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Molecular Subtyping of Hepatocellular Carcinoma and Precision Systematic Treatment Strategies

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Abstract: Hepatocellular carcinoma (HCC) is a highly heterogeneous malignant tumor determined by multiple molecular driver events and tumor microenvironment remodeling. Multidisciplinary integrated studies have systematically revealed that HCC can be classified into several functional subtypes with internal consistency in multi-level molecular characteristics but significant differences among subtypes, including Wnt/β-catenin activated type, proliferative/chromosomal instability type, metabolic/hepatocyte-like type, and immune microenvironment-dominant type. These subtypes exhibit fundamental differences in signaling pathway dependence, immune ecological architecture, and therapeutic sensitivity, directly determining the efficacy of targeted therapy and immunotherapy. Current systemic therapies still face significant challenges in patient selection and resistance control, highlighting the necessity of precision treatment based on molecular subtyping. This review summarizes the biological basis of major molecular subtypes of HCC, focuses on subtype-guided strategies for immunotherapy combination, targeted therapy combination, and metabolic intervention, and emphasizes the potential value of dynamic subtyping and resistance monitoring in precision systemic therapy.

Keywords: Hepatocellular carcinoma, Molecular subtyping, Tumor microenvironment, Precision system therapy

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1. Etiological evolution and biological heterogeneity basis of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer globally, with its occurrence closely associated with a background of chronic liver disease, including viral hepatitis, cirrhosis, and the increasingly prominent metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). With improved prevention and control of viral hepatitis and the increasing burden of metabolism-related liver diseases, the etiological composition and disease spectrum of HCC exhibit continuous evolution and significant heterogeneity [1].

In clinical practice, the majority of hepatocellular carcinoma (HCC) patients are diagnosed at intermediate or advanced stages and often present with varying degrees of hepatic dysfunction. This condition partially limits the efficacy of radical local therapies and imposes higher requirements on the safety and tolerability of systemic treatments [2].

At the biological level, high-throughput sequencing and multi-omics integration studies have demonstrated that hepatocellular carcinoma (HCC) is not a single disease entity but rather consists of multiple tumor subpopulations with systematic differences in driver gene events, differentiation status, metabolic characteristics, and tumor microenvironment (TME) [3-5]. This multidimensional heterogeneity not only determines tumor invasion behavior and patient survival outcomes but also profoundly influences the efficacy of targeted therapy, immunotherapy, and metabolic interventions. Therefore, systematic molecular and biological typing of HCC is a critical prerequisite for understanding its heterogeneity and advancing precision systemic treatment strategies [6,7].

2. Functional molecular subtypes and biological characteristics of hepatocellular carcinoma

The molecular subtyping of early hepatocellular carcinoma is primarily established based on transcriptomic studies, such as Boyault's G1-G6 subtyping, Hoshida's S1-S3 subtyping, and Chiang's five-category classification system. Subsequently, multi-omics integrated studies have further systematically refined and functionally annotated these subtypes [8]. Different subtypes exhibit highly consistent and reproducible systematic differences in driver gene profiles, activation status of key signaling pathways, genomic stability, epigenetic regulatory background, tumor microenvironment composition, and metabolic phenotypes, which are closely associated with histological differentiation degree, clinical aggressiveness, and treatment sensitivity [9]. The following section focuses on hepatocellular carcinoma subtypes that have been repeatedly validated across multiple independent studies, demonstrating clear biological significance and potential clinical translational value.

2.1. Wnt/β-catenin activation type: Carcinogenic signal-driven and immune rejection phenotype

This subtype has been repeatedly identified across multiple typing systems (e.g., Boyault's G5/G6, Chiang's CTNNB1-related class, and Hoshida's S3). The classic molecular feature involves mutations in the hot region of CTNNB1 (encoding β-catenin), such as in exon 3, which lead to β-catenin stabilization and nuclear translocation, subsequently activating the expression of downstream Wnt/β-catenin signaling genes (e.g., GLUL, LGR5, AXIN2) [10].

At the histological level, this subtype predominantly manifests as moderately to highly differentiated tumors, with some retaining hepatocyte-specific metabolic functions, relatively low cellular proliferative activity, and overall high genomic stability [11]. Although its growth rate may be relatively slow, it exhibits a highly characteristic immune rejection state from an immunological perspective.

