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THE ROLE OF IMMUNE CELLS IN OBESITY-RELATED LIVER CANCER

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Abstract

Introduction. Obesity is an established independent risk factor for hepatocellular carcinoma, the third leading cause of cancer-related mortality worldwide. In Kazakhstan, where obesity affects over 20 % of the adult population and liver cancer incidence has risen steadily, this association carries urgent public health significance. Despite a well-documented epidemiological link, the mechanisms by which obesity undermines antitumor immunity and reshapes the hepatic microenvironment remain incompletely characterized. This review analyses how innate and adaptive immune populations are remodeled across the NAFLD-to-HCC continuum under chronic metabolic stress.

Objective. Analysis of current scientific evidence on the role of immune and inflammatory mechanisms in the development of liver cancer in the context of obesity, and systematization of data on how metabolic disturbances influence antitumor immune responses and the hepatic microenvironment.

Materials and methods. A systematic literature search was conducted across PubMed, Google Scholar, Scopus, and Web of Science databases, covering international and domestic publications from 2000 to 2026.

Results. Obesity-associated hepatocellular carcinoma develops through a progressive immunometabolic cascade in which visceral adipose tissue assembles an immunosuppressive microenvironment – via expansion of myeloid-derived suppressor cells, NK cell dysfunction, and $CD8^+$ T cell exhaustion – before malignant transformation occurs. Tregs are depleted in obese adipose tissue yet accumulate in hepatocellular carcinoma; NK cell activation in NASH drives hepatocyte damage rather than tumor protection. Functional polarisation state, not cellular abundance, determines the pathological outcome.

Conclusions. Obesity promotes HCC through chronic adipose inflammation, insulin resistance, and metabolic reprogramming of the tumor microenvironment, exhausting cytotoxic $CD8^+$ T cells and NK cells while expanding immunosuppressive Tregs and MDSCs. Liver cancer progression is driven not only by viral or toxic factors but by obesity-induced immune imbalance in which systemic metabolic stress becomes a key enabler of tumor immune evasion.

Keywords: *Obesity, liver cancer, immune response, hepatocellular carcinoma, nonalcoholic fatty liver disease.*

Introduction

The estimates for global levels of overweight and obesity (Body Mass Index ≥ 25kg/m²), also referred to as high Body Mass Index (hereinafter – BMI) throughout this Atlas, suggest that over 4 billion people may be affected by 2035, compared with over 2.6 billion in 2020. This reflects an increase from 38 % of the world's population in 2020 to over 50 % by 2035 (figures exclude children under 5 years old). The prevalence of obesity (BMI ≥30kg/m²) alone is anticipated to rise from 14 % to 24 % of the population over the same period, affecting nearly 2 billion adults, children, and adolescents by 2035. The rising prevalence of obesity

is expected to be steepest among children and adolescents, rising from 10 % to 20 % of the world's boys during the period 2020 to 2035, and rising from 8 % to 18 % of the world's girls [1]. Given the vast socio-economic diversity across Asia, the burden and management of liver cancer vary significantly between subregions. Among these, Central Asia stands out as a region where multiple risk factors and determinants of liver cancer interact in complex ways [2]. Across regions, the highest average all-cause mortality rates from 2014 to 2023 were in East Kazakhstan (7.29 per 100,000), West Kazakhstan (7.26 per 100,000), and Pavlodar (6.50 per 100,000)regions. The regions with the lowest mortality rates were Astana (3.40 per 100,000) and Almaty (3.87 per 100,000). (Mortality-to-incidence ratios) MIR values were high, averaging 0.85, and increased from 0.67 to 0.88 over the study period [3].

Materials and methods

A narrative literature review informed by a systematic literature search was conducted to examine the role of immune cells in the development of obesity-associated liver cancer. The literature search was performed using the PubMed, Google Scholar, Scopus, and Web of Science databases and covered publications published between 2000 and 2026.

Peer-reviewed original research articles and review papers were considered for inclusion. Eligible studies reported on immune and inflammatory mechanisms involved in obesity-related liver cancer, the impact of metabolic disturbances on antitumor immune responses, functional alterations in immune cell populations-including $CD4^+$ and $CD8^+$ T lymphocytes, natural killer (NK) cells, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), macrophages, and dendritic cells-as well as the pathogenesis of nonalcoholic fatty liver disease (hereinafter – NAFLD), nonalcoholic steatohepatitis (hereinafter – NASH), and their progression to hepatocellular carcinoma (hereinafter – HCC).

The search strategy included the following keywords and their combinations: «liver cancer», «obesity», «hepatocellular carcinoma», «nonalcoholic fatty liver disease», «immune cells», «hepatitis B virus», and «hepatitis C virus». Conference abstracts without full-text availability, non-peer-reviewed publications, and studies not relevant to the objectives of this review were excluded.

A total of more than 350 publications were initially identified across all databases. After removing duplicate records and screening titles and abstracts for relevance, 92 articles underwent full-text assessment. Ultimately, 68 publications that met the eligibility criteria and most comprehensively reflected the current evidence on obesity-related liver cancer and immune mechanisms were included in the final qualitative synthesis.

