Hepatocellular Carcinoma's Molecular Markers: The New Trend as Diagnostic/Prognostic Markers!

To the editor,

The current emerging molecular markers of hepatocellular carcinoma including molecular, immune-histochemical IHC and serological markers, and their potential role as diagnostic/prognostic markers from a pathogenic perspective have shown researchers great interest.[1] HCC is considered the most common primary liver malignancy; Risk factors for HCC vary from region to region. HBV and HCV represent the most common ones. Furthermore, ALD, obesity, and NAFLD are important risk factors and are increasing in incidence. As known that hepatocarcinogenesis mainly converges on the vicious circle of inflammation and regeneration processes increasing the risk of genomic instability and carcinogenesis; These pathogenic mechanisms represent 80–90% of HCC, that arises in a cirrhotic and non-cirrhotic liver (HBV or NAFLD cases)[2,3]. It's well known that the serum AFP, AFP-L3 and DCP are the most used non-invasive circulating biomarkers for HCC diagnosis in clinical practice; however, they are not included in the diagnostic criteria for HCC in the American or European guidelines owing to their low sensitivity and specificity.[4] Hence, the idea of using molecular markers as diagnostic/prognostic tools for HCC detection was proposed focusing on the following: The molecular markers that have been strongly related to high-grade dysplasia include telomere shortening, telomerase reverse transcriptase TERT activation, and cell-cycle checkpoint inactivation owing to the detection of CTNNB1 related mutations, TP53 mutations, altered methylations and DNA amplification earlier in HCC that end with aggressive behaviour. Regarding this, the IHC markers that support HCC diagnosis include polyclonal CEA, CD10, HepPar, arginase-1 and albumin ISH; moreover, glypican-3, glutamine synthetase GS, HSP70, CD34, alpha-fetoprotein AFP and clusterin have been recommended in identifying hepatocellular malignancy in several international guidelines, so far, several HCC genetic studies are evaluating various molecular markers particularly autophagy-related genes and their regulatory proteins[5,6]. On the other hand, the molecular markers of prognostic value include cytokeratin 19 CK19 positivity and increased miR-1180-3p expression that have been associated with aggressive behaviour with a tendency to metastasize, poor overall sur-

Table 1 The Role of Common Molecular Markers in the Diagnosis or Prognosis of Hepatocellular Carcinoma.

Type (test method)	Marker	Role
Serology	AFP	Screening for HCC[a]
	AFP_L3	Screening for HCC[b]
	DCP	Diagnosis of HCC[b]
Immunohistochemistry IHC	TP53 mutation	Diagnosis of HCC[c]
	HSP70	Diagnosis of HCC[c]
	Glypican_3	Diagnosis of HCC[c]
	Glutamine Synthetase	Diagnosis of HCC[c]
	CK19	Prognosis of HCC[c]
	PD_L_1	Therapeutic response for HCC[c]
Sequencing	$CTNNB_1$ mutation	Diagnosis of HCC[c] (early)
	TP53 mutation	Diagnosis of HCC[c] (early)
Southern blot	Telomere lengthening	Diagnosis of dysplasia[b]
RT-PCR	miR-1180-3P	Prognosis of HCC[b]

AFP, Alpha Fetoprotein; AFP_L3, LCA-bound fraction of AFP; DCP, Des-gamma-carboxy prothrombin; HSP70, Heat shock protein 70; CK19, Cytokeratin 19; PD_L1, programmed death-ligand 1; CTNNB1, Catenin beta-1; miR, microRNA; TP53, Tumor protein p53; HCC, Hepatocellular carcinoma.
[a] Commonly used in practice, however yielding controversial results.
[b] So far not confirmed yet, still under investigations.
[c] Used in practice (confirmed).

Abbreviations: AFP: alpha-fetoprotein; AFP-L3: alpha-fetoprotein- L3; ALD: alcoholic liver disease; DCP: Des-gamma-carboxy prothrombin; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease

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vival and resistance to locoregional therapies[7,8]. Also, Immune checkpoint proteins drive signalling pathways including PD-1, PD-L1 and CTLA4 can be used as therapeutic targets; Tumor mutation burden and microsatellite instability MSI/mismatch repair MMR have been evaluated to assess the response to HCC immunotherapy[9,10]. In conclusion, the molecular markers have shown promising results as diagnostic/prognostic tools in hepatocellular carcinoma opening the gate for the idea of developing novel therapies targeting these markers, however further studies on a larger scale are needed with a comparative analysis to strengthen their efficacy (Table 1).

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

N. B. collected the data, designed, and wrote the letter with critical final revision and editing.

CONFLICTS OF INTEREST

The author declares that no competing interests.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed from previous several studies as mentioned in references and if any data is needed, it will be available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This letter does not contain any studies with human or animal subjects performed by the author.

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