

Pinpointing and targeting novel drivers of pancreatic cancer progression and metastasis using TRAP-seq.

Michael Trpceski^{1,2}, Alice Tran¹, Anna Howell¹, Kenny Ip^{1,2}, Cecilia Chambers^{1,2}, Jef Servaes¹, Maaïke De Moes¹, Stephan Oranth¹, Jessie Zhu^{1,2}, Shona Ritchie^{1,2}, Daniel Reed^{1,2}, Marjan Naeini^{1,2}, Leonard Goldstein^{1,2}, Grazi Vieira¹, Robert Weatheritt^{1,2}, Herbert Herzog^{1,2}, Kendelle Murphy^{1,2}, Patrick Caswell³, Johanna Ivaska⁴, Paul Timpson^{1,2}, David Herrmann^{1,2}.

- 1. The Garvan Institute of Medical Research & The Kinghorn Cancer Centre, Sydney, NSW, Australia,**
- 2. St Vincent's Clinical School, Faculty of Medicine, UNSW, Sydney, NSW, Australia.**
- 3. Manchester Centre for Cell-Matrix Research, The University of Manchester, Manchester, UK.**
- 4. Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku, Finland.**

Introduction

Pancreatic cancer (PC) has a dismal 5-year survival rate of only 13%¹, which can be attributed to its rapid metastatic spread and resistance to therapies. Here, we used innovative Translating-Ribosome-Affinity-Purification followed by RNA-sequencing (TRAP-seq) to assess the deregulated transcriptome of metastatic PC and identify potential novel therapeutic targets.

Methods

Mouse models of PC are driven by a *Kras*^{G12D} mutation and either loss of *Trp53* (KPflC; poorly metastatic) or a gain-of-function mutation in *Trp53* (KPC; highly metastatic)². TRAP-seq of primary tumours identified 200 genes that were translationally deregulated. From these, a candidate gene that was exclusively upregulated in the translating mRNAs of the KPC TRAP tumours, when compared to the KPflC TRAP tumours was selected as a novel target for further investigation.

Results

In vitro metastasis models were used to investigate candidate gene function. Excitingly, KPC cancer cells with target knockdown exhibited a reduced capacity to migrate and invade as well as grow in suspension, when compared to control. Moreover, target knockdown *in vivo* exhibited a significant reduction in liver metastasis in an intrasplenic transplant model. This was further corroborated by an almost complete depletion of liver metastases and significant increase in survival in mice bearing target knockdown tumours, which was further enhanced upon combination with chemotherapy.

Conclusion

Together, these findings suggest that the novel gene identified using TRAP-seq is required for the highly metastatic phenotype typically observed in the KPC model. Future investigations in patient-derived models may provide further insight into potential co-targeting to improve chemotherapeutic response and reduce metastasis.

References:

1. Siegel, R.L., et al., *Cancer Statistics, 2025*. CA: A Cancer Journal for Clinicians, 2025. 75(1): p. 10-45.
2. Morton, J.P., et al., *Mutant P53 Drives Metastasis and Overcomes Growth Arrest/Senescence in Pancreatic Cancer*. Proceedings of the National Academy of Sciences, 2010. 107(1): p. 246-251.