Comprehensive molecular profiling of paired patient samples of primary and metastatic (met) pancreatic ductal adenocarcinoma (PDAC)

N.D. Trivedi1, R. Feldman2, H. Wang3, N.R. Karki4, J. Marshall1, B.A. Weinberg1

1 Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; 2 Caris Life Sciences, Phoenix, AZ; 3 Georgetown University, Washington, DC; 4 MedStar Harbor Hospital, Baltimore, MD

Abstract (#4114)

Background: Pancreatic cancer is the third leading cause of cancer-related death in the U.S. The vast majority of pancreatic cancers are PDAC (90%). Most patients with PDAC die from complications of met disease, thus it is vital to better understand the molecular changes that promote met spread. Prior studies have shown few molecular changes between primary and met PDAC in unpaired analyses, but limited data exist on large-scale comparisons between paired samples from the same patient.

Methods: We analyzed next-generation sequencing (NGS) and immunohistochemistry (IHC) data from 123 patients with multiple PDAC tumors profiled by Caris Life Sciences and compared paired primary and met samples from the same patient. After patients with unrelated secondary primary cancers were excluded, 113 pairs were used for analysis. McNemar’s test was used to compare primary and met tumor pairs.

Results: The most common sites of mets were liver (33%), lung (19%), and peritoneum (18%). The average time between samples was 21.3 months (range 1-92). KRAS status changed in 13.2% of pairs (5.7% gained, 7.5% lost, n = 53, P = 0.710), TP53 status changed in 16.1% (16.1% gained, 0% lost, n = 53, P = 0.025), and SMAD4 status changed in 14.8% (7.4% gained, 7.4% lost, n = 27, P = 1.000). Mets gained expression of TOPO1 (37.5%, n = 80, P = 0.037), PD-1 (11%, n = 30, P = 0.003), PDGFRB (9%, n = 14, P = 0.005), and PBRM1 (9%, n = 14, P = 0.005). Table 1. Biomarkers tested by IHC, CNV or ISH demonstrating heterogeneity between paired samples Table 2. Genes tested by NGS demonstrating heterogeneity

Introduction

The prevailing thinking about PDAC is that primary and metastatic lesions have similar frequencies of genetic mutations. In addition, metastatic lesions are thought to have the same driver mutations no matter which organ they occupy. The majority of the data in this area are drawn from studies which examine either metastatic lesions alone or in tandem with unpaired analyses of primary tumors. By comparing the molecular profiles of paired patient samples, we hope to further investigate the mutations involved in metastasis of PDAC.

Results

Figure 1. Changes in KRAS Status by NGS

Figure 2. Changes in TP53 Status by NGS

Figure 3. Changes in TOP2A Status by IHC

Figure 4. Changes in SMAD4 Status by NGS

Table 1. Biomarkers tested by IHC, CNV or ISH demonstrating heterogeneity between paired samples

Table 2. Genes tested by NGS demonstrating heterogeneity between paired samples

Table 3. Changes in TMB in mutations per megabase (mts)

Conclusions

• KRAS mutational status between primary and met PDAC pairs changed more often than previously reported
• TOPO1, PD-1, and PTEN expression between primary and met PDAC pairs were significantly discordant
• There was a significant increase in TMB in met PDAC
• The discordance in mutational status and TMB between primary and met PDAC could yield new targets for future therapies

References


Highlighted Examples of Matched Pairs

Figure 5. IHC staining of biomarkers that change expression between primary and metastatic disease (a: TOP2A primary, b: TOP2A met, c: PD-L1 sp142 primary, d: PD-L1 sp142 met)

Table 4. 58 year-old female, lifelong non-smoker with pancreatic adenocarcinoma. Profiling results are shown from the initial biopsy of head of pancreas which occurred in Dec. 2016 and biopsy of metastatic disease in para-aortic lymph nodes, 5 months later in May 2017.

Table 5. 20 year-old male, lifetime heavy drinker with pancreatic adenocarcinoma. Profiling results are shown from the initial biopsy of head of pancreas which occurred in Oct. 2016 and biopsy of metastatic disease in para-aortic lymph nodes, 9 months later in July 2017.