Extensive studies have demonstrated that Wnt/β-catenin-activated hepatocellular carcinoma (HCC) is typically associated with significantly reduced immune cell infiltration, exhibiting an immune-excluded or immune-desert phenotype. Mechanistic research suggests that Wnt signaling may limit effector T cell infiltration into the tumor core by suppressing chemokine expression and impairing dendritic cell (DC) recruitment and antigen presentation function, thereby leading to primary resistance to PD-1/PD-L1 immune checkpoint inhibitors (ICI). However, single-cell transcriptomics and spatial transcriptomics studies further reveal significant spatial structural and cellular state heterogeneity within this subtype [12]. Consequently, this subtype is widely regarded as a critical research model for exploring Wnt pathway regulation, tumor microenvironment (TME) remodeling, and immunotherapy combination strategies.

2.2. Proliferative/chromosomal instability type: Genomic aberration-driven highly aggressive phenotype

This subtype roughly corresponds to Boyault's G1~G3, Chiang's proliferation type, and Hoshida's S1/S2 subtypes. Its core molecular characteristics include significant upregulation of genes related to cell cycle regulation and DNA damage repair, TP53 mutations, and widespread chromosomal copy number variations [13,14].

Furthermore, this subtype is often associated with amplification or aberrant activation of proto-oncogenes such as

MYC, CCND1, and FGF19/FGFR4, which further drive rapid tumor cell proliferation, invasive growth, and treatment resistance [13–15]. Multiple large-scale multi-omics studies, including TCGA, have consistently demonstrated the high concordance of this subtype across genomic, transcriptomic, and clinical outcomes. Its hallmark features include poor prognosis, significantly elevated risk of early recurrence, and pronounced heterogeneity in response to systemic therapy [13].

In terms of histological and clinical characteristics, this subtype predominantly exhibits poorly differentiated status, with a higher incidence of vascular invasion and satellite nodules, often accompanied by elevated serum alpha-fetoprotein (AFP) levels [16,17]. From a treatment dependency perspective, these tumors are highly dependent on proliferative, vascular, and growth signaling pathways, making multi-target tyrosine kinase inhibitors (TKIs) and anti-angiogenic therapies (e.g., VEGF/VEGFR inhibitors) potentially beneficial for patients. However, due to widespread signal pathway redundancy and compensatory activation, single-targeted agents often fail to maintain long-term efficacy, necessitating exploration of combination or sequential cross-pathway inhibition strategies based on subtype matching [15,18]. Notably, the FGF19-FGFR4 pathway demonstrates clear targeting potential in patients with specific molecular backgrounds, representing one of the key directions in current translational research and clinical trials [19].

2.3. Metabolic/Hepatocyte-like phenotype: Differentiation lineage and metabolic program characteristics

Metabolic status serves as a critical dimension for understanding the biological heterogeneity and therapeutic response of hepatocellular carcinoma (HCC). Metabolic/hepatocyte-like subtypes typically retain or partially retain hepatocyte-specific metabolic functions, including cytochrome P450 (CYP) enzyme system activity, bile acid metabolism, and fatty acid oxidation capacity. These tumors exhibit higher histological differentiation, relative genomic stability, and generally favorable prognosis [20]. In contrast, certain HCC cases demonstrate significant metabolic reprogramming features, such as enhanced glycolytic pathways or abnormal activation of specific lipid metabolism routes. Such tumors are often associated with activation of pro-proliferative and dedifferentiation signaling pathways, including PI3K/AKT/mTOR, NOTCH, and TGF-β, and are closely linked to aggressive phenotypes and poor prognosis.

The integration of single-cell sequencing with multi-omics studies enables the identification of subtypes with strong metabolic-immune coupling, such as glycan-HCC, characterized by glycosylation-related pathways or lipid-HCC, dominated by abnormal lipid metabolism. These findings suggest that tumor metabolic states can shape the immune microenvironment through multiple mechanisms and influence treatment sensitivity [20–23]. Consequently, metabolic targeted therapies and metabolic-immune combination interventions are increasingly becoming key research directions for this type of hepatocellular carcinoma.

