Non-ductal pancreatic tumor classification by whole genome DNA prolfiling

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# Abstract

*Background and aim:* Histopathological diagnosis of acinar cell carcinoma’s (ACC), solid pseudopapillary neoplasm (SPN) and pancreatic neuroendocrine neoplasms (PanNETs) may be challenging in daily clinical practice. As the cancer methylome harbors characteristics reflecting the cell of origin allowing identification of tumor origin, here we build a methylation profiling based classifier in order to facilitate differentiation between ACC, SPN and PanNETs.  
*Methods:  
Results:  
Conclusion:*

# Introduction

Around 90% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDACs), while the remainder (10%) is derived from non-ductal structures. The latter include acinar cell carcinoma (ACC), solid pseudopapillary neoplasms (SPN) and pancreatic neuroendocrine *tumors* (?) (PanNETs). This , which together comprise around 10% of pancreatic cancers.

~~Acinar cell carcinoma’s (ACC), solid pseudopapillary neoplasm (SPN) and pancreatic neuroendocrine neoplasms (PanNETs) comprise 1%, 2% and 5% of all pancreatic neoplasms respectively and are the most commonly occurring neoplasms that arise from non-ductal structures of the pancreas in adults [1, 2].~~

Behavior varies widely: while SPNs are predominantly indolent, ACCs and PanNETs come close to the aggressiveness of PDAC [3-6]. ACC, SPN and PanNETs are similar with regard to histomorphology and immunophenotype [1, 2]. Immunohistochemistry and molecular genetics have contributed to an improved classification of these tumors. Still, differentiation sometimes remains challenging while it is crucial for therapeutic decision making.

Whole genome methylation-based tumor classification is increasingly used for tumor classification [7], and the WHO recommends the routine application in tumor of the central nervous szstem (REF). DNA methylation is a covalent modification of cytosine residues and is involved in gene expression regulation. Hypermethylation of specific gene promotor regions can lead to transcriptional inactivation, including tumor suppressor genes [8, 9]. Besides somatically acquired DNA methylation changes, the cancer methylome harbors characteristics reflecting the cell of origin (REF). This tissue specificity is what makes DNA methylation profiling well suited for the identification of tumor origin (REF). Furthermore, archival formalin-fixed, paraffin embedded (FFPE) tissues can be used for DNA methylation analysis. Based on this rationale numerous classifiers have been developed for cancer classification and some are routinely used in daily practice [10-15]. Similarly, Hackeng et al. developed a classifier for distinguishing neuroendocrine tumors from different locations, including PanNETs [16]. Additionally, Jäkel et al. compared methylomes of ACCs, PanNETs and PDAC and showed that tumor types could be distinguished on methylation profiles [17]. Together, these data suggest potential applicability of methylation profiling for classification of non-ductal pancreatic tumors.

To facilitate diagnosis within non-ductal pancreatic tumors ACC, SPN and PanNET, we built a methylation-based prediction model. We evaluated random forest classifiers, neural networks and gradient boosting machines and present an approach to distinguish between non-ductal pancreatic cancers with almost perfect accuracy.

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