Chapter 1

Introduction

1.1 Background

Pancreatic ductal adenocarcinoma (PDAC) refers to the uncontrolled proliferation of differentiated pancreatic epithelial cells that may develop into invasive carcinoma (Dhillon & Betancourt, 2020; Wijnen et al., 2021). With a 5-year survival rate stooping below 10%, PDAC has been crowned as the deadliest abdominal malignancy that accounts for over 90% of the cancers in the pancreas (Jain & Bhardwaj, 2020; Mukund et al., 2024). The alarming state of PDAC is particularly underscored by its near-equivalent incidence-to-mortality ratio, with 510,992 new cases and 467,409 deaths reported in 2022 alone by WHO GLOBOCAN. Moreover, the current epidemiological trends and stagnant survival rates of the disease suggest that PDAC will become the second leading cause of cancer-related mortality by 2030 (Mukund et al., 2024; Principe et al., 2021). This trajectory is driven by two primary factors: late diagnosis and limited response towards available treatments (Sarantis et al., 2020).

There is an absence of reliable biomarkers for early PDAC detection and a lack of diagnostic techniques that are capable of effectively screening the deep retroperitoneal layer of the pancreas. Moreover, PDAC presents with an asymptomatic nature, which overall contributes to the complexity of diagnosing the disease (Mukund et al., 2024; Sarantis et al., 2020). The majority of PDAC cases are thus detected at a later or advanced stage, where the disease has metastasized, rendering them no longer eligible for surgical resection, which is the primary treatment approach for PDAC. Even among those who undergo surgery, recurrence rates reach up to 62% within 12 months, necessitating a heavy reliance on systemic therapies to treat the disease instead (Mukund et al., 2024)

Commonly employed PDAC chemotherapeutic drugs, FOLFIRINOX and gemcitabine, offer a significant increase in overall survival (OS). However, both agents are frequently accompanied by severe side

effects, including hematologic toxicity and pulmonary complications, which may permanently compromise the patients' quality of life (Lambert et al., 2017; Haydock et al., 2018; Liben and Warren, 2023). This treatment regimen is often employed in combination with radiotherapy to prevent disease recurrence, yet it is associated with numerous cases of upper gastrointestinal toxicity (Yasuda et al., 2025). While targeted therapies represent a promising avenue, their advancement in PDAC has been limited. To date, the EGFR-inhibitor erlotinib remains the only FDA-approved targeted agent for PDAC, offering minimal improvements in patient outcomes (Moore et al., 2007; Fang et al., 2023). This limited efficacy is largely attributed to the high degree of genomic instability in PDAC, which gives rise to heterogeneous and often rare genetic mutations harbored by each patient, complicating the development of universally effective targeted therapies. Given this challenge, a potentially more effective strategy would be to target the genes responsible for driving the underlying genomic instability itself, rather than focusing on frequently mutated driver genes.

Preliminary *in silico* data mining performed by a previous investigator in the Department of Cancer Biology and Drug Discovery at Taipei Medical University has pinpointed RMI2 as a gene responsible for worsening the progression of PDAC. In normal cells, RMI2 is one of the central components involved in maintaining genome stability through dissolution of Holliday junctions during homologous recombination DNA repair (NCBI, 2025; Hudson et al., 2016). However, aberrant overexpression of RMI2 has been associated with reduced OS and poorer prognosis in PDAC patients. Further pathway analysis suggests that RMI2 is involved not only in DNA repair but also in the initiation of DNA replication, implicating its potential role in cell cycle regulation. These observations are supported by experimental data showing that RMI2 knockdown in AsPC-1 cells significantly reduces cell proliferation compared to control cells, highlighting its oncogenic potential in PDAC. Collectively, current evidence suggests that RMI2 may promote PDAC cell proliferation by modulating cell cycle progression through its involvement in DNA replication and repair. Despite these insights, the precise molecular mechanisms remain poorly understood. A deeper understanding of the RMI2 mechanism

may facilitate the identification of novel therapeutic targets and diagnostic biomarkers, contributing to more effective strategies against this aggressive malignancy.

1.2 Objective

This study aims to elucidate the molecular mechanism by which RMI2 enhances the proliferation rate in PDAC cells by analyzing the downstream of DNA repair-associated proteins involved in DNA replication during the cell cycle.

1.3 Hypothesis

This study hypothesized that knockdown of RMI2 would attenuate the expression of DNA replication checkpoint proteins (pATR/pCHK1) due to increased levels of DNA damage, thus impairing cell cycle progression.