2.4. Immune and microenvironment-dominant type: Structural features of tumor microenvironment and immune ecology characteristics

The tumor microenvironment is one of the key factors driving the heterogeneity of hepatocellular carcinoma (HCC) and exerts a decisive influence on its immunological phenotype. From an immunological ecology perspective, HCC exhibits a continuum ranging from immune-hot (characterized by abundant activated $CD8^+$ T cells, activated dendritic cells (DCs), and NK cells accompanied by IFN-γ signaling) to immune-excluded or immune-desert states (where immune cells are obstructed by dense stroma or abnormal vascular architecture) [24].

Patients with immune-hot tumors are generally more likely to benefit from immune checkpoint inhibitors (ICIs) monotherapy or ICI combination therapy with anti-angiogenic agents. In contrast, immune-cold or immune-excluded tumors exhibit limited efficacy of single ICI therapies due to tumor-associated fibroblasts (CAF)-mediated stromal barriers, enrichment of immunosuppressive myeloid cells, and abnormal vascular architecture, which hinder effective infiltration of effector immune cells into the tumor core [25]. Studies have demonstrated that the immune-vascular combination strategy (atezolizumab + bevacizumab) significantly improves overall survival and progression-free survival in patients with unresectable hepatocellular carcinoma, establishing a robust clinical foundation for tumor microenvironment (TME)-

guided therapy [26].

There is a clear coupling relationship between molecule-driven events and TME status. For instance, CTNNB1 activation is typically associated with immune rejection phenotypes, while proliferative/chromosomal instability tumors are more likely to exhibit enhanced VEGF-A/VEGFR signaling and an immunosuppressive microenvironment [27]. Therefore, systematically incorporating TME features into the classification framework can facilitate more accurate prediction of ICI and targeted therapy efficacy, while providing critical biological insights for elucidating drug resistance mechanisms [28].

3. Limitations of current systemic therapies against molecular heterogeneity

3.1. Impact of molecular and immune heterogeneity on systemic therapeutic efficacy

The multidimensional heterogeneity of hepatocellular carcinoma directly leads to significant differences in systemic treatment responses among various subtypes. The Wnt/β-catenin activated type, immune-hot/immune-cold type, metabolic reprogramming type, and proliferative/chromosomal instability type exhibit fundamental distinctions in tumor microenvironment (TME) characteristics and pathway dependence, profoundly influencing the therapeutic efficacy of immune checkpoint inhibitors (ICI) and targeted therapies [25]. Taking the Wnt/β-catenin activated subtype as an example, its inadequate intratumoral T-cell infiltration and impaired dendritic cell (DC) recruitment partially explain its inherent resistance to PD-1/PD-L1 therapy [29,30]. Therefore, reliance solely on traditional clinical or pathological indicators fails to adequately account for heterogeneous responses to systemic treatments across patients, highlighting the necessity of incorporating molecular and immunological subtypes into clinical classification systems.

3.2. Mechanisms of targeted therapy resistance and the necessity of combination therapy

Multitarget TKIs (such as sorafenib and lenvatinib) have partially improved survival outcomes in patients with advanced hepatocellular carcinoma (HCC), but their efficacy is often limited by tumor clone evolution, compensatory activation of signaling pathways, and drug resistance mediated by factors such as the tumor microenvironment (TME). Proliferative/chromosomal instability tumors typically exhibit multiple driver pathways (including VEGF, FGF19/FGFR4, PI3K/AKT/mTOR, and RAS/MAPK), with compensatory activation among pathways and tumor stem cell characteristics collectively contributing to rapid failure of single TKI therapy [31]. Additionally, redistribution of immunosuppressive cells within the TME, cytokine imbalance, and enhanced stromal barriers promote TKI and immune checkpoint inhibitor (ICI) resistance to varying degrees, particularly in immunosuppressive or immune-rejection HCC [24].

The REFLECT study (lenvatinib versus sorafenib) demonstrated that, despite comparable overall efficacy, significant variations in benefit levels were observed among different patients, further highlighting the necessity of stratification strategies to identify more suitable treatment populations [32]. Therefore, stratification-based combination therapies with cross-pathway inhibitors or sequential treatment strategies, as well as combination therapies targeting both tumor cells and the microenvironment, represent key approaches to overcoming hepatocellular carcinoma resistance.

