AB004. S004. Differences in cancer metabolism between subtypes of pancreatic ductal adenocarcinoma (PDAC) are associated with survival and offer therapeutic opportunities

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Background: Overall survival (OS) of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor. Of patients eligible for surgery (20%), around 15% present with a recurrence within 6 months, while 10% survive over 5 years after diagnosis. Detailed clinicopathological and molecular knowledge of factors influencing survival will lead to better prognosticators and preselection of individual patients for specific treatment strategies.

Methods: Fresh frozen PDAC resection specimens from Academic Medical Centre Amsterdam (1993–2015) were histopathologically revised, and clinicopathological details were collected. From samples with a tumor cellularity of ≥30% (n=90), mRNA, miRNA, and DNA were used for next generation sequencing at multiple levels. Corresponding formalin-fixed paraffin-embedded (FFPE) blocks were selected for tissue microarrays.

Results: Unsupervised consensus clustering of gene expression profiles of 90 PDAC cases revealed four subgroups with divergent survival rates: secretory, epithelial, compound pancreatic, and mesenchymal subtypes, which remained after correction for potential confounders (a.o. LNM, differentiation grade, radical resection; multivariate Cox regression analysis). Supervised clustering demonstrated 10,041 genes to be differentially expressed between the subgroups, with prominent over-representation of ribosomal genes and oxidative phosphorylation (OXPHOS), dividing tumors in two major classes: secretory and epithelial vs. compound pancreatic and mesenchymal subgroups. These classes do not correspond in terms of median OS: secretory and mesenchymal with 14.7 and 14.0 m ('short') and epithelial and compound pancreatic with 31.8 and 21.5 m ('long'). Between 'short' and 'long' survivors, 683 genes were differentially expressed, associated with biosynthesis of macromolecules. Nutrients from extracellular space (Val, Leu, Ile) are converted into intermediates for the TCA cycle, creating increased metabolic flexibility in tumors of patients with shorter OS. To determine clinical relevance and identify biomarkers, we are currently characterizing the subtypes at the miRNA, mutational, copy number, and immunohistochemical level.

Conclusions: In our well-defined single-center set of 90 PDAC, we identified four transcriptomics-based subgroups with different survival outcomes that show a correlation with altered metabolic features. Complete characterization of metabolic liabilities will help to further identify prognosticators, f.i. measurement of elevated plasma levels of specific amino acids, and provide leads for targeted therapies, like mTOR inhibitors and anti-diabetic drugs.

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