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Type	Oral communication
Session	(Multi-)Omics Data Integration and Analysis
Title	Integrated multi-omics data analysis to identify therapeutic vulnerabilities in liver cancer cell lines.
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Motivation

Hepatocellular carcinomas (HCCs) are heterogeneous aggressive malignancies with poor prognosis at advanced stages. Due to this molecular heterogeneity, most of the new agents tested in clinical trials showed low efficacy and limited survival benefit.
Here, we integrated multi-omics and pharmacological data in a large panel of liver cancer cell lines to capture the molecular heterogeneity of HCC and identify new effective therapies and markers of drug response.

Methods

We performed whole-exome, RNA and microRNA sequencing and quantification of 126 proteins in 34 liver cancer cell lines. We screened 31 anti-cancer compounds for their ability to reduce cell viability. Correlation analysis and Elastic net regression were used to identify molecular features associated with drug response. Molecular profiles of liver cancer cell lines and HCC primary tumors were compared.

Results

The 34 liver cancer cell lines recapitulated the most common molecular alterations identified in the more proliferative and aggressive HCCs. Unsupervised consensus classification identified three robust transcriptomic subgroups of cell lines related to the differentiation state and associated with the global drug response rate, with the most differentiated CL1 subgroup showing the highest drug sensitivity. Elastic net regression identified a large number of molecular markers related to drug response with a median of 95 associated features per drug [0-139] and uncovered strong associations. In particular, we found the expression of 5 genes (HSD17B7, RORC, MRPS14, SERINC2, LAD1) that predict accurately the response to the MEK1/2 inhibitors trametinib and refametinib.
Correlation analysis identified specific agents that could target efficiently tumors with features of the progenitor subclass of HCCs. We found that cell lines with inactivating mutations in TSC1/TSC2 and TP53 were sensitive to the mTOR inhibitor rapamycin and the AURKA inhibitor alisertib, respectively. MET amplification was related to hypersensitivity to cabozantinib and sorafenib combined with MEK1/2 inhibitors showed a synergistic anti-proliferative effect.

In conclusion, liver cancer cell lines represent prominent preclinical biological models for drug-biomarker

discovery in HCC allowing the identification of distinct molecular contexts associated with specific therapeutic vulnerabilities that might be used to select patients for clinical trials.
All data generated by this study are freely accessible to the scientific community (http://lccl.zucmanlab.com, available from June 2019).

Info
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Availability	http://lccl.zucmanlab.com

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