3.3. Bottlenecks in the translation of molecular subtyping into clinical decision-making

Although classification systems such as those developed by Boyault, Hoshida, and Chiang have been repeatedly validated in both biological and predictive aspects, they have not yet been widely incorporated into routine clinical guidelines or transformed into standardized clinical decision-making tools [31]. Key limitations include heterogeneity across different study cohorts, lack of unified and operational biomarker detection standards, and insufficient prospective validation data. To achieve a precision treatment pathway encompassing “classification-treatment matching-dynamic monitoring-real-time adjustment,” it is imperative to establish classification methods implementable on clinical testing platforms and conduct systematic prospective validation in multicenter cohorts [28].

4. Precision systematic treatment strategy for hepatocellular carcinoma based on molecular subtyping

4.1. Individualized immunotherapy strategies based on immunotypic analysis

Precision immunotherapy should be based on accurate identification of immune subtypes in hepatocellular carcinoma. By integrating immune activity scores, ICI-related gene signatures, and molecular subtyping information, it is possible to more accurately predict ICI benefit populations and guide personalized immunotherapy regimens. For immune-hot tumors, ICI monotherapy or ICI combined with anti-angiogenic therapy is typically the first-line approach. In contrast, for non-inflammatory (non-inflamed) tumors, particularly immune-rejection subtypes with high Wnt signaling, monotherapy with ICI alone is often insufficient to restore effector T cell function. Combined strategies, such as ICI combined with anti-VEGF, anti-TGF-β agents, or therapies promoting dendritic cell (DC) recruitment and activation, are preferred to enhance T-cell infiltration and improve immune responses [25,33]. Emphasizing standardized detection of candidate biomarkers (e.g., CTNNB1 status, immune cell infiltration characteristics, and IFN-γ-related signatures) will facilitate the practical application of immune subtyping in clinical decision-making [12].

4.2. Targeted combination therapy strategy guided by molecular driving pathways

Targeted combination therapy with subtype-specific matching for specific driver pathways is one of the core strategies for achieving precision systemic treatment. For proliferative/chromosomal instability tumors, given the significant activation of VEGF-A/VEGFR and FGF19/FGFR4 pathways, the combination of VEGF inhibitors with ICI or the introduction of FGFR4 inhibitors in FGF19-positive patients may provide additional benefits by improving the tumor microenvironment (TME) and enhancing immune responses [34]. In the Wnt-high subtype, although direct inhibition of the Wnt pathway remains technically challenging, immune rejection can be indirectly overcome through downstream effect modulation, RNA interference strategies, or combined TME remodeling approaches [35]. Overall, a rational combination of molecular targeting and immunomodulation must be based on robust biological evidence and validated for safety and efficacy through prospective clinical trials.

5. Conclusion

In summary, hepatocellular carcinoma is not a single disease entity, but rather a highly heterogeneous collection of molecular subtypes formed through the combined effects of multiple molecular driver events and dynamic remodeling of the tumor microenvironment. The molecular classification system established through multi-omics integration systematically delineates the biological characteristics and therapeutic response differences among various subtypes from dimensions such as signaling pathway dependence, immune ecology, and metabolic programs, thereby providing a mechanistic foundation for precision systemic therapy.

Current evidence-based medical studies indicate that traditional treatment models relying on clinical staging and pathological characteristics struggle to explain significant interpatient variability in therapeutic outcomes. Although molecular subtype-guided stratification strategies demonstrate value in optimizing patient selection and improving efficacy prediction, single treatment approaches often fail to sustain long-term efficacy due to factors such as tumor clonal evolution, compensatory activation of signaling pathways, and adaptive remodeling of the microenvironment. Treatment resistance remains a critical factor limiting long-term prognosis.

Therefore, the key to precision therapy lies in establishing an integrated framework of "classification-intervention-monitoring": developing a standardized and clinically accessible molecular classification system to achieve treatment matching; designing cross-pathway combination intervention strategies based on subtype-driven mechanisms to overcome drug resistance; and leveraging liquid biopsy, single-cell, and spatial multi-omics technologies to enable dynamic monitoring of molecular classification and temporal optimization of treatment strategies.

