Chapter 1

Introduction

1.1 Background

Pancreatic cancer and its most common subtypes known as Pancreatic Ductal Adenocarcinoma (PDAC) is commonly associated with high lethality as well as low survival chances as median survival is around 9.3 months with the 5-year survival rate being 10.5% (Li, Feng, et al., 2022). Low survival is found to be correlated with advanced age and late diagnosis, where the tumor has already advanced to a stage where treatment is ineffective (Logan et al., 2022). At an advanced stage, the cancer has a high chance of already metastasizing and coupled with the complicated microenvironment of the cancer needing a more specific treatment target to increase survival (Sarantis et al., 2020). In other types of cancer, this is usually done through the use of cancer biomarkers where a particular trait is targeted for its possible role to affect cancer progression. In PDAC however, there is a lack of approved biomarkers, especially prognostic biomarkers, where only carbohydrate antigen 19-9 (CA19-9) is approved by the US's Food and Drug Administration (Gu & Minko, 2024). As such, it is highly important for more prognostic biomarkers to be discovered as it is highly correlated with tumor recurrence and risk stratification which can lower the mortality rate (Wang, Zhong, et al., 2020; Cui et al. 2020).

Current research trends for biomarker research lean towards the use of transcriptomics analysis, specifically towards the use of non-coding RNA (ncRNAs) such as long non-coding RNAs (lncRNAs) (Tsimberidou et al., 2020; Mattick et al., 2023). This is due to ncRNAs having a role in the regulation of gene expression and playing an active role in cell growth and differentiation which is an important part of cancer progression (He et al., 2023). This is also compounded by the currently known ratio of RNA, where almost 78% of RNA transcripts is of the ncRNA type with the largest variant being lncRNAs (El-Helkan et al., 2022). Several of which has been found to regulate the tumor microenvironment in PDAC

as well as regulating the growth, invasion, migration, and angiogenesis in said cancer (Zhao et al., 2023).

Aside from lncRNAs, there are also other factors that may play a role in tumorigenesis and cancer progression. Of note is Copy Number Aberration (CNA), this is where errors during repair, stress during replication, and other events related to DNA replication error causes the genome to become aneuploidy and unstable (Steele et al., 2022). It has been found that in PDAC patients with high CNA is correlated to lower prognosis indicating that CNA has a role in cancer progression and outcome in PDAC (Liu et al., 2022). As such, correlation between both lncRNA and CNA events such as duplication or deletion could be explored to find possible prognostic markers using lncRNA. Previous studies on the matter have been done in several other cancers such as cervical cancer, bladder cancer, and colorectal cancer where CNA was proven to affect the expression of several lncRNA that causes poor prognosis (Zhong, Lu, et al., 2021; Liu et al., 2023; Wang et al., 2024).

1.2 Objective

This research aims to identify PDAC prognostic markers from CNA driven lncRNA using *in silico* techniques. The Cancer Genome Atlas Program (TCGA) as well as the Genotype-Tissue Expression (GTEx) Project will be utilized to identify differential lncRNA driven CNA. Highly correlated lncRNA will be tested for their prognostic value using cox analysis. The functional enrichment analysis will be conducted to elucidate the possible function and regulatory mechanism of the potential prognostic marker.

1.3 Hypothesis

This study hypothesizes that pancreatic cancer patients exhibit multiple differentially expressed lncRNA, with only a small subset being driven by CNA, and that they may serve as novel potential prognostic markers.