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"An Integrative Bioinformatics Approach to Biomarker Discovery in Pancreatic Cancer"

Background: Despite remarkable progress and intensified screening, pancreatic cancer (PC) remains one of the leading causes of cancer-related deaths. According to the American Cancer Society, there were an estimated 66,440 new cases of PC and 51,750 deaths from the disease in the United States in 2024. Clinically PC follows an aggressive clinical course with very poor survival rates and limited treatment options as the disease responds poorly to chemotherapy. Sadly, both the incidence of and death rates of PC have been gradually rising, even as incidence and mortality of other common cancers have been declining. There is an urgent need to understand the macular mechanisms that contribute to the development and progression of pancreatic tumors. With the availability of genomics data on PC, we are now well-positioned to address this known gap and critical unmet medical need. Here we used integrative bioinformatics approaches combing gene expression and somatic mutation data to dissect the molecular basis of pancreatic ductal adenocarcinomas (PDACs), and to discover potential clinically actionable diagnostic and prognostic biomarkers and therapeutic targets.

Method: We used publicly available gene expression and somatic mutation data in PDACs from the Cancer Genome Atlas (TCGA). The gene expression data set consisted of 556 tumor and 83 control samples. The tumor samples were distributed as 261 alive and 160 dead. Somatic mutations were derived from the same tumor samples using exome sequencing. We compared gene expression values between tumors and controls, and between dead versus alive using DESEQ2 to identify differentially expressed genes (DEGs). Using integrative analysis, DEGs from each analysis were evaluated for the presence and frequency of somatic mutations. For each analysis, we performed functional and pathway enrichment analyses to characterize the molecular functions and identify signaling pathways enriched for somatic mutations.

Results: Comparing gene expression values between tumor and control samples produced a signature of 15,560 DEGs, of which 9,149 harbored somatic mutations, including KRAS and TP53, which are known PDAC biomarkers. Comparing gene expression values between dead and alive produced a signature of 12,764 DEGs, of which 11,236 harbored somatic mutations. There were differences in somatic mutations profiles between alive and dead. Enrichment analysis revealed important signaling pathways enriched for somatic mutations.

Conclusion: Integrative bioinformatics is a powerful approach for dissecting the molecular basis of PDAC, and for the discovery of potential clinically actionable diagnostic and prognostic biomarkers and potential therapeutic targets. Further research to identify molecular predictors of survival and development of Machine Learning algorithms to identify patients at high risk of developing aggressive disease who could be prioritized for treatment is recommended.