THE SUBTYPES OF PANCREATIC DUCTAL ADENOCARCINOMAS

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Abstract: Being the 4th leading cause of cancer deaths in the U.S. and with a global increase in incidence, above 80% of pancreatic cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection is the only hope for a cure, the answer is probably in early screening, proper classification and right therapy. The advancing research will likely lead to a better understanding of Pancreatic Ductal Adenocarcinoma (PDAC) as well as enhance the techniques for screening, diagnosis, accurate subtyping and enable the use of targeted therapy. Thus, instead of clubbing together various subtypes of PDAC for trials, improving the subcategorization will ensure statistical significance for the academicians, and the clinicians would avoid administration of placebo drug to a vast number of patients.

Key words: pancreatic cancer, subtypes, genetic, proteomic, phosphoproteomic.

INTRODUCTION
Pancreatic cancer is the 4th leading cause of cancer death in the USA, and is increasing globally. The cure rate, although showing improvement, is still very low, approximating at less than 7%. It is often diagnosed at a very late stage, when curative treatments are limited. Above 80% of these cancers are locally advanced or metastatic at the time of diagnosis. As surgical resection is the only hope for a cure, the answer is probably in early screening, proper classification and right therapy (1). The advancing research technologies and easy accessibility, will hopefully lead to a better understanding of Pancreatic Ductal Adenocarcinoma (PDAC) as well as enhance the techniques for screening, diagnosis, accurate subtyping and enable the use of targeted therapy.

Though PDAC is the most common form of pancreatic cancer, its causes and risk factors are largely unknown. In spite of the emergence of various treatment modalities, very few randomized trials have shown a drastic alteration in PDAC management. This is attributed to inadequate statistical significance leading to the hypothesis that PDAC is an aggregate of many diseases. Scientifically, the fundamental differentiation in PDAC lies in its genetic mutations and variable activation of them. Sporadic mutations (p16, TP53, KRAS, BRAF, SMAD4 mutations) are much more common than inherited genetic mutations and associated syndromes (p16, TP53 mutations). The different prognosis and managements for each PDAC probably stem from these variable genetic mutations (2).

The vast genetic studies on PDAC have failed to affect the clinical decision making, thus, paving way for addition of proteomic data to these studies. Proteomics improves the functional accuracy of data while, genomics is concerned with physical information. In addition to this data, phosphorylation of proteins lets us know about the active proteins.

The challenge has been to Subtype PDAC so that we do not cluster the different types in the same group, wishing one modality will treat all of them. This would help us in designing better future clinical trials. With newer techniques, we have been able to subtype PDAC. These classification systems have not been universally accepted, thus, this field is in a stage of exponential growth and promise. The first classification was tried by Collison and group in 2011. It has been debated and restructured with newer subtyping coming out more recently. We had previously reported 3 classifications in a previous paper (2).

Subtypes
Collisson et al (3) and his team used Gene expression analysis and used 62 designated gene signatures to subtype Pancreatic Cancer tissue it into “classical”,...
“quasi-mesenchymal (QM)”, and “exocrine - like”. The “Classical” subtype showed favorable prognosis. The “classical” subtype had high expression of epithelial and adhesion-associated genes. The “Quasi-Mesenchymal”) subtype showed high expression of mesenchymal associated genes and the “exocrine-like” subtype similarly showed relatively high expression of exocrine enzyme genes.

Moffitt et al on genetic analysis subtyped it into two tumor subtypes on the basis of two different tissues. The micro-dissected and analyzed the tumor cells and stromal cells. On the basis of genetic analysis of the ductal cells the subtyping was classified into “classical” and “basal-like” and on the basis of the stromal cells into “normal” and “activated”. The “Classical” ductal subtype again showed favorable prognosis when compared to “basal - like”. Patients with “activated” stromal subtype had a worse prognosis (4).

To identify metabolomic clustering within PDAC, Daemen A. et al. (5) investigated the PDAC metabolite profile. They quantified 256 metabolites and studied 38 PDAC cell lines. They identified three subtypes that showed different profiles associated with glycolysis, lipogenesis, and redox pathways. A subtype was defined by “reduced proliferative capacity”, while the other two showed distinct metabolite levels associated with glycolysis, lipogenesis, and redox pathways. These were named subtypes “glycolytic” and “lipogenic” subtypes. In PDAC clinical samples, functional relevance in disease progression was suggested by the following association: The “lipogenic” subtype is associated with: “cell-cell adhesion and epithelial-mesenchyme transition, mRNA metabolism and receptor tyrosine kinase signaling. Further investigation showed that the three subtypes were conserved in the both the series. These receptor tyrosine kinase enriched cell lines exhibited enhanced sensitivity to EGFR inhibitors which may act a prognostic marker for response to therapy.

