Translating '–omics' results into precision medicine for hepatocellular carcinoma

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Competing interests statement

The authors declare no competing interests.

Abstract

A large-scale comprehensive analysis of hepatocellular carcinoma (HCC) based on the integration of six distinct data platforms has pinpointed novel oncogenic processes and prognostic subgroups. These findings confirm previously identified molecular subclasses and fuel the need for a clear strategy of precision medicine in HCC.

Refers to Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell 169, 1327–1341.e23 (2017).

The molecular landscape of HCC has changed dramatically over the past decade, aided by the advent of next-generation sequencing technologies that have uncovered the most frequently mutated oncogenic drivers (TERT promoter, TP53, CTNNB1), chromosomal aberrations (1q, 8p, high-level gains of 11q13 and 6p21) and dysregulated signalling pathways (RAS– MAPK, Wnt, mechanistic target of rapamycin (mTOR), IGF2)1,2. After thoroughly analysing >1,000 cases, the landscape of mutations and targetable drivers in HCC has been defined2. In addition, in an attempt to replicate the success obtained in proof‑of‑concept trials, such as crizotinib in ALK-rearranged lung cancers among others, great effort has been dedicated to the identification of subgroups of patients with specific molecular traits and tumour phenotypes2. Nonetheless, these advancements in the understanding of the molecular oncogenic drivers have not yet been translated into precision- medicine-driven trials1. In fact, effective targeted therapeutic options for patients with advanced HCC remain scarce and include the multityrosine kinase inhibitors sorafenib (first-line therapy)3, lenvatinib, just reported to be noninferior to sorafenib, and regorafenib (second-line therapy)4.

In an effort to gain further insights into the underlying oncogenic processes and potential therapeutic targets, investigators from The Cancer Genome Atlas (TCGA) network have now taken the next step and performed large-scale molecular subtyping of HCC tumours, particularly in US patients5, thereby complementing previous efforts with European6 and Japanese patients7. Through the integrative analysis of DNA somatic mutations and copy number aberrations (n = 363 HCCs) with DNA methylation, proteomic, mRNA and microRNA expression profiling (n = 196), the highly powered analysis elegantly unveils novel potential oncogenic processes, such as metabolic reprogramming, and prognostic subgroups, such as those with isocitrate dehydrogenase 1 (IDH1), IDH2 and TP53 signatures5. Owing to the large sample size, the study not only confirms the most significantly mutated genes (TERT (44%), TP53 (31%), CTNNB1 (27%), ARID1A (7%)) previously reported6,7, but also identifies low-rate mutations in eight novel candidate drivers (prevalence 1–4%), including genes altered in other cancers, such as LZTR1, EEF1A and SMARCA4 (REF. 5). Perhaps more interesting, the analysis suggests the existence of three prognostic molecular subgroups (termed iCluster1–3; FIG. 1). In particular, a TP53 signature associated with chromosomal instability and poor prognosis could further improve clinically relevant clustering of HCC, whereas IDH mutations in four tumours unveils a molecular subgroup with stem-cell-like features and close genomic similarity to cholangiocarcinoma5.

Taken together, these data provide important insights into the genomic landscape of HCC and represent a notable comprehensive integrative genomic characterization of this neoplasm. Nonetheless, the clinical effect of such findings remains to be elucidated. The multiplatform clustering represents a solid confirmation of proposed molecular classifications, as the molecular traits and prognostic clusters show a high similarity to major subgroups previously reported (proliferation and nonproliferation)2, thereby further refining the paradigm of HCC molecular classification (FIG. 1). For example, the iCluster1 subgroup — characterized by high

expression of proliferation marker genes and poor prognosis — highly resembles the previously reported proliferation subgroup2, whereas the characteristics of the iCluster2 subgroup (CTNNB1 mutations, less microvascular invasion) recall those of the nonproliferation class. Furthermore, except for mutations in TERT and CTNNB1, and promoter hypermethylation of CDKN2A, all pathway alterations seem evenly distributed among the three clusters, failing to provide sufficiently distinct multilevel molecular characterization and guide future treatment decision making. Similarly, the prognostic value of the distinct subgroups (iCluster1, IDH1/2, TP53) need to be further investigated, carrying out logistic regression analyses in fully annotated datasets and extensively validated.

