Evaluating Flavonoids in Pancreatic Cancer Therapy: Targeting Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1B (DYRK1B)

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Y. Lin[I], K. Hsu[I], **W. HuangFu**[I]

[I]College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan

Pancreatic cancer presents significant treatment challenges, characterized by high mortality rates and limited effectiveness of current therapies such as surgery, radiation, and chemotherapy. Despite the use of various chemotherapy drugs, the majority of patients with pancreatic cancer develop metastasis, and the cancer cells often exhibit strong resistance to chemotherapy, resulting in poor outcomes. Studies have shown that pancreatic cancer cells can escape chemotherapeutic attack by entering a quiescent state during cell division. In this state, they express elevated levels of dual-specificity tyrosine-phosphorylation-regulated kinase 1B (DYRK1B), which contributes to their survival by inducing quiescence and reducing reactive oxygen species (ROS), thereby evading drug effects.

Our research focused on developing inhibitors of DYRK1B as a novel therapeutic strategy to force cancer cells out of quiescence and make them more susceptible to chemotherapy. We discovered a promising DYRK1B inhibitor, Fv03, through computer simulations and enzyme-based assays. In tests on PANC-1 pancreatic cancer cells, which express high levels of DYRK1B and are resistant to the chemotherapy drug gemcitabine, Fv03 effectively killed these cells. Fv03 also decreased the phosphorylation of p27Kip1, indicating successful inhibition of DYRK1B's activity. This inhibition increased ROS levels in PANC-1 cells, causing cell death. However, Fv03 did not exhibit a synergistic effect when combined with gemcitabine. Future efforts will focus on optimizing Fv03 to improve its efficacy in blocking DYRK1B and to elucidate the molecular mechanism by which it promotes cancer cell death. This study lays the groundwork for further exploration of DYRK1B as a target for pancreatic cancer treatment and opens up new avenues for developing effective therapies for this devastating disease.