The Mutational Landscape of Circulating Tumor Cells in Pancreatic Cancer

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INTRODUCTION

- Pancreatic cancer has a high recurrence rate (~83-87%) even after receiving surgery and adjuvant chemotherapy.
- The overall survival rate of patients with early tumor recurrence is significantly lower than those without, highlighting the importance of developing strategies for predicting recurrence.
- The mutation profile of circulating tumor cells (CTCs) from pancreatic cancer patients has not been well studied.[1,2]
- In this study, we investigated the mutational profiles of CTCs from the peripheral blood and CTCs from the portal vein and compared these to somatic mutations found in the resected tumor.

METHODS

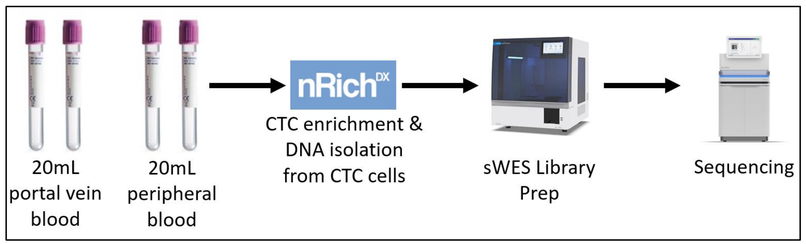

Figure 1. Workflow schematic.

- Seven pancreatic cancer patients underwent surgery after neoadjuvant therapy for curative intent.
- For each patient at surgery we collected 20mL of peripheral blood, 20mL of portal vein blood and the resected tumor sample.
- The blood was processed for CTCs using the CTC Enrichment Kit (Epithelial Origin, nRich^{Dx}) and DNA was isolated from the CTCs using the Revolution cfDNA Max 20 Kit (nRich^{Dx}).
- CTC DNA and resected tumor samples were submitted for whole exome sequencing (WES).
- The Agilent Magnis NGS Prep System was used for automated library preparation of the SureSelect Human All Exon V8 panel (Agilent).
- Single indexed libraries were sequenced on the Illumina Nova-Seq 6000 (paired-end, 150bp).
- Sequencing data and variant analysis was performed using an in-house comprehensive bioinformatics platform for genomic data (AUGMET).

RESULTS

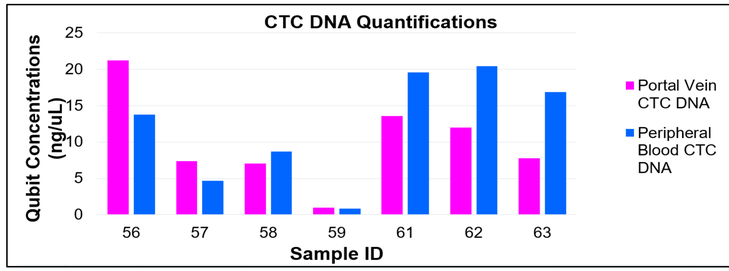

Figure 2. Barplot of CTC DNA Concentrations by Qubit from portal and peripheral blood samples.

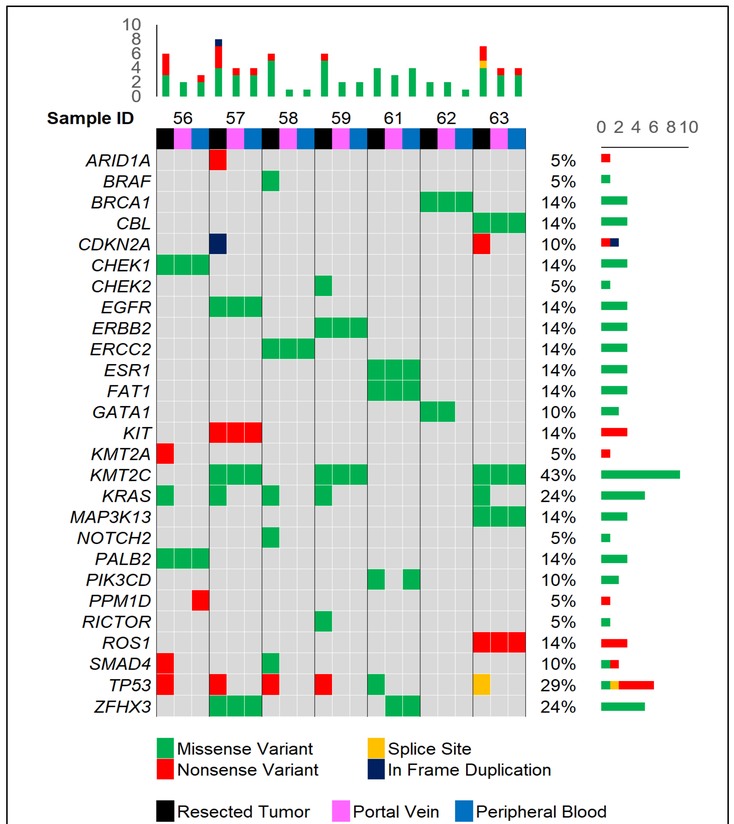

Figure 3. Oncoplot showing variants detected in resected sample, portal vein and peripheral blood sample. Top stacked barplot depicts the number of variants found in each sample. Stacked barplot to the right indicates how many samples in the cohort had a variant in the gene.

- Most patients experienced a reduction in tumor size from neoadjuvant therapy before surgery.
- Despite tumor size reduction, DNA was obtained from CTCs in both the peripheral blood and portal vein.
- Tumor mutational burden for CTCs from the portal vein and from the peripheral blood were comparable to each other and comparable to the resected tumor sample.
- Similar variants were detected in the resected tumor as in the CTCs and the CTC variants detected were variants with high variant allele frequencies in the corresponding resected sample.
- CTC variants were detected in the following genes: *BRCA1*, *CHEK1*, *CHEK2*, *EGFR, KIT*, and *PALB2*.

Table 1. Tumor mutational burden of samples.

Sample ID	Resected Sample Tumor Percent	Tumor Mutational Burden		
		Resected Sample TMB	CTC Portal Vein TMB	CTC Peripheral Blood TMB
56	50-60%	7	6	6
57	50-60%	5	5	5
58	30-40%	5	7	5
59	70-80%	6	6	6
61	30-40%	6	6	6
62	20%	5	6	6
63	30-35%	6	7	6

CONCLUSIONS

- Variants detected in the CTCs regardless of location of origin were also detected in the resected tumor sample after neoadjuvant therapy.
- Variants in the portal vein CTCs were also detected in CTCs from the peripheral blood.
- Tumor mutational burden was comparable between CTCs (regardless of draw location) and resected tumor.
- CTC mutational signatures may allow for personalized treatment post surgery.
- This study provides insight into why recurrence happens and may enable us to predict which individuals are likely to experience it.

REFERENCES

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