**DISCUSSION**

The premalignant lesions like IPMNs and MCNs are detectable with radiological and endoscopic ultrasound imaging. We are unable to predict accurately which cysts can be safely monitored, and which likely to progress to infiltrating carcinoma. A major help to the clinician was the establishment of consensus guidelines by a consortium of the international association of Pancreatology at a meeting held in Sendai, Japan, in 2006, followed by a revision of the guidelines in 2012 (8, 9). Though the original and the revised Sendai guidelines are extremely helpful, they rely on indirect measurements of risk. Studies to validate these guidelines have not been successful in confirming them. Therefore, more reliable markers are needed for the management of individual patients. Many studies correlating the grades of (Pancreatic Intra epithelial Neoplasia) PanIN lesions and genetic mutations have been done. One by Saiki et. al (10) has shown that approximately 45% of PanIN-I lesions were found to harbor KRAS mutation, thus suggesting that one of the earliest genetic mutations is activation of KRAS. After it the inactivating mutations of CDKN2A may be responsible for PanIN-II and inactivation of TP53 and SMAD4 are generally associated with PanIN-III. Similarly, Fritz et. al (11) found the expression of SPARC is lost in 50% of low and moderate grade dysplasia, while it is lost in 80% of the IPMNs with high-grade dysplasia.

**CONCLUSION**

In this bioinformatics driven era it would not be prudent for the academicians and clinicians to put all kinds of PDAC in the same arm of a clinical trial. For the academicians, it would only surmount to bias and achieving statistical significance would be very difficult, while for the clinicians, we would be knowingly giving a placebo drug to a vast number of patients. The
sub-classifications that emerge with the rapidly evolving novel technologies will provide an opportunity to not only better the understanding of the etiology and progress of PDAC, but will also help in targeting the therapy selectively and may give clues to early detection of this aggressive carcinoma, thereby improving the mortality and 5 year survival rates. Therefore, it’s wise to follow and grow the growing field of Subtyping the Pancreatic Ductal Adenocarcinoma.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

Source of Funding
There were no external funding source for this study.

Abbreviations
PDAC — Pancreatic Ductal Adenocarcinoma
USA — United States of America
TP53 — Tumor Protein p53
KRAS — V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog: It is a protein encoding Gene.
BRAF — v-Raf murine sarcoma viral oncogene homolog B: It is a protein encoding Gene.
SMAD4 — It is a protein encoding Gene that plays a role in maintaining balance between atrophy and hypertrophy: Mothers against decapentaplegic homolog 4.
QM — Quasi Mesenchymal type of Pancreatic Adenocarcinoma.
ADEX — Aberrantly Differentiated Endocrine eXocrine type of Pancreatic Adenocarcinoma.
ATCC — ATCC is a company in Washington, DC, USA.
TKCC — The Kinghorn Cancer Centre, Australia.
EGFR — Epidermal Growth Factor Receptor.
IPMN — Intraductal papillary mucinous neoplasm.
MCN — Mucinous Cystic Neoplasms.
PanIN — Pancreatic Intra epithelial Neoplasia.
SPARC — Secreted Protein Acidic & Rich in Cysteine: It is a protein encoding Gene.

REFERENCES

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Sažetak

PODТИPOВI PANKREASNOГ DUГТАЛNOГ ADENOKARCINOMА

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Karcinom pankreasa predstavlja četvrti po redu uzrok smrti od karcinoma u Sjedinjenim Američkim Državama. Porast incidence kao i činjenica da preko 80% pankreashnih karcinoma je lokalno uznapredovalo ili sa prisutnim metastatskim promenama u vreme postavljanja dijagnoze, stavlja ga u fokus istraživanja danasnjice. S obzirom da je jedina nada za izačenje hirurška resekacija, unapređenje leži u ranom skriningu, odgovarajućoj klasifikaciji, kao i ispravnoj terapiji. Uznapredovala istraživanja na ovom polju će najverovatnije dovesti do boljeg razumevanja pankreaskog duktalnog adenokarcinoma (AKPD), kao i unapređenja tehnika skrininga, dijagnostike, do ažuriranja subtipizacije i omogućavanja upotrebe ciljane terapije. S toga, umesto raportiranja o raznovrsnim subtipovima AKPD, unapređenje subkategorizacije će obezbediti statističku značajnost za akademike, a ujedno će i kliničari izbacić uvođenje placebo leka velikom broju pacijenata.

Ključne reči: karcinom pankreasa, subtipovi, genetika, proteomik, fosfoproteomik.

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