Overall, the integrated application of molecular typing, tumor microenvironment analysis, and dynamic monitoring constitutes a critical foundation for advancing hepatocellular carcinoma treatment from empirical approaches to mechanism-driven precision medicine, while providing a methodological framework for continuous optimization of therapeutic strategies in intermediate-and advanced-stage patients.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Nakamura T, Masuda A, Nakano D, et al., 2025, Pathogenic Mechanisms of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)-Associated Hepatocellular Carcinoma. Cells, 14(6): 428.

[2] Choi DT, Davila JA, Sansgiry S, et al., 2021, Factors Associated With Delay of Diagnosis of Hepatocellular Carcinoma in Patients With Cirrhosis. Clin Gastroenterol Hepatol, 19(8): 1679–1687.

[3] Boyault S, Rickman DS, de Reyniès A, et al., 2007, Transcriptome Classification of HCC Is Related to Gene Alterations and to New Therapeutic Targets. Hepatology, 45(1): 42–52.

[4] Hoshida Y, Nijman SM, Kobayashi M, et al., 2009, Integrative Transcriptome Analysis Reveals Common Molecular Subclasses of Human Hepatocellular Carcinoma. Cancer Res, 69(18): 7385–7392.

[5] Lin YY, Qi Y, Lu JY, et al., 2008, A Comprehensive Synthetic Genetic Interaction Network Governing Yeast Histone Acetylation and Deacetylation. Genes Dev, 22(15): 2062–2074.

[6] Shen Y, Xiong W, Gu Q, et al., 2021, Multi-Omics Integrative Analysis Uncovers Molecular Subtypes and mRNAs as Therapeutic Targets for Liver Cancer. Front Med (Lausanne), 8: 654635.

[7] Hasin Y, Seldin M, Lusis A, 2017, Multi-Omics Approaches to Disease. Genome Biol, 18(1): 83.

[8] Kim SH, 2025, Transforming Liver Cancer Therapy: Integrating Molecular Profiling with Precision and Transplant-Based Care. Cancers (Basel), 17(22): 3671.

[9] Nevi L, Aiello C, Molinaro F, et al., 2025, Decoding the Molecular and Genomic Landscape of Hepatocellular Carcinoma: Biomarker Discovery, Classification Frameworks, and Therapeutic Targeting. npj Gut and Liver, 2(1): 25.

[10] Dantzer C, Dif L, Vaché J, et al., 2024, Specific Features of β-Catenin-Mutated Hepatocellular Carcinomas. Br J Cancer, 131(12): 1871–1880.

[11] Torbenson M, McCabe CE, O'Brien DR, et al., 2022, Morphological Heterogeneity in Beta-Catenin-Mutated Hepatocellular Carcinomas: Implications for Tumor Molecular Classification. Hum Pathol, 119: 15–27.

[12] Pinyol R, Sia D, Llovet JM, 2019, Immune Exclusion-Wnt/CTNNB1 Class Predicts Resistance to Immunotherapies in HCC. Clin Cancer Res, 25(7): 2021–2023.

[13] Cancer Genome Atlas Research Network, et al., 2017, Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell, 169(7): 1327–1341.e23.

[14] Schulze K, Imbeaud S, Letouzé E, et al., 2015, Exome Sequencing of Hepatocellular Carcinomas Identifies New Mutational Signatures and Potential Therapeutic Targets. Nature Genetics, 47(5): 505–511.

[15] Llovet JM, Montal R, Sia D, et al., 2018, Molecular Therapies and Precision Medicine for Hepatocellular Carcinoma. Nat Rev Clin Oncol, 15(10): 599–616.

[16] Ziol M, Poté N, Amaddeo G, et al., 2018, Macrotrabecular-Massive Hepatocellular Carcinoma: A Distinctive Histological Subtype with Clinical Relevance. Hepatology, 68(1): 103–112.

[17] Mulé S, Galletto Pregliasco A, Tenenhaus A, et al., 2020, Multiphase Liver MRI for Identifying the Macrotrabecular-Massive Subtype of Hepatocellular Carcinoma. Radiology, 295(3): 562–571.