In terms of future therapeutic efforts, the authors highlight several potentially targetable drivers. This goal is certainly the major challenge, as we previously reported that HCC has few targetable drivers that account for less than one-third of patients with HCC, as opposed to cholangiocarcinoma, in which FGFR2 fusion proteins and IDH mutations are present in ~30% and 20% of patients, respectively1,2,6,8. In fact, most recurrently altered genes in HCC (TERT, TP53, CTNNB1) remain as unactionable targets, whereas the few targetable alterations occur only in a small fraction of patients (<10%)1. The first biomarker-driven clinical trials have recently emerged in HCC. For example, FGFR4 inhibitors are being tested (ClinicalTrials.gov; NCT02508467) in patients with high-level amplifications of chromosome 11q13 (FGF19), with more trials expected to follow1. In this regard, investigators of the TCGA network propose the use of MDM4 inhibitors in patients with wild-type TP53 and elevated MDM4 expression, or IDH inhibitors in patients with IDH1 or IDH2 mutations5. If this novel approach is confirmed in experimental studies, it can be added to the armamentarium of therapeutic strategies to be tested in early clinical trials.

Activating mutations in IDH1 and/or IDH2 have been frequently reported (~20%) in intrahepatic cholangiocarcinoma and result in the acquisition of abnormal enzymatic activity that leads to altered cell differentiation and survival8. By contrast, IDH1 or IDH2 mutations have been rarely reported in HCC (<1%) and the data reported by TCGA (4 of 196 mutations; 2%) is in line with previous reports5–7. The relevance of these mutations towards HCC has been somewhat challenged because, as in the latest study, they always occurred in cholangiocarcinoma-like HCCs. Herein, the authors5 identify a subgroup of HCC (~10%) with an expression profile similar to the IDH-mutated HCCs that resemble the subgroup of mutant IDH1 or IDH2 intrahepatic cholangiocarcinoma with stem-celllike features and poor prognosis signatures of HCC8. These findings further fuel the hypothesis that liver cancers might share a common progenitor precursor, at least in the subset of tumours with progenitor-like features and poor outcome8.

As in other solid tumours, a new treatment paradigm is emerging. Recent results suggest that nivolumab, a monoclonal antibody against programmed cell death protein 1 (PD1) that modulates the immune system, produces durable responses in advanced HCCs (objective response rate of 20% and median survival of 16 months)9. However, clinical benefit is not

related to PDL1 (the PD1 ligand) status on tumour cells9, highlighting the need to identify alternative biomarkers to select ideal candidates for immunotherapy. To this end, the observation by TCGA investigators that 22% of patients with HCC display high or moderate levels of lymphocyte infiltration is of great interest5. This discovery is consistent with data recently reported by our group defining the 'immune class' of tumours in ~27% of patients with HCC, which is characterized by high infiltration of immune cells, expression of PD1 and PDL1, and active IFNγ signalling10. Further investigation of the antitumour immune responses and the interplay between cancer cells and the microenvironment will be critical for understanding if this subgroup of patients might benefit from these therapies. In conclusion, genomics have improved the understanding of the biology of HCC, but this knowledge has not yet been translated into clinical practice. This study further fuels the concept that investigators are striding down the right path towards precison medicine in HCC.

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Figure 1. Molecular classification of HCC. The figure shows the overlap between 3 iClusters identified from the analysis conducted by the The Cancer Genome Atlas (TCGA) Network (a)5 and the two major clusters previously proposed by Zucman-Rossi et al. (b)2. Bold text indicates common characteristics between the clusters of both proposals. See Zucman-Rossi et al.2 for details on subclasses termed S1–S3 and Cluster A or B. AFP, α-fetoprotein.

A)	**iCluster1**	**iCluster2**	**iCluster3**
Clinical features	• Asian ethnicity • High-grade tumours • Macrovascular invasion • Worse outcome		• Low-grade tumours • Less microvascular invasion • Better outcome
DNA somatic alterations	• BAP1 mutations	• High chromosome instability • Chromosome17p loss • CDKN2A hypermethylation • TERT, CTNNB1 and TP53 mutations	
Prognostic gene signatures	• IDH1/2 signature • S2 subtype		• CDKN2A hypermethylation • TERT mutations • CTNNB1 mutations

B)	**Proliferation**		**Non-Proliferation**
	Progenitor-like	**Hepatocyte-like**	**Hepatocyte-like**
Clinical features	• HBV • High AFP • Poor differentiation • Vascular invasion • Worse outcome		• HCV • Low AFP • Well–moderate differentiation • Less vascular invasion • Better outcome
DNA somatic alterations	• Chromosome 11q13 amplification (FGF19)	• Poor differentiation • Vascular invasion • Worse outcome	• CTNNB1 mutations
Prognostic gene signatures	• EPCAM • S2 subtype • Hepatoblastoma C2 • Hepatoblast-like • Cluster A • Vascular invasion	• Late TGFβ • S1 subtype • Cluster A	• S3 subtype • Cluster B