Results

Obesity arises from a chronic imbalance between energy intake and expenditure, yet framing it purely as a behavioral failure obscures the structural determinants – limited access to nutritious food, inadequate physical activity infrastructure, and weak regulatory environments – that systematically predispose populations to excess adiposity [4]. The global epidemiological shift is analytically telling: obesity, once considered a disease of affluence, is now rising fastest in low- and middle-income countries, where it paradoxically coexists with undernutrition – a dual burden that challenges both causal narratives and intervention frameworks simultaneously.

Kazakhstan-specific data illustrate this complexity in a national context. While over 20 % of the adult population is affected, the officially registered pediatric caseload appears disproportionately low relative to the reported tenfold increase in childhood prevalence over four decades [5], suggesting systematic underdiagnosis rather than genuine epidemiological containment. The strong parental transmission signal – up to tenfold increased risk when both parents are obese [6] – remains mechanistically ambiguous: cross-sectional study designs cannot disentangle genetic predisposition from shared dietary environments, and longitudinal evidence capable of separating these pathways is absent from the Kazakhstani literature.

At the pathophysiological level, obesity's heterogeneity is underappreciated in population-level analyses. Monogenic, polygenic, and syndromic forms differ fundamentally in their environmental modifiability [7; 8], yet surveillance data and intervention studies rarely stratify by obesity subtype. The insulin resistance pathway – through which proinflammatory cytokines promote chronic low-grade inflammation in adipose tissue and create conditions permissive for tumor initiation [9; 10] – represents the most evidentially developed mechanistic link

to cancer risk, though the relative contributions of hyperinsulinemia, dyslipidaemia, and gut microbiota-mediated energy dysregulation [11] to downstream malignancy risk have not been systematically ranked, leaving the causal architecture insufficiently resolved for precision prevention.

Liver cancer

Obesity is increasingly recognized as an independent driver of hepatocellular carcinoma, operating through multiple intersecting mechanisms – impaired antitumor immunity, altered tissue biomechanics, and metabolic dysregulation involving hyperinsulinemia, pro-inflammatory cytokines, and adipokines – with visceral fat accumulation appearing particularly implicated in disease progression [12; 13]. This mechanistic complexity sits in productive tension with epidemiological data: while traditional risk factors such as HBV, HCV, alcohol use, and cirrhosis account for the vast majority of cases (notably, cirrhosis underlies nearly 90 % of HCC diagnoses), the rising obesity epidemic introduces a partially independent causal pathway that existing surveillance frameworks may inadequately capture [14; 15].

Global incidence trends reveal an important asymmetry: liver cancer mortality has reversed in men. However, it continues to rise in women, a divergence that remains insufficiently explained and points to gaps in understanding sex-specific metabolic and hormonal mediators of obesity-related hepatocarcinogenesis [16]. Kazakhstan-specific data reinforce rather than resolve this complexity – a decade-long upward trend in incidence and mortality, heavy concentration in the 60-74 age group, and frequent comorbidities including diabetes and hypertension suggest a converging metabolic-infectious risk profile, yet the causal weight of obesity relative to viral hepatitis in this population has not been systematically disentangled [17; 18].

A further unresolved question concerns tumor heterogeneity: emerging evidence of monoclonal origin in combined HCC–cholangiocarcinoma suggests that microenvironmental factors – potentially including obesity-driven inflammation – may shape subtype divergence, with direct implications for treatment response that remain poorly characterized [19].

Association between obesity and liver cancer

The pathway from obesity to hepatocellular carcinoma is increasingly understood as a continuum mediated by metabolic dysfunction rather than a single causal mechanism. Nonalcoholic fatty liver disease (hereinafter – NAFLD) – defined by hepatic triglyceride accumulation exceeding 5 % in the absence of alcohol or viral etiology — serves as the critical inflection point: while the majority of NAFLD cases remain stable, progression to nonalcoholic steatohepatitis (NASH) occurs in approximately one-fifth of patients, introducing necroinflammation and fibrosis that may ultimately culminate in cirrhosis and HCC [20; 21]. What remains analytically underexplored is why only a subset of obese individuals with NAFLD undergo this transition – a gap that points to the insufficiency of BMI-based risk stratification alone.

Several converging mechanisms have been proposed, yet their relative contributions remain contested. TNF-α, elevated in obesity, implicates inflammatory signaling across multiple carcinogenic stages [22], while hyperinsulinemia and IGF-1 pathway activation introduce a distinct mitogenic dimension [23]. Notably, cholesterol emerges as an underappreciated lipotoxic driver: experimental evidence demonstrates that dietary cholesterol – rather than fat intake alone – is sufficient to sequentially induce steatosis, steatohepatitis, fibrosis, and HCC in animal models [24], a finding that challenges the conventional focus on caloric excess and warrants greater translational attention. The diabetes–cancer relationship adds further complexity: evidence suggests that cancer risk elevation is concentrated within the first three months following a diabetes diagnosis rather than accumulating progressively [25] – a counterintuitive temporal pattern that questions whether diabetes itself is causal or whether shared upstream metabolic dysregulation drives both conditions simultaneously.

A largely neglected dimension of this cascade is the role of sarcopenia: cirrhosis-associated muscle wasting may compound HCC prognosis independently of tumor characteristics [26], yet it is rarely integrated into obesity-liver cancer risk models – representing a meaningful gap in both research design and clinical risk assessment.