[18] Harding JJ, Nandakumar S, Armenia J, et al., 2019, Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies. Clin Cancer Res, 25(7): 2116–2126.

[19] Hagel M, Miduturu C, Sheets M, et al., 2015, First Selective Small Molecule Inhibitor of FGFR4 for the Treatment of Hepatocellular Carcinomas with an Activated FGFR4 Signaling Pathway. Cancer Discovery, 5(4): 424–437.

[20] Yang C, Huang X, Liu Z, et al., 2020, Metabolism-Associated Molecular Classification of Hepatocellular Carcinoma. Mol Oncol, 14(4): 896–913.

[21] Qu Y, Gong X, Zhao Z, et al., 2024, Establishment and Validation of Novel Prognostic Subtypes in Hepatocellular Carcinoma Based on Bile Acid Metabolism Gene Signatures Using Bulk and Single-Cell RNA-Seq Data. Int J Mol Sci, 25(2): 919.

[22] Bidkhori G, Benfeitas R, Klevstig M, et al., 2018, Metabolic Network-Based Stratification of Hepatocellular Carcinoma Reveals Three Distinct Tumor Subtypes. Proc Natl Acad Sci USA, 115(50): E11874–E11883.

[23] He Z, Chen Q, He W, et al., 2023, Hepatocellular Carcinoma Subtypes Based on Metabolic Pathways Reveals Potential Therapeutic Targets. Front Oncol, 13: 1086604.

[24] Kurebayashi Y, Ojima H, Tsujikawa H, et al., 2018, Landscape of Immune Microenvironment in Hepatocellular Carcinoma and Its Additional Impact on Histological and Molecular Classification. Hepatology, 68(3): 1025–1041.

[25] Sangro B, Sarobe P, Hervás-Stubbs S, et al., 2021, Advances in Immunotherapy for Hepatocellular Carcinoma. Nat Rev Gastroenterol Hepatol, 18(8): 525–543.

[26] Finn RS, Qin S, Ikeda M, et al., 2020, Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med, 382(20): 1894–1905.

[27] Ruiz de Galarreta M, Bresnahan E, Molina-Sánchez P, et al., 2019, β-Catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 Therapy in Hepatocellular Carcinoma. Cancer Discovery, 9(8): 1124–1141.

[28] Zheng J, Wang S, Xia L, et al., 2025, Hepatocellular Carcinoma: Signaling Pathways and Therapeutic Advances. Signal Transduction and Targeted Therapy, 10(1): 35.

[29] Aoki T, Nishida N, Kurebayashi Y, et al., 2024, Two Distinct Characteristics of Immune Microenvironment in Human Hepatocellular Carcinoma with Wnt/β-Catenin Mutations. Liver Cancer, 13(3): 285–305.

[30] Kwee SA, Tiirikainen M, 2021, Beta-Catenin Activation and Immunotherapy Resistance in Hepatocellular Carcinoma: Mechanisms and Biomarkers. Hepatoma Res, 2021: 7.

[31] Wu Y, Liu Z, Xu X, 2020, Molecular Subtyping of Hepatocellular Carcinoma: A Step Toward Precision Medicine. Cancer Commun (Lond), 40(12): 681–693.

[32] Kudo M, Finn RS, Qin S, et al., 2018, Lenvatinib versus Sorafenib in First-Line Treatment of Patients with Unresectable Hepatocellular Carcinoma: A Randomised Phase 3 Non-Inferiority Trial. Lancet (London, England), 391(10126): 1163–1173.

[33] Xu W, Nie C, Lv H, et al., 2022, Molecular Subtypes Based on Wnt-Signaling Gene Expression Predict Prognosis and Tumor Microenvironment in Hepatocellular Carcinoma. Front Immunol, 13: 1010554.

[34] Tai DWM, Le TBU, Prawira A, et al., 2021, Targeted Inhibition of FGF19/FGFR Cascade Improves Antitumor Immunity and Response Rate in Hepatocellular Carcinoma. Hepatol Int, 15(5): 1236–1246.

[35] Lehrich BM, Delgado ER, Yasaka TM, et al., 2025, Precision Targeting of β-Catenin Induces Tumor Reprogramming and Immunity in Hepatocellular Cancers. Nat Commun, 16(1): 5009.