

Categories	Datasets information					HCC molecular subclasses		
	N★	Dominant etiology	Clinical stage	Analyzed molecular information	References	Non-proliferation class	Proliferation class	
Transcriptome classification of HCC	603†	HBV (43%), HCV, alcohol	BCLC (0,A,B,C) Edmondson (I,II,III, IV)	Gene expression	Hoshida [1]	S3 Liver function retention; WNT/CTNNB1	S2 Progenitor-like; Proliferation	S1 TGFβ-WNT activation; Proliferation
	103	HCV	BCLC (0,A,B,C) O/A (80%)	Gene expression, Gene mutation, DNA copy number	Chiang [2]	Immune Poly 7 WNT/CTNNB1 CTNNB1 mutation	Proliferation, KRT19 (+) Proliferation, AKT activation	
	642†	HBV, HCV, alcohol	BCLC (0,A,B,C) Edmondson (I,II,III, IV)	Gene expression	Lachenmayer [3]	WNT/CTNNB1 Liver-related WNT; CTNNB1 mutation	WNT/TGFβ Classical WNT	
	139	HBV (58%), HCV	Edmondson (II,III, IV)	Gene expression	Coulouarn [4]	Late-TGFβ TGFβ activation		
	91	HBV (58%) HCV, Alcohol	Edmondson (II,III, IV)	Gene expression	Lee [5]	Cluster B	Cluster A Proliferation; ubiquitination; Met	
	113	HBV (48%), HCV	BCLC (A,B,C,D)	Gene expression	Sohn [6]	Silence of Hippo Silence of Hippo signatures		
	61	HBV, HCV, alcohol	Edmondson (II,III, IV)	Gene expression	Lee [7]	Hepatoblast-like Progenitor-like; AP1&TGFβ activation		
	228	HBV (21%), HCV, alcohol	BCLC (0,A,B,C) O/A (87%)	Gene expression, Gene mutation	Sia [8]	Immune class Adaptive immune IFN; T cells; Cytotoxic	Immune class Exhausted immune TGFβ activation; T-exhaustion; M2-macrophage	
	123	HBV(30%), HCV, alcohol	Edmondson (I, II, III, IV)	Gene expression, Gene mutation, LOH, HBV copy number, promoter methylation	Boyault [9]	G 5-6 WNT activation [G6] CTNNB1 mutation [G5-6]	G 1-3 Chromosomal instability [G1-3], AKT activation [G2], Cell cycle [G3], AXIN1 [G1-2] & TP53 [G3] mutations	
	Clinical features					Zucman-Rossi [10]		
Proteome classification of HCC	101★ Paired	HBV(100%)	BCLC (0, A) O/A (100%)	Protein expression, Gene expression, Somatic mutation, HBV integration	This study	S-I (n=36) Liver function retention; WNT/CTNNB1; CTNNB1 mutation;	S-II (n=32) Proliferation; Partial liver function retention/ WNT/CTNNB1/ CTNNB1 mutation	S-III (n=33) Proliferation; TGFβ activation; Progenitor-like; Metabolic dysregulation
						Immune class (10/36) Adaptive (10/10)	Immune class (30/33) Adaptive (12/30) Exhausted (18/30)	
	Clinical features							

Reported transcriptome-based subclasses of HCC Molecular characteristics Immune classes in HBV-related early-stage HCC

HBV: hepatitis B virus, HCV: hepatitis C virus, Edmondson: Edmondson and Steiner grading system, BCLC: Barcelona Clinic Liver Cancer staging system

★ Number of samples used to define classification, ☆ 199 samples (101 tumors and 98 paired non-tumor samples) used for proteome analysis. 101 tumor samples used to define proteomic subtypes, 199 samples used to identify signature proteins for each subtype. † Gene expression datasets collected from eight independent HCC cohorts.

Comparative analysis of proteome and transcriptome subclasses. Basic datasets information was displayed on the left panel. The right panel summarized the major HCC subclasses (grey box), and its relative molecular characteristics (blue box). The relationship between the molecular subclasses and the correlation with the clinical features were referenced to Zucman-Rossi et al.¹⁰ and Hoshida et al.¹¹. The novel characteristics captured by proteomics are indicated with red characters, while the features identified by both proteome and transcriptome are shown in black colour. Correspondence between proteomic and mRNA subclasses was evaluated by single sample GSEA analysis using the signature genes collected from literatures and defined by proteomics (Extended Data Fig. 7a). Moreover, the clinical features were also employed to define the correlation between the subclasses.

Reference:

- Hoshida, Y. et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. *Cancer Research* 69, 7385-7392 (2009).
- Chiang, D. Y. et al. Focal gains of VEGFA and molecular classification of hepatocellular carcinoma. *Cancer Research* 68, 6779-6788 (2008).
- Lachenmayer, A. et al. Wnt-pathway activation in two molecular classes of hepatocellular carcinoma and experimental modulation by sorafenib. *Clinical cancer research : an official journal of the American Association for Cancer Research* 18, 4997-5007 (2012).
- Coulouarn, C., Factor, V. M. & Thorgeirsson, S. S. Transforming growth factor-beta gene expression signature in mouse hepatocytes predicts clinical outcome in human cancer. *Hepatology* 47, 2059-2067 (2008).
- Lee, J. S. et al. A novel prognostic subtype of hepatocellular carcinoma by gene expression profiling. *Hepatology* 40, 667-676 (2004).
- Sohn, B. H. et al. Inactivation of Hippo pathway is significantly associated with poor prognosis in hepatocellular carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 22, 1256-1264 (2016).
- Lee, J. S. et al. A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells. *Nature Medicine* 12, 410-416 (2006).
- Sia, D. et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. *Gastroenterology* 153, 812-826 (2017).
- Boyault, S. et al. Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. *Hepatology* 45, 42-52 (2007).
- Zucman-Rossi, J., Villanueva, A., Nault, J.-C. & Llovet, J. M. Genetic landscape and biomarkers of hepatocellular carcinoma. *Gastroenterology* 149, 1226-1239 (2015).
- Hoshida, Y. et al. Molecular classification and novel targets in hepatocellular carcinoma: recent advancements. *Seminars in liver disease* 30, 35-51 (2010).