Immune cells

The liver occupies a uniquely paradoxical immunological position: its tightly regulated tolerogenic environment – maintained through the dynamic balance between immunosuppressive cells (Tregs, MDSCs) and effector populations (CD8+ T

cells, NK cells) – is essential for homeostasis, yet this same tolerance-promoting architecture creates conditions that tumors can exploit [27]. In HCC and cholangiocarcinoma, the tumor immune microenvironment (hereinafter – TIME) reflects this duality: the cellular machinery designed to prevent autoimmune damage to the liver becomes repurposed to facilitate immune escape, directly limiting the efficacy of immunotherapy and worsening survival outcomes [28].

What remains analytically underresolved is the precise sequence by which chronic inflammatory insults – whether viral, lipotoxic, or iron-mediated – erode immunosurveillance capacity and cross the threshold into tolerogenesis, thereby permitting tumor establishment [29]. These triggers are mechanistically distinct yet produce convergent outcomes, raising an important unresolved question: whether the immunosuppressive TIME in obesity-related HCC is qualitatively different from that driven by viral hepatitis, or whether both ultimately converge on the same tolerogenic endpoint through different upstream pathways. This distinction carries direct therapeutic implications, as immunotherapy response rates vary substantially across HCC aetiologies – a heterogeneity that current trial designs insufficiently account for and that represents one of the most consequential gaps in translational liver cancer research.

T cells

T lymphocytes occupy a central yet mechanistically ambiguous role in the obesity–liver cancer axis. In visceral adipose tissue (hereinafter – VAT), T cells are recruited early in response to a high-fat diet – notably before macrophage infiltration – suggesting they act as initiators rather than mere amplifiers of metabolic inflammation [30]. This temporal primacy is analytically significant: it repositions T cells from secondary responders to upstream orchestrators of the chronic inflammatory milieu that ultimately drives hepatic pathology.

However, the T-cell response in this context is not uniformly pathological. The core issue is a shift in subset equilibrium: the expansion of pro-inflammatory $CD4^+$ and $CD8^+$ populations, alongside the depletion of regulatory T cells (Tregs), tips the balance toward sustained inflammation in VAT [31]. In the liver, $CD8^+$ T cells drive NASH progression through macrophage recruitment and hepatic stellate cell activation [32] – yet the same T-cell populations are essential for antitumor immunosurveillance. This creates a fundamental paradox: the chronic activation that promotes fibrosis may simultaneously exhaust the cytotoxic T-cell compartment, impairing the immune response precisely when tumor control becomes critical.

A further unresolved tension concerns directionality. Evidence indicates that T cells promote fibrosis progression, while advancing cirrhosis, in turn, impairs T-cell function [33] – a bidirectional feedback loop whose net effect on HCC susceptibility has not been formally modeled. Whether interventions targeting T-cell subset rebalancing in early metabolic disease could interrupt this cascade before irreversible fibrotic remodeling occurs remains an open and therapeutically consequential question.

$CD4^+$

$CD4^+$ T cells present one of the more analytically complex pictures in obesity-related hepatocarcinogenesis, precisely because their functional role shifts – sometimes reverses – depending on disease stage and tissue compartment. Under homeostatic conditions, Th1-polarised $CD4^+$ cells coordinate antitumor immunity by driving cytotoxic T lymphocyte expansion and sustaining pro-inflammatory cytokine signaling within the tumor microenvironment [34]. Yet this protective capacity is systematically undermined by obesity: high-fat diet conditions reduce circulating $CD4^+$ populations, accelerate tumor growth, and drive exhaustion of residual cells [35] – establishing a metabolic immunosuppression that precedes, and likely facilitates, malignant progression.

The NASH context introduces a further paradox. $CD4^+$ T cell recruitment to the liver actively promotes hepatic inflammation and fibrosis, and their depletion ameliorates NASH pathology in experimental models [36]. This stands in direct tension with evidence that $CD4^+$-mediated senescence surveillance of premalignant hepatocytes is a critical tumor-suppressive mechanism [37]: the same population that drives fibrotic injury also clears early malignant cells. This dual role has not been reconciled in the literature and represents a fundamental gap: targeting $CD4^+$ cells therapeutically risks dismantling a key antitumor checkpoint while relieving the inflammatory burden.

Human-tissue data further sharpen this complexity: within established HCC tumors, $CD4^+$ cells paradoxically display high activation along-

side pronounced exhaustion, while their recruitment to the tumor core – relative to peritumoral tissue – is impaired [38]. This spatial and functional dissociation suggests that the relevant question is not simply whether $CD4^+$ cells are present, but whether the tumor microenvironment selectively excludes functional effectors while permitting dysfunctional ones – a distinction with direct implications for immunotherapy design that remains insufficiently explored.

Regulatory T cells (Tregs)

Regulatory T cells (Tregs) exemplify the interpretive difficulty that pervades obesity-related liver immunology: their functional consequences vary fundamentally depending on tissue compartment, disease stage, and the specific inflammatory context in which they operate. In visceral adipose tissue, Treg depletion under high-fat diet conditions shifts the immune balance toward pro-inflammatory effector dominance [39], positioning Tregs as guardians of metabolic homeostasis. Yet in the established HCC microenvironment, Treg accumulation suppresses antitumor effector responses and facilitates immune escape [40] – making the same population a driver of tumor progression. This context-dependency is not merely a biological nuance; it represents a fundamental obstacle to therapeutic targeting, as interventions that restore Treg activity in metabolic disease may simultaneously accelerate tumor immune evasion.

The literature further reveals unresolved contradictions within specific disease stages. In adult NAFLD, hepatic $FOXP3^+$ Tregs are decreased while Th17 cells expand [41] – a pro-inflammatory configuration consistent with fibrotic progression. Yet in NASH mouse models on high-fat/high-carbohydrate diets, intrahepatic Tregs are paradoxically elevated [42]. Whether this discrepancy reflects genuine species differences, dietary composition effects, or methodological inconsistency across studies has not been systematically addressed. Compounding this, the observation that pediatric NAFLD shows a higher Treg proportion than adults [43] introduces a developmental dimension that existing mechanistic frameworks do not adequately incorporate.

Collectively, the Treg/effector ratio – spanning Th17, $CD8^+$, and Th1 populations – emerges as a dynamic and spatially heterogeneous variable whose net immunological effect cannot be inferred from any single tissue measurement, underscoring the need for longitudinal, multi-compartment studies that current research designs have yet to deliver [44].

Natural killer

Natural killer cells present a particularly instructive case of functional duality in obesity-related liver pathology: they are simultaneously depleted and dysfunctional in ways that undermine tumor surveillance, yet in certain contexts their activation actively drives hepatic damage rather than preventing it. In obesity, NK cells show reduced expression of activating receptors, impaired cytotoxicity toward malignant cells, and accelerated exhaustion upon target contact [45-47] – a convergent pattern of immunological attrition that creates permissive conditions for tumor establishment. -This is reinforced in NAFLD, where high-grade steatosis associates specifically with depletion of the CD56dim NK subset and downregulation of NKG2D [48], mirroring the receptor-level impairments observed in diet-induced obesity models and suggesting a mechanistically coherent pathway from metabolic dysfunction to compromised innate surveillance.

However, the NASH context introduces a critical contradiction: activated hepatic NK cells in NASH promote hepatocyte damage via JAK/STAT signaling and drive disease progression [49] – meaning that residual NK activity in the inflamed liver is not merely ineffective against tumors but may actively accelerate the fibrotic milieu that enables HCC development. This inverts the straightforward depletion narrative and raises an unresolved question: whether NK cell dysfunction in obesity-related liver disease represents a failure of quantity, quality, or inappropriate anatomical activation – distinctions with fundamentally different therapeutic implications.

Clinical data from HCC patients further sharpen this: reduced peripheral NK cell frequency, particularly within the CD56dim subset, correlates with disease stage and worse post-resection survival [50; 51]. Yet whether NK cell depletion is a cause or consequence of tumor progression – and whether restoration of NK function at advanced disease stages would be therapeutically meaningful – remains unestablished, representing one of the more consequential mechanistic gaps in obesity-associated HCC immunology.

Macrophages

Macrophages represent perhaps the most functionally plastic component of the obesity-liver

cancer axis, and it is precisely this plasticity – rather than simple activation or depletion – that makes them both central to disease progression and difficult to target therapeutically. In lean adipose tissue, resident macrophages maintain homeostasis through efferocytosis and lipid buffering [52]. In the steatotic liver, lipotoxic loading of Kupffer cells shifts this phenotype toward pro-inflammatory polarisation [53], and within the established HCC microenvironment, tumor-imposed acidity drives macrophages further toward immunosuppressive configurations that actively facilitate immune escape [54]. This sequential reprogramming across disease stages suggests that macrophage phenotype is less a fixed cellular property than a readout of the local microenvironment – a distinction with important implications for interpreting cross-sectional studies that capture only a single disease snapshot.

A critical contradiction emerges from viral hepatitis data: during early HBV/HCV infection, pro-inflammatory macrophages restrict viral replication, but chronic infection progressively suppresses this capacity and substitutes an immunoregulatory phenotype [55]. The mechanism driving this transition is incompletely characterized, and whether obesity-driven metabolic reprogramming accelerates or independently recapitulates this shift remains unexamined. The IL-23 pathway activated by HBV-infected hepatocytes [56] represents one candidate mechanism, but its interaction with obesity-related metabolic signals has not been investigated.

Perhaps the most analytically striking finding concerns the dissociation between macrophage infiltration and tumor outcome: D6-deficient mice show increased hepatic macrophage accumulation without accelerated HCC progression [57] – directly challenging the assumption that macrophage quantity predicts tumor-promoting activity. This underscores that macrophage polarisation state, rather than abundance, is the functionally relevant variable, and that current research frameworks that rely on infiltration metrics may systematically mischaracterize the macrophage contribution to hepatocarcinogenesis.

Dendritic cells

Dendritic cells occupy a strategically pivotal position in tumor immunology as the primary bridge between innate sensing and adaptive effector responses — yet in both obesity and HCC, this bridging function is systematically compromised through distinct but potentially interacting mechanisms. In adipose tissue, obesity paradoxically activates DCs: BMI positively correlates with DC accumulation in subcutaneous adipose tissue, and obesity upregulates costimulatory molecules (MHC, CD40, CD80, CD86) on adipose tissue DCs [58;59]. This activation, however, occurs in a chronic low-grade inflammatory context [60] that is functionally distinct from the acute, tumor-directed activation required for effective immunosurveillance — raising the unresolved question of whether obesity-conditioned DCs are genuinely immunostimulatory or merely chronically stimulated in ways that ultimately exhaust or misdirect adaptive responses.

In established HCC, the picture inverts: circulating pDC and cDC frequencies are reduced relative to healthy controls [61], and the tumor microenvironment systematically impairs DC maturation and antigen presentation [62]. A critical contradiction emerges here: intratumoral pDC accumulation, rather than indicating effective immune activation, is associated with increased Treg infiltration and a poorer prognosis [63]. This dissociation between DC presence and functional competence mirrors findings in macrophage biology and suggests a broader pattern: immune cell recruitment to the tumor site does not reliably indicate antitumor activity and may instead reflect tolerogenic reprogramming.

The mechanistic link between obesity-induced DC activation and the dysfunctional DC phenotype observed in hepatocellular carcinoma has not been directly investigated. Whether chronic metabolic processing of DC in adipose tissue promotes their tolerogenic, rather than immunostimulatory, behavior in the tumor context represents a significant and therapeutically relevant gap in current research.

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells represent one of the most mechanistically direct links between obesity-induced immune dysregulation and hepatocarcinogenesis. Unlike other immune populations whose roles shift contextually, MDSCs maintain a consistently immunosuppressive function across disease stages - expanding in adipose tissue, accumulating in the cirrhotic liver, and escalating further in established HCC [64]. This stage-wise

amplification is analytically significant: it suggests that MDSC expansion is not merely a consequence of tumor establishment but an accumulating liability initiated by metabolic dysfunction, with obesity providing the earliest stimulus for expansion even in tumor-free mice [65].

The NASH context reinforces this interpretation: MDSC accumulation tracks with lipid accumulation and hepatic inflammation [66], positioning these cells at the intersection of metabolic and immune pathology – and implying that the immunosuppressive microenvironment enabling HCC may be partially assembled before malignant transformation occurs. This has an important and underexplored implication: current immunotherapy trial designs that enroll patients at the HCC stage may intervene too late, after MDSC-mediated suppression is already deeply entrenched.

Mechanistic evidence further reveals that MDSCs do not merely suppress immunity passively but actively remodel the tumor stroma: MDSC-driven activation of tumor-associated fibroblasts via IL-6/FGF1 signalling promotes HCC progression and, critically, contributes to sorafenib resistance [67]. This finding introduces MDSCs as a resistance mechanism rather than simply an immune checkpoint. Whether MDSC targeting could restore sorafenib sensitivity, and whether obesity-expanded MDSC populations are phenotypically or functionally distinct from those arising in viral hepatitis contexts [68], remain open questions that current research has not adequately addressed.

Table 1 summarizes the principal immune cell populations involved in obesity-associated hepatocellular carcinoma and highlights their functional changes during the progression from obesity and NAFLD/NASH to HCC. Chronic metabolic inflammation profoundly alters both innate and adaptive immune responses. T cells, particularly $CD4^+$ and $CD8^+$ subsets, initiate and sustain inflammatory responses that contribute to hepatic fibrosis while gradually losing their antitumor activity. Regulatory T cells (Tregs) accumulate within the tumor microenvironment, suppressing cytotoxic immune responses and facilitating immune evasion. Natural killer (NK) cells exhibit impaired cytotoxicity and reduced expression of activating receptors, resulting in diminished tumor surveillance despite persistent inflammatory activity. Macrophages undergo metabolic reprogramming and polarization toward tumor-promoting phenotypes, whereas dendritic cells display impaired antigen presentation and reduced T-cell activation. Expansion of myeloid-derived suppressor cells (hereinafter - MDSCs) further reinforces the immunosuppressive microenvironment by inhibiting effector lymphocyte function and contributing to tumor progression and therapeutic resistance. Collectively, these findings demonstrate that obesity-associated HCC develops through coordinated dysregulation of multiple immune cell populations rather than dysfunction of a single immune compartment, emphasizing the importance of immunometabolic mechanisms in hepatocarcinogenesis.

Table 1. Functional alterations of immune cell populations in obesity-associated hepatocellular carcinoma

Immune cell population	Changes in obesity / NAFLD / NASH	Role in HCC	Key references
T cells	Early recruitment into visceral adipose tissue and shift toward pro-inflammatory subsets.	Promote chronic inflammation, fibrosis, and impaired antitumor surveillance.	Wang & Wu, 2018 [30]; Wang et al., 2021 [31]; Breuer et al., 2020 [32]; Lurje et al., 2020 [33]
$CD4^+$ T cells	Functional plasticity in NAFLD/NASH; involved in inflammation and antitumor immunity.	May support premalignant-cell surveillance but also contribute to fibrosis and chronic inflammation.	Montauti et al., 2024 [34]; Sutti & Albano, 2020 [36]; Miao et al., 2024 [37]; Chaoul et al., 2020 [38]
Regulatory T cells (Tregs)	Reduced or functionally altered in metabolic inflammation; enriched in HCC microenvironment.	Suppress cytotoxic antitumor responses and promote immune escape.	Mendoza-Pérez et al., 2022 [39]; Dituri et al., 2021 [40]; Cairoli et al., 2021 [41]; Dywicki et al., 2022 [42]; Zhang et al., 2022 [44]

Natural killer (NK) cells	NAFLD/NASH is associated with impaired NK-cell phenotype, reduced NKG2D expression, and inflammatory activation.	Impaired NK surveillance may facilitate HCC progression; activated NK cells can aggravate NASH injury.	Viel et al., 2017 [47]; Diedrich et al., 2020 [48]; Wang et al., 2022 [49]; Polidoro et al., 2020 [50]; Wu et al., 2020 [51]
Macrophages / Kupffer cells	Obesity and steatosis promote macrophage metabolic reprogramming and inflammatory polarization.	Tumor-associated macrophages contribute to HCC progression, prognosis, and therapy resistance.	Boutens & Stienstra, 2016 [52]; Daemen & Schilling, 2020 [53]; Krenkel & Tacke, 2017 [55]; Zang et al., 2018 [56]; Arvanitakis et al., 2022 [57]
Dendritic cells (DCs)	Obesity alters adipose-tissue immune-cell states; HCC impairs DC function and antigen presentation.	Dysfunctional DCs reduce effective T-cell activation and support tumor immune tolerance.	Hildreth et al., 2021 [58]; Martín-Sierra et al., 2019 [61]; Li et al., 2024 [62]; Zhou et al., 2019 [63]
Myeloid-derived suppressor cells (MDSCs)	Expand in obesity-related inflammation, cirrhosis, liver disease, and HCC.	Suppress antitumor immunity and contribute to HCC progression and sorafenib resistance.	Elwan et al., 2018 [64]; Turbitt et al., 2019 [65]; Sun et al., 2023 [66]; Deng et al., 2022 [67]; Li et al., 2020 [68]

Note. This table summarizes the principal immune cell populations implicated in obesity-associated hepatocellular carcinoma and their functional alterations during the progression from obesity to NAFLD, NASH, and HCC. The information is synthesized from the studies included in this narrative review.

Abbreviations: NAFLD – nonalcoholic fatty liver disease; NASH – nonalcoholic steatohepatitis; HCC – hepatocellular carcinoma; NK – natural killer; Tregs – regulatory T cells; DCs – dendritic cells; MDSCs – myeloid-derived suppressor cells.

Discussion

The evidence reviewed across this work converges on a central argument: obesity-associated hepatocellular carcinoma is not adequately characterized as a downstream complication of excess adiposity, but rather as the endpoint of a progressive immunometabolic cascade in which chronic metabolic dysfunction and immune system remodeling are deeply intertwined and mutually reinforcing. Understanding this cascade-and identifying where it can be interrupted-represents the core translational challenge.

The initiating role of visceral adipose tissue deserves particular analytical emphasis. VAT is not merely a passive energy reservoir but an active immunological organ: it recruits T cells before macrophages under high-fat diet conditions, depletes Tregs with advancing obesity, and activates dendritic cells in ways that appear to precondition systemic immune responses toward chronic low-grade inflammation rather than targeted tumor surveillance [30; 39; 60]. This early immunological reprogramming in adipose tissue is rarely incorporated into liver cancer risk models, which typically focus on hepatic pathology alone – a structural gap that likely contributes to the failure of BMI-based screening to identify high-risk individuals before irreversible hepatic remodeling has occurred.

The NAFLD-to-HCC transition emerges from this review as the critical and most undercharacterised window for intervention. Several immunological perturbations identified in NASH – MDSC expansion tracking with lipid accumulation [66], NK cell receptor downregulation correlating with steatosis severity [48], and $CD8^+$ T cell-driven stellate cell activation [32] – indicate that the immunosuppressive architecture of established HCC is being assembled at premalignant stages. This has a direct and underappreciated clinical implication: immunotherapy trials enrolling patients at the HCC stage may be intervening after the immune microenvironment has already been comprehensively restructured, which may partly explain the modest and heterogeneous response rates observed across checkpoint inhibitor studies in this population.

Several important contradictions identified across the reviewed literature warrant explicit ac-

knowledgment rather than being resolved by omission. Tregs exemplify the core interpretive difficulty: their depletion in obese VAT promotes metabolic inflammation, yet their accumulation in HCC facilitates immune escape [39; 40] – and their role in NASH is contested between human and murine data [41;42]. Similarly, NK cell residual activation in NASH drives hepatocyte damage via JAK/STAT signaling [49] rather than providing tumor protection, inverting the straightforward assumption that NK cell activity is uniformly beneficial. $CD4^+$ T cells present an analogous paradox: they perform essential senescence surveillance of premalignant hepatocytes [37] while simultaneously driving fibrotic progression in NASH [36]. These contradictions are not merely biological curiosities – they represent fundamental obstacles to therapeutic targeting, as interventions designed to restore immune activity in one compartment risk accelerating pathology in another.

The macrophage and MDSC data collectively suggest that polarisation state and functional context – rather than cellular abundance – determine pathological outcome. The dissociation between macrophage infiltration and HCC progression in D6-deficient mice [57] and the demonstration that MDSCs promote sorafenib resistance through IL-6/FGF1 stromal remodeling [67] both argue against infiltration metrics as reliable surrogate endpoints and point toward functional phenotyping as the necessary methodological standard for future studies. This reorientation has practical significance specifically for the Kazakhstani context. Given the co-prevalence of HBV/HCV infection and obesity-related metabolic disease in the regional population, the assumption that immune dysregulation follows a uniform pattern regardless of etiology is unlikely to hold, and aetiologically stratified immune profiling represents a research priority that current national data cannot address.

Taken together, these findings argue for a reconceptualization of obesity-associated HCC prevention: from a focus on BMI reduction as the primary endpoint toward earlier immunometabolic risk stratification, incorporating visceral adiposity measures, insulin resistance indices, and immune biomarker panels at the NAFLD stage. Whether such stratification can meaningfully predict HCC risk and guide early intervention – metabolic, immunological, or combined – in high-burden regional populations remains the central unanswered question that the existing evidence base, despite its breadth, has not yet resolved.

Conclusions

The convergence of rising obesity prevalence and persistently unfavorable hepatocellular carcinoma outcomes – particularly in regions of Kazakhstan with elevated mortality-to-incidence ratios – points to an urgent need to move beyond descriptive epidemiology toward mechanistically informed prevention. The evidence reviewed here establishes that obesity-driven HCC does not represent a single pathological pathway. However, rather, a cascade of compounding immunometabolic failures: insulin resistance and lipotoxicity restructure the hepatic microenvironment, while the sequential depletion of $CD8^+$ T cells and NK cells, the expansion of Tregs and MDSCs, and the polarisation of macrophages and dendritic cells toward tolerogenic phenotypes collectively dismantle antitumor surveillance before malignant transformation is clinically detectable. Critically, several of these immune perturbations – MDSC expansion, NK cell exhaustion, Treg accumulation – are already measurable at the NAFLD and NASH stages, suggesting that the immunosuppressive architecture enabling HCC is assembled well before diagnosis.

This has concrete practical implications. First, BMI-based screening is insufficient: visceral adiposity, insulin resistance indices, and immune biomarker panels should be evaluated as complementary stratification tools, particularly in the high-risk 40–49 age group identified in Kazakhstani surveillance data. Second, the documented resistance of obesity-associated HCC to sorafenib – partly mediated by MDSC-driven stromal remodeling – argues for combination strategies targeting both metabolic and immune axes rather than sequential monotherapy. Third, the near-absence of longitudinal, multi-compartment immunological studies in the Kazakhstani population represents a structural gap: national cohort data linking metabolic trajectories to immune phenotyping and liver cancer outcomes would substantially strengthen the evidence base for locally adapted prevention protocols.

From a research perspective, three directions warrant prioritisation: longitudinal studies tracking immune subset dynamics from early obesity through NAFLD progression to HCC in the regional population; mechanistic investigation of

whether obesity-conditioned MDSCs and dendritic cells are phenotypically distinct from those arising in viral hepatitis contexts, given the co-prevalence of HBV/HCV in Kazakhstan; and clinical trials evaluating whether early metabolic intervention – dietary, pharmacological, or surgical – can reverse measurable immune dysregulation and reduce HCC incidence, rather than simply modifying BMI as a surrogate endpoint.

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СЕМІЗДІККЕ БАЙЛАНЫСТЫ БАУЫР ҚАТЕРЛІ ІСІГІНДЕГІ ИММУНДЫҚ ЖАСУШАЛАРДЫҢ РӨЛІ

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Аңдатпа

Кіріспе. Семіздік гепатоцеллюлярлы карциноманың тәуелсіз қауіп факторы ретінде танылған, ол дүниежүзі бойынша қатерлі ісіктен болатын өлімнің үшінші жетекші себебі болып табылады. Қазақстанда ересек халықтың 20 %-дан астамы семіздікпен ауырады және бауыр қатерлі ісігінің таралуы тұрақты өсу үрдісін көрсетеді, бұл аталған байланысқа жедел денсаулық сақтау маңызын береді. Семіздік пен гепатоцеллюлярлы карцинома арасындағы эпидемиологиялық байланыс жақсы дәлелденгеніне қарамастан, семіздіктің ісікке қарсы иммунитетті бұзу және бауырдың микроортасын қалыптастыру механизмдері толық зерттелмеген. Осы шолу созылмалы метаболикалық стресс жағдайында алкогольсіз майлы бауыр ауруыдан гепатоцеллюлярлы карциномаға дейінгі үдерісте туа біткен және адаптивті иммундық жасушалардың қалай өзгеретінін талдайды.

Мақсаты: Семіздік жағдайында бауыр қатерлі ісігінің дамуындағы иммундық және қабыну механизмдерінің рөліне қатысты қазіргі ғылыми деректерді талдау, сондай-ақ метаболикалық бұзылыстардың ісікке қарсы иммундық жауапқа және бауырдың микроортасына әсері туралы мәліметтерді жүйелеу.

Материалдар мен әдістер: Жүйелі әдебиетті іздеуі PubMed, Google Scholar, Scopus және Web of Science халықаралық деректер қорларында 2000 жылдан 2026 жылға дейінгі кезеңдегі халықаралық және отандық басылымдарды қамти отырып жүргізілді.

Нәтижелер мен талқылау: Семіздікпен байланысты гепатоцеллюлярлы карцинома висцеральды май ұлпасы қатерлі өзгеріс пайда болғанға дейін иммуносупрессивті микроортаны қалыптастыратын прогрессивті иммунометаболикалық каскад арқылы дамиды - миелоидтан алынған супрессорлық жасушалар (MDSC) кеңеюі, NK-жасушалардың дисфункциясы және $CD8^+$

Т-жасушалардың сарқылуы арқылы. Реттеуші Т-жасушалар (Treg) семіз май ұлпасында азаяды, бірақ гепатоцеллюлярлы карциномада жиналады; алкогольсіз стеатогепатит кезіндегі NK-жасушалардың белсенділігі ісіктен қорғаудың орнына гепатоциттерге зақым келтіреді. Патологиялық нәтижені жасушалардың саны емес, олардың функционалдық поляризация күйі анықтайды.

Қорытынды: Семіздік май ұлпасының созылмалы қабынуы, инсулинрезистенттілік және ісік микроортасының метаболикалық қайта бағдарламалануы арқылы гепатоцеллюлярлы карцинома дамуын жеделдетеді, цитотоксикалық $CD8^+$ Т-жасушалары мен NK-жасушаларын сарқып, иммуносупрессивті Treg және MDSC-ның кеңеюіне ықпал етеді. Бауыр қатерлі ісігінің прогрессиясы тек вирустық немесе уытты факторлармен ғана емес, сонымен қатар семіздік туындататын иммундық теңгерімсіздікпен де байланысты, онда жүйелі метаболикалық стресс ісіктің иммундық бақылаудан жасырынуының негізгі факторына айналады.

Түйін сөздер: *семіздік, бауыр қатерлі ісігі, иммундық жауап, гепатоцеллюлярлы карцинома, алкогольсіз майлы бауыр ауруы.*

РОЛЬ ИММУННЫХ КЛЕТОК ПРИ РАКЕ ПЕЧЕНИ, СВЯЗАННОЙ С ОЖИРЕНИЕМ

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Аннотация

Введение. Ожирение является установленным независимым фактором риска развития гепатоцеллюлярной карциномы – третьей по значимости причины смертности от онкологических заболеваний в мире. В Казахстане, где ожирением страдает более 20 % взрослого населения, а заболеваемость раком печени неуклонно растёт, данная связь приобретает особую значимость для общественного здравоохранения. Несмотря на хорошо задокументированную эпидемиологическую взаимосвязь, механизмы, посредством которых ожирение нарушает противоопухолевый иммунитет и перестраивает микроокружение печени, остаются недостаточно изученными. В настоящем обзоре анализируется, каким образом популяции врождённого и адаптивного иммунитета подвергаются функциональному ремоделированию на протяжении континуума от неалкогольной жировой болезни печени до гепатоцеллюлярной карциномы в условиях хронического метаболического стресса.

Цель. Анализ современных научных данных о роли иммунных и воспалительных механизмов в развитии рака печени в контексте ожирения, а также систематизация сведений о том, каким образом метаболические нарушения влияют на противоопухолевый иммунный ответ и микроокружение печени.

Материалы и методы. Систематический поиск литературы проводился в международных базах данных PubMed, Google Scholar, Scopus и Web of Science и охватывал международные и отечественные публикации за период с 2000 по 2026 год.

Результаты. Гепатоцеллюлярной карцинома, ассоциированная с ожирением, развивается через прогрессирующий иммунометаболический каскад, при котором висцеральная жировая ткань формирует иммуносупрессивную микросреду – за счёт экспансии супрессорных клеток миелоидного происхождения (Myeloid-Derived Suppressor Cells, MDSC), дисфункции NK-клеток и истощения CD8+ Т-лимфоцитов – ещё до начала злокачественной трансформации. Регуляторные Т-клетки (Tregs) истощаются в жировой ткани при ожирении, однако накапливаются при гепатоцеллюлярной карциноме; активация NK-клеток при неалкогольном стеатогепатите приводит к повреждению гепатоцитов, а не к противоопухолевой защите. Определяющим фактором патологического исхода является функциональное состояние поляризации клеток, а не их количественная представленность

Выводы. Ожирение способствует развитию гепатоцеллюлярной карциномы через хроническое воспаление жировой ткани, инсулинорезистентность и метаболическое перепрограммирование

опухолевого микроокружения, что приводит к истощению цитотоксических $CD8^+$ Т-клеток и NK-клеток при одновременном расширении иммуносупрессивных Treg и MDSC. Прогрессирование рака печени определяется не только вирусными или токсическими факторами, но и вызванным ожирением иммунным дисбалансом, при котором системный метаболический стресс становится ключевым фактором, способствующим ускользанию опухоли от иммунного надзора.

Ключевые слова: *ожирение, рак печени, иммунный ответ, воспаление, гепатоцеллюлярная карцинома, неалкогольной жировой болезни печени.*

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