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THE ROLE OF ALPHA-FETOPROTEIN IN SUPPRESSING ANTITUMOR IMMUNE RESPONSE IN HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) is one of the most aggressive and deadly malignant tumors, characterized by treatment complexity and high resistance to immunotherapy. Alpha-fetoprotein (AFP) is traditionally used as a diagnostic marker for HCC. Recent studies reveal its key role in carcinogenesis and in forming a