Gene Set adaptation through graph generation enhances signature discrimination power and validates metabolism-related prognostic signatures in Hepatocellular Carcinoma

S. Barace[1], JM. Herranz[1,2], E. Santamaria[1,2], S. Arcelus[1], N. Torrea[1], S. Infante[1], G. Garcia-Porrero[3], C. de Andrea[3], J. de la Fuente[4], M. Avila[1,2], B. Sangro[2,3,5], M. Hernaez[4], J. Argemi[1,3,5,6]

1. Hepatology Program, CIMA, Pamplona, Spain 2. CiberEHD, Madrid, Spain 3. Clinica Universidad de Navarra, Pamplona, Spain 4. Computational Biology Program, CIMA, Pamplona, Spain, 5. Instituto de Investigacion de Navarra (IdisNA), 6. Division of Gastroenterology Hepatology and Nutrition, University of Pittsburgh, PA, USA

ILCA conference
The world's leading liver cancer meeting
2 - 5 September 2021
WWW.ILCA2021.ORG

INTRODUCTION

Hepatocellular carcinoma is a devastating cancer disease. Most patients are detected at advanced stages when curative treatments are not feasible. At these stages, systemic therapies including immune check-point inhibitors offer limited survival advantage (1).
Metabolic reshaping of cancer cell is one of the hallmarks of cancer and has been poorly studied in HCC (2).
Transcriptomic classification of HCC has led to a better understanding of immune and proliferation classes with potential usefulness in clinical decision making, but no transcriptomic classification of HCC metabolism has been validated yet (3).

AIM

1. Develop a method for Gene Set adaptation to HCC-specific transcriptomes.
2. Adapt existing metabolic Gene Sets in published cohorts (TCGA-LIHC, LICA) to establish HCC-specific signatures.
3. Analyze prognostic significance of metabolic HCC-Adapted Signatures (HCC-AS).

METHOD

RNAseq data from LIHC (N=371) and LICA (N=160) cohorts were downloaded through Xenabrowser and ICGC data portal, respectively.
Metabolic pathways were collected from Molecular Signature Database (MSigDB) and the Metabolic Atlas (4).
Two filtering methods were performed to remove poorly coexpressed genes in each pathway: node centrality (NC) and median gene-gene correlation (MGGC) (5,6). Iterative random partitions from LIHC cohort were used to avoid overfitting using sample function of base package (7).
Statistics analyses were performed using STATA software and survminer package (7). Plots were performed using ggplots, pheatmap (7) and DrawVenn (8).

CONCLUSIONS

1. NC and MGGC thresholds were established to produce HCC-AS by cross-validation in randomly-obtained 60 partitions of LIHC cohort.
2. HCC-AS obtained after applying NC and MGGC-based filtering improved their performance for survival discrimination in HCC patients in LIHC cohort when compared to non-adapted published signatures.
3. Tryptophan, beta oxidation in mitochondria or the serotonin pathway were validated in LICA cohort, while other HCC-AS had trend significancy.
4. HCC-AS unveil three HCC metabolic subclasses. MetClass 1 are highly metabolic, low grade, low AFP, Hoshida C3, highly CTNNB1 mutated and Chiang Poly7 class cancers. MetClass 2 were high grade, Hoshida C2, Chiang Proliferation class and iCluster1, high % of TP53 mutated and worse prognosis . MetClass3 mixed MetClass1 and etcClass2 features.
5. Extracellular matrix (ECM)-related metabolic signatures such as ketaran and condroitin sulfate did not clustered with MetClasses. Patients with low MetECM were high CTNNB1-mut and Hoshida C3.
6. This method can be applied to adapt any gene set to HCC transcriptome.

REFERENCES

(1) Gastroenterology, 157,3 (2019)
(2) Gastroenterology 2015;149:1226–1239
(3) Nature Reviews Dis Primers 2, 16018 (2016).
(4) Science Sig, 13, 624 (2020)
(5) BMC Bioinformatics 14, 7 (2013).
(6) InterJournal, Complex Systems 1695. (2006).
(7) Bioconductor R Packages
(8) http://bioinformatics.psb.ugent.be/webtools/Venn/

CONTACT

Josepmaria Argemi, MD, PhD.
Stress & Liver Cancer Lab
Liver Unit. Clinica Universidad de Navarra
Hepatology Program, CIMA
Universidad de Navarra
Pamplona, Spain
jargemi@unav.es

RESULTS