PROJECT TITLE

A Master Cancer Signaling Regulator as a Novel Pancreatic Cancer Biomarker

PRINCIPAL INVESTIGATOR
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SCIENTIFIC SUMMARY

Background

As one of the most aggressive human cancers, pancreatic cancer (PDAC) has near-uniform mortality, with the 5-year survival rate under 11%, and is projected to be the 2nd leading cause of cancer deaths by 2030. Surgical resection remains to be the only potential curative treatment for PDAC, but up to 60% of these patients experience disease recurrence within six months after surgery. Prognostic biomarkers are urgently needed for selecting suitable patients for resection to maximize survival advantage and reduce morbidity and mortality.

Standard of care

Current selection paradigms for surgical resection in PDAC are based on the anatomical relationship of the tumour to adjacent vessels, overall disease burden, and the patient's performance status. Whilst clinically applicable, such paradigms lack any objective reference to tumour biology. Despite numerous PDAC biomarker studies, cancer antigen 19-9 remains the only clinically validated marker in routine practice. However, this biomarker has poor sensitivity and is unrelated to tumor biology. Additional markers especially those underlying tumor malignancy are sorely needed.

Research question

Proline-directed protein phosphorylation is a central signaling mechanism in cancer. We have discovered that upon phosphorylation, protein structure and function can be further regulated by a single unique proline isomerase, Pin1. Pin1 is highly regulated to keep the balance of oncoproteins and tumor suppressors. However, in most human cancers, Pin1 is overexpressed to drive cancer malignancy and drug resistance by turning on over 70 tumor-causing proteins and turning off over 30 tumor-suppressing proteins. In contrast, genetic changes that decrease Pin1 are associated with reduced risk for cancer in humans.

In PDAC patients, Pin1 overexpression in cancer cells is correlated with poor outcome. We have further discovered that Pin1 overexpression in both cancer cells and cancer-associated fibroblasts correlates with even worse outcome, ~4-year survival disadvantage after surgery, extraordinary for PDAC. Strikingly, targeting Pin1 using repurposed drugs renders aggressive PDAC eradicable by immunochemotherapy, for the first time, which have been confirmed, with human trials to be launched hopefully in 2024. These results suggest that Pin1 is not only an attractive therapeutic target but also a promising prognostic biomarker for PDAC.

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SCIENTIFIC SUMMARY (CONTINUED)

Proposed research/methods

Here we have assembled a multi-disciplinary team with requisite expertise to evaluate the potential of Pin1 as a prognostic PDAC biomarker. Aim 1 will develop a clinically acceptable assay for Pin1 using immunohistochemistry followed by QuPath analysis at Western and OICR to establish analytic metrics for reproducible and clinically relevant measurement of Pin1 biomarker. Aim 2 will use a high-quality independent cohort from OICR to confirm that Pin1 overexpression in cancer cells and cancer-associated fibroblasts is a prognostic biomarker for PDAC patient survival after surgery.

Potential benefit

We anticipate that Pin1 will be a sensitive and reliable PDAC prognostic biomarker that will help identify patients with favorable tumour biology for resection to maximize survival advantage and reduce morbidity and mortality. As effective Pin1 inhibitors also induce its protein degradation, Pin1 biomarker will be valuable for stratifying PDAC patients and monitoring their therapeutic response in clinical trials targeting Pin1, which are under active investigation.

Our research aims to provide an easy-to-implement tool for accurate prognostication and early detection of progression, and thus potential early intervention, with a simple blood test. In the long term, accurate prognostication at diagnosis could lead to a new paradigm of treatment for osteosarcoma patients with stratification of treatment intensity based on risk rather than “one size fits all” aggressive chemotherapy.