Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ38838

Mechanisms of Resistance to Atezolizumab Combined with Bevacizumab (a+T) Therapy in Advanced Hepatocellular Carcinoma

Xiru Huang

School of Biological and Food Engineering, Suzhou University of Technology, Suzhou, China
xiruhuang0915@gmail.com

Abstract. Hepatocellular carcinoma has a high degree of malignancy, most of which have been diagnosed in the middle and late stages, and systematic treatment is the main treatment. Atezolizumab combined with bevacizumab is a first-line standard regimen, but primary and secondary drug resistance occurs frequently, which seriously affects the long-term efficacy. The existing research focuses on a single pathway or cell subsets, lacks systematic integration, and the core factors of primary drug resistance and clinical classification system are still unclear. This article starts with the classification of drug resistance, and compares the characteristics of primary and secondary drug resistance; the mechanisms of myeloid cell remodeling, adaptive immunity, immune rejection and tumor dedifferentiation in the microenvironment are described. The three signal axes drive drug resistance through metabolic reprogramming, oxidative stress and macrophage polarization. Drug resistance is a dynamic process of molecular abnormalities and immunosuppression. This paper points out the current deficiencies in mechanism integration, primary initiation and clinical classification, and proposes that in the future, multi-omics and spatial transcriptome technology should be used to construct a multi-dimensional classification system, explore intervention targets, and provide a theoretical reference for individualized reversal strategies.

Keywords: Hepatocellular carcinoma, Drug resistance, tumor-associated macrophages

1. Introduction

Hepatocellular carcinoma (HCC) is the most common pathological type of primary liver cancer, with a high global mortality rate, and the incidence burden of HCC in China is particularly severe [1]. Due to the insidious early clinical manifestations of the disease, most patients are diagnosed at an advanced stage and lose the opportunity for radical treatment such as surgery and liver transplantation. Systemic treatment has become the main treatment for patients with advanced HCC [2].

Atezolizumab combined with bevacizumab (T+A) has been shown in the IMbrave150 study to significantly improve the prognosis of patients with advanced HCC due to its synergistic anti-tumor effects of immune checkpoint inhibition and anti-angiogenesis, and has now become the first-line

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.HZ38838

standard treatment for unresectable hepatocellular carcinoma. However, frequent resistance to T+A in clinical practice greatly limits the long-term efficacy of this regimen.

The high tumor heterogeneity of HCC leads to extremely complex drug resistance mechanisms, involving multiple mechanisms such as tumor metabolic reprogramming, immune microenvironment dysregulation, and abnormal activation of multiple pro-cancer signals [3]. Although some drug resistance characteristics have been preliminarily elucidated with the help of multi-omics technologies, there are still problems such as fragmented mechanism research, unclear core mechanisms of primary drug resistance, and lack of clinical drug resistance classification system [4, 5]. Based on this, this paper systematically reviews the drug resistance classification, microenvironment and molecular regulatory mechanisms of the T+A regimen, summarizes the shortcomings of existing research, and aims to provide a theoretical basis for discovering drug resistance biomarkers and developing drug resistance reversal strategies.

2. Definition of primary and secondary resistance to the T+A regimen

In the clinical treatment of HCC, resistance to the atezolizumab plus bevacizumab (T+A) regimen is mainly divided into two categories: primary resistance and secondary resistance. These two types differ significantly in their timing of occurrence, baseline tumor immune characteristics, molecular expression profiles, and immune escape mechanisms, which are also the core reasons for the differentiation of clinical efficacy and treatment failure in patients. Based on existing HCC clinical samples and basic mechanism studies, the specific definitions and related molecular characteristics of the two types of resistance are as follows.

2.1. Primary drug resistance

Primary drug resistance is also called inherent drug resistance. It means advanced HCC patients do not get an effective treatment response after the first T+A combination therapy. The tumor is not controlled well. A drug-resistant phenotype appears early in treatment and shows disease progression. This resistance is not caused by the drug treatment. It is set by the baseline tumor's own molecular features and the immune microenvironment state.

From molecular and immunological views, tumor tissues of HCC patients with primary drug resistance often show continued activation of pro-cancer pathways and a stable immunosuppressive microenvironment. HES1 is very highly expressed in tumor tissue. It keeps the NOTCH signaling pathway active. This helps HCC tumor cells grow, invade, and stay stem-like. Also, HCC-specific tumor markers like GPC3 and AFP are highly expressed. This means the tumor is very malignant. At the immune level, the TME has typical "cold tumor" features. There are fewer $CD8^+$ T cells. Teff effector immune signals are low. PD-L1 (CD274) expression is much lower. So anti-tumor immune responses are not activated well. At the same time, the Treg/Teff ratio in the patient's tumor tissue is very high. This shows that myeloid-derived inflammatory suppressor signals are too active.

2.2. Secondary drug resistance

Secondary drug resistance is also called acquired drug resistance. It is the most common type of drug resistance in T+A combined therapy for advanced HCC. These patients respond well to T+A combined therapy at baseline. Early treatment can stop tumor growth, shrink tumor lesions, and give disease stabilization or partial remission [6]. But with long-term continuous drug treatment pressure,

DOI: 10.54254/2753-8818/2026.HZ38838

HCC tumor cells change their genes, metabolism, and the tumor microenvironment. They slowly become drug resistant. This leads to tumor regrowth, progression, and treatment failure.

These patients have a very good anti-tumor immune microenvironment at baseline. This is very different from patients with primary drug resistance. Many $CD8^+$ T cells and Teff effector cells enter the tumor tissue. PD-L1 is highly expressed. The immune response is good. HES1, GPC3, and AFP are lowly expressed. These are molecules linked to cancer and stem cells. The tumor malignancy phenotype is weak. So they can get significant clinical benefits from T+A treatment in the early stage [2].

3. TME-mediated T+A regimen resistance mechanism

TME is the core site regulating the immunotherapy response and resistance in HCC. The phenotypic remodeling and functional imbalance of myeloid immune cells and adaptive immune cells, as well as the disordered spatial distribution of immune cells and the stem remodeling of tumor cells, are key microenvironmental mechanisms mediating T+A regimen resistance [6]. Under long-term T+A drug pressure screening, the HCC TME will change from an "immune hot state" to an "immune cold state", forming a stable immunosuppressive pattern, which will eventually weaken or even completely offset the immune activation effect of atezolizumab and the anti-angiogenic effect of bevacizumab, inducing treatment resistance. This chapter will systematically describe the microenvironmental regulation mechanism of T+A resistance in HCC from three levels: myeloid cell remodeling, adaptive immune dysregulation, immune rejection and tumor dedifferentiation.

3.1. Remodeling of immunosuppressive myeloid cells

Myeloid cells are an important immunoregulatory cell subset in the TME of HCC, mainly including tumor-associated macrophages (TAMs), monocytes, tumor-associated neutrophils (TANs), etc. During the T+A drug resistance process, various myeloid cells undergo phenotypic polarization and functional remodeling, accumulate in large quantities in tumor lesions and construct an immunosuppressive barrier, blocking the body's anti-tumor immune response, becoming an important cellular basis for driving HCC resistance to combined immunotherapy [7].

3.1.1. $TREM2^+$ TAMs

$TREM2^+$ TAMs are the core myeloid cell subset mediating HCC T+A drug resistance and are specifically highly enriched in drug-resistant HCC tumor tissues [6]. Among them, $TREM2^+$ lipid-associated macrophages (LAMs) can clear apoptotic tumor cells through cell burial, while continuously delivering energy metabolism substrates such as fatty acids to surviving HCC tumor cells to meet the metabolic needs of rapid tumor cell proliferation, and at the same time provide a stable microenvironment for tumor immune escape.

3.1.2. $CD14^+$ monocytes

$CD14^+$ Monocytes are a key immune cell subset that mediates primary resistance to T+A in HCC and are specifically enriched in the TME of patients with primary resistance. This cell subset can work synergistically with $TREM2^+$ TAMs to jointly construct a dense tumor immunosuppressive barrier. $CD14^+$ Monocytes can reshape TME homeostasis by secreting a variety of anti-inflammatory and pro-tumor cytokines, inhibit the activation and infiltration of effector T cells, and at the same time promote the proliferation and invasion of HCC tumor cells, continuously creating a

DOI: 10.54254/2753-8818/2026.HZ38838

microenvironment conducive to tumor immune escape, ultimately leading to patients' lack of response to initial T+A treatment and inducing primary resistance [7].

3.1.3. PD-l1$^+$ TANs

Abnormal phenotypic polarization of TANs is an important inducing factor for T+A resistance in HCC. HCC tumor cells highly express galectin-4, which can specifically recruit peripheral neutrophils to infiltrate tumor lesions by regulating the CXCL6–CXCR2 signaling axis and induce them to polarize into the PD-L1$^+$ pro-tumor phenotype [8]. High-level infiltration of PD-L1$^+$ TANs in tumor tissues can directly bind to PD-1 receptors on the surface of effector T cells, inhibit T cell immune function, and at the same time exacerbate the immunosuppression of TME, which is closely related to poor prognosis, tumor progression and drug resistance in HCC patients treated with T+A.

3.2. Dysregulation of adaptive immune cells

Adaptive immune cells, with CD8$^+$ effector T cells and regulatory T cells (Tregs) as the core, are the core effector cells for the T+A regimen to exert anti-tumor effects. In drug-resistant HCCTME, there are common problems such as dysfunction, imbalance in number and abnormal spatial distribution of adaptive immune cells, mainly manifested as CD8$^+$ T cell depletion and rejection, abnormal enrichment of Treg cells, and disordered spatial distribution of immune macrophages, which completely destroy the body's anti-tumor immune balance and mediate drug resistance to T+A therapy [2].

3.2.1. CD8$^+$ t cell exhaustion and rejection

T cell exhaustion is mainly manifested in the continuous reception of multiple inhibitory signals by CD8$^+$ T cells infiltrating the tumor parenchyma, leading to cellular dysfunction and loss of cytotoxic activity. Its molecular regulatory mechanism is complex. In addition to the classic PD-1/PD-L1 immunosuppressive pathway, HCC tumor cells can secrete exosomes carrying PPARα, which, by adsorbing miR-27b-3p, relieve its inhibitory effect on T cell exhaustion factors, inducing CD8$^+$ T cell dysfunction. Simultaneously, HCC cells highly express ISG15, which can directly inhibit CD8$^+$ T cell activity, effector cytokine secretion, and cytotoxic function. In addition, metabolic disorders are also an important cause of T cell exhaustion. CD36 can activate the oxLDL-p38-CEBPB signaling axis, upregulate the expression of iron uptake protein transferrin receptor 1 (TfR1), leading to a large accumulation of ferrous ions in CD8$^+$ T cells. Excessive iron ions induce lipid peroxidation damage, which ultimately severely impairs the anti-tumor effector function of T cells [9].

T cell rejection is a physical immunosuppression mode, which means that peripheral and intratumoral CD8$^+$ T cells are physically blocked from the tumor matrix and cannot penetrate the tumor parenchyma to contact tumor cells. The fibrosis barrier and disordered expression of chemokines in HCCTME, together with the multiple immunosuppressive network constructed by Treg cells and myeloid-derived suppressor cells, jointly mediate T cell rejection, resulting in the lack of infiltration of effector T cells in the tumor core area, the inability to effectively initiate anti-tumor immunity, and the induction of T+A treatment resistance [9].

DOI: 10.54254/2753-8818/2026.HZ38838

3.2.2. Enrichment of tregs

Tregs are key immunosuppressive cells in the TME. Their abnormal enrichment in HCC lesions is an important factor mediating T+A drug resistance. They mainly expand through two pathways: active recruitment and local transformation.

At the level of active recruitment, androgens can stimulate HCC tumor cells to highly express and secrete the chemokine CCL2, specifically recruiting peripheral mature T cells to migrate and aggregate to the tumor lesion, increasing the local Treg cell reserve. Inflammatory signals such as tumor necrosis factor can further enhance the recruitment process of Tregs through the bypass pathway. At the level of local transformation, the TME of HCC highly expresses cytokines such as TGF-β1, which can induce normal $CD4^+$ naive T cells in the TME to differentiate into induced Treg cells with strong immunosuppressive function [10].

Many enriched Treg cells can suppress the immune system in several ways. They keep consuming immune-activating factors like IL-2 in the tumor microenvironment (TME). They also secrete inhibitory cytokines like IL-10 and TGF-β. This directly causes $CD8^+$ T cell depletion and loss of activity. They can also promote abnormal tumor angiogenesis. They enhance the invasive and metastatic abilities of HCC tumor cells.

3.2.3. Spatial redistribution of $CXCL10^+$ macrophages

In HCC patients sensitive to T+A therapy, $CXCL10^+$ macrophages infiltrate the tumor parenchyma well. They are distributed close to HCC tumor cells. This distribution helps recruit and enrich $CD8^+$ effector T cells to the core tumor region. It allows direct contact between effector T cells and tumor cells.

In the tumor tissue of patients with T+A resistance, $CXCL10^+$ macrophages are mostly found at the edge of the tumor. They stay in the outer stroma. They cannot enter the tumor parenchyma. This means $CXCL10^+$ macrophages cannot control the immune response inside the tumor well. $CD8^+$ T cells do not enter the tumor enough. The anti-tumor immune effect is not activated [11].

3.3. Immune rejection and tumor dedifferentiation

Immune rejection and tumor dedifferentiation are two important pathological features of secondary T+A resistance in HCC. They work together to reshape the malignant phenotype of the tumor and the immune microenvironment [6].

Immune rejection is the core obstacle to immunotherapy resistance in HCC. It shows as a physical barrier. This barrier stops anti-tumor immune cells like $CD8^+$ effector T cells from entering the tumor matrix barrier and killing tumor cells. This leads to an immune-exempt state in the tumor core region. The immune-activating effect of atezolizumab cannot work inside the tumor lesion. This is a significant starting factor in the failure of T+A therapy.

Tumor dedifferentiation is a key cellular mechanism for adaptive drug resistance in HCC. It means mature HCC tumor cells lose their original mature function and traits. They go backward in development and gain stem cell-like features. These features are like primitive hepatic progenitors and hematoblasts. Dedifferentiated HCC tumor cells have much stronger proliferative, invasive, metastatic, and anti-apoptotic abilities. The tumor stem cell characteristics help tumor cells escape immune surveillance and resist drug killing effects.

DOI: 10.54254/2753-8818/2026.HZ38838

4. T+A resistance mechanism mediated by molecular pathways and signaling axes

In the process of drug resistance in advanced HCC treated with T+A combination therapy, the immunosuppressive remodeling of TME, the imbalance of immune cell function and spatial disorder all have an upstream molecular regulatory basis. Tumor cells can initiate multiple drug resistance signaling axes through metabolic reprogramming, oxidative stress response and abnormal activation of immune interaction signals, thereby inducing immune escape and weakening the anti-tumor effect of drugs from the root [4]. Combining the cellular drug resistance mechanism of TME mentioned above, this chapter further focuses on the three core molecular signaling pathways that have been confirmed so far, systematically elucidating the specific molecular mechanisms by which the Galectin-4/LDHA/HIF-1α/CXCL6, NRF2–COX2–PGE2 and TREM2-SYK-CEBPα signaling axes regulate primary and secondary drug resistance of T+A, clarifying the regulatory role of different pathways in metabolic remodeling, construction of immune cold microenvironment and myeloid cell polarization, and improving the molecular theoretical system of HCC T+A drug resistance.

4.1. The galectin-4/LDHA/HIF-1α/CXCL6 signaling axis

The Galectin-4/LDHA/HIF-1α/CXCL6 signaling axis, by regulating TANs infiltration, mediates both $CD8^+$T cell inhibition and rejection, and is a key pathway driving secondary resistance of HCC to T+A [8]. Under T+A pressure, Galectin-4 is highly expressed; it binds LDHA and stops TRIM28 from removing LDHA, so aerobic glycolysis increases and lactate accumulates; the lactate changes HIF-1α by lactylation and raises its transcription activity, upregulates CXCL6, and brings in neutrophils that become $PD\text{-}L1^+$ TANs through CXCR2; these TANs directly reduce $CD8^+$ T cell function through PD-L1/PD-1, and they also build a physical wall that blocks $CD8^+$ T cell entry and causes exhaustion; finally, the immunosuppressive microenvironment is rebuilt, the anti-tumor effect of T+A is blocked, and drug resistance develops.

4.2. NRF2–COX2–PGE2 signaling axis

Metabolic problems caused by oxidative stress make the immune microenvironment in HCC cold through the NRF2–COX2–PGE2 pathway, and this pathway is important in primary resistance to T+A; reactive oxygen species in tumor cells activate NRF2, raise COX2 expression, and cause a lot of PGE2 to be made; PGE2 blocks anti-tumor immunity in several ways: it stops dendritic cells from maturing and presenting antigens, lowers $CD8^+$ T cell function, and brings in Treg/MDSCs, so effector T cells do not enter the tumor enough and the immune response fails; this makes atezolizumab unable to work and causes T+A treatment failure [12].

4.3. TREM2-SYK-CEBPα signaling axis

The TREM2-SYK-CEBPα signal is a main pathway that controls the type change of tumor-associated macrophages. It mainly produces drug-resistant $TREM2^+$ macrophages, and it works as a key upstream mechanism that builds the myeloid immunosuppressive barrier in HCC and drives T+A drug resistance [13].

In HCC tumor cells that are highly active in metabolism, SQLE expression goes up; this promotes the production and buildup of oxidized low-density lipoprotein. oxLDL then acts as a ligand, it binds to TREM2 receptors on the macrophage surface. This activates the downstream SYK kinase pathway in the cell, makes SYK phosphorylated, and further causes the transcription factor

DOI: 10.54254/2753-8818/2026.HZ38838

CEBPα to be phosphorylated and activated. This initiates the transcriptional program for a pro-tumor phenotype in macrophages, ultimately driving ordinary macrophages to differentiate into a $TREM2^+$ pro-tumor, immunosuppressive phenotype.

The abundant $TREM2^+$ tumor-associated macrophages can eliminate apoptotic tumor cells through burial and continuously recycle metabolic substrates such as fatty acids to supply tumor cells, meeting the high-speed metabolic needs of drug-resistant tumors; at the same time, they continuously activate pro-cancer signaling pathways such as MYC and TGF-β, promoting tumor proliferation, invasion and metastasis. $TREM2^+$ macrophage infiltration mediated by this pathway can build a stable myeloid immunosuppressive barrier, significantly inhibit the infiltration and effector function of intratumoral $CD8^+$T cells, causing persistent anti-tumor immunodeficiency, and ultimately stably inducing HCC cells to develop resistance to T+A combination therapy [13, 14].

5. Limitations of existing research

The core cells and molecular mechanisms behind the primary and secondary drug resistance in patients with advanced liver cancer after receiving T + A regimen have been preliminarily elucidated by current studies. These studies also point out that tumor microenvironment remodeling, immune cell dysfunction, and multiple metabolic and immune-related signaling pathways play a key role in the process of drug resistance, which can help explain the differences in clinical treatment responses and provide basic theoretical support for finding drug resistance-related targets. However, the existing research on the mechanism of drug resistance is still relatively scattered, the main mechanism is still unclear, and the clinical transformation is not enough. Therefore, it is difficult to fully explain the complex drug resistance in real clinical practice, and it is difficult to effectively guide the drug resistance intervention for different patients.

5.1. Insufficient elucidation of fragmented and heterogeneous drug resistance mechanisms

Hepatocellular carcinoma itself has high heterogeneity. The emergence of drug resistance is driven by a variety of factors such as genetic variation, metabolic changes, and microenvironment disorders, and is not caused by a single pathway. Most of the current studies only focus on individual cell subsets or a certain signal axis. There is still a lack of integration at the system level for the mutual regulation, compensatory activation and conversion over time between different pathways. Therefore, it is difficult to construct a complete drug resistance regulatory network.

5.2. The core mechanisms of primary drug resistance are not fully understood

The adaptive evolution induced by drug pressure is the cause of secondary drug resistance, and this mechanism is relatively clear. Primary drug resistance is more determined by the inherent characteristics of the tumor before treatment. Many individual differences such as immune status, metabolic level, and liver function will affect it. Therefore, the phenotype is more complex. At present, only the overall performance of the immune cold microenvironment is known, and the upstream key targets for initiating drug resistance have not been located. Therefore, it is difficult to explain the phenomenon that some patients with good immune characteristics are still ineffective in treatment.

DOI: 10.54254/2753-8818/2026.HZ38838

5.3. Lack of a standardized clinical molecular subtyping system for drug resistance

Clinically, a unified and standardized classification of drug resistance types and patient grouping schemes have not yet been formed. Most of the existing markers are from small sample studies, and the detection standards are not uniform and the repeatability is poor. At the same time, genome, metabolomics, immune microenvironment and clinical indicators have not been integrated to construct a multi-dimensional model, so it can neither accurately distinguish the types of drug resistance nor guide individualized follow-up treatment, which has become a major obstacle to the clinical implementation of basic research.

6. Conclusion

This article systematically reviewed the primary and secondary drug resistance mechanisms of T+A treatment in advanced HCC, integrating analysis from three levels: drug resistance classification, microenvironment regulation, and molecular pathways. Primary resistance is caused by baseline immunosuppression and is unresponsive to initial treatment; secondary resistance is seen in patients who benefited early on, caused by drug-induced immune escape and adaptive evolution. In terms of microenvironment, myeloid cells were remodeled, CD8 positive T cells were depleted or rejected, and the number of regulatory T cells increased. These changes together formed an inhibitory barrier, and immune rejection and tumor cell dedifferentiation also accelerated the development of drug resistance. In terms of molecules, the three signal axes promote drug resistance by adjusting metabolic pathways, causing oxidative stress, and polarizing macrophages. Together, they constitute an upstream regulatory network for drug resistance. In summary, T+A resistance is a dynamic process of co-evolution of molecular abnormalities and microenvironmental inhibition. Current mechanistic research remains fragmented, the core factors of primary drug resistance remain unclear, and a standardized classification system is lacking in clinical practice. Future research should leverage multi-omics and spatial transcriptomics technologies to construct multidimensional classification models, identify interventionable targets, and provide a basis for precisely reversing drug resistance.

References

[1] Garcia, J., Hernandez, M., Rodriguez, L., et al. (2022). Mechanisms of primary and acquired resistance to immune checkpoint inhibitors in patients with hepatocellular carcinoma. *Cancers, 14*(19), 4616.

[2] Zhu, A. X., Abbas, A. R., Kobayashi, M., et al. (2022). Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. *Nature Medicine, 28*(8), 1599–1611.

[3] Wang, H., Li, P., Zhang, Y., et al. (2024). The association between tumour heterogeneity and immune evasion mechanisms in hepatocellular carcinoma and its clinical implications. *British Journal of Cancer, 130*(5), 789–801.

[4] Lombardi, P., Pinyol, R., & Llovet, J. M. (2025). Clinical and molecular characterisation of primary refractoriness to atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma. *bioRxiv*.

[5] Li, X., Wang, Y., Zhang, H., et al. (2025). Single-cell RNA sequencing-derived signatures define response patterns to atezolizumab + bevacizumab in advanced hepatocellular carcinoma. *Journal of Hepatology, 82*(6), 1036–1049.

[6] Chen, M., Liu, S., Zhou, J., et al. (2021). Atezolizumab plus bevacizumab combination enables an unresectable hepatocellular carcinoma resectable and links immune exclusion and tumor dedifferentiation to acquired resistance. *Experimental Hematology & Oncology, 10*(1), 112.

[7] Zhang, Y., Liu, H., Zheng, S., et al. (2025). Immunosuppressive CD14+ monocytes are enriched in patients with hepatocellular carcinoma and worse liver function (Child-Pugh B) and are associated with unfavorable immunotherapy outcomes. *Journal for ImmunoTherapy of Cancer, 13*(Suppl. 2), A808.

DOI: 10.54254/2753-8818/2026.HZ38838

[8] Xu, W., Zhao, Y., Weng, J., et al. (2026). Galectin-4 drives anti-PD-L1/bevacizumab resistance by regulating metabolic adaptation and tumour-associated neutrophils in hepatocellular carcinoma. *Gut, 75*(3), 620–631.
[9] Park, J., Kim, S., Lee, J., et al. (2025). CD36 promotes iron accumulation and dysfunction in CD8+ T cells via the p38-CEBPB-TfR1 axis in early-stage hepatocellular carcinoma. *Clinical and Molecular Hepatology, 31*(2), 345–354.
[10] Liu, Y., Zhang, Q., Wang, L., et al. (2026). Nrf2-mediated metabolic reprogramming drives regulatory T cell accumulation in hepatocellular carcinoma. *Nature Communications, 17*(1), 1056.
[11] Jiang, D., Chen, M., Zhou, X., et al. (2026). Single-cell spatial transcriptomics of advanced HCC identifies association of CD8+ T-pure clusters with response and TREM2+ macrophage pure clusters with resistance to atezolizumab plus bevacizumab. *EASL Liver Cancer Summit*.
[12] Yamamoto, S., Kodama, T., Tanaka, Y., et al. (2026). NRF2–COX2–PGE2 axis drives immune cold tumors and predicts resistance to combination immunotherapy in hepatocellular carcinoma. *Hepatology, 83*(4), 1210–1223.
[13] Wang, Q., Chen, J., Li, Y., et al. (2025). Metabolism archetype cancer cells induce protumor TREM2+ macrophages via oxLDL-mediated metabolic interplay in hepatocellular carcinoma. *Nature Communications, 16*(1), 2890.
[14] Zhang, L., Xu, W., Wu, Y., et al. (2026). Tumor cells metabolically resist immune-checkpoint therapy by macrophage efferocytosis-mediated fatty acid recycling. *Cancer Cell, 44*(6), 1235–1254.