contributes to the suggestion of a drug combination strategy including the modification of mitochondrial dynamics in conjunction with mitochondrial ETC complex inhibition-mediated induction of disease. According to the research conducted thus far, changes in mitochondrial Drp1 render gastric cancer cells susceptible to activation of mitochondrial malfunction and consequent cell death, even at suboptimal concentrations. These cells are already impaired in mitophagy due to their Pink1 deficiency. Once completed, this investigation may reveal specific therapeutic approaches that repurpose currently existing medications that interact with mitochondrial metabolism and function. Successful expression mapping in the future patterns of several proteins controlling the dynamics of mitochondria and mitophagy might be useful in determining the kinds and stages of cancer in addition to offering specialized noncanonical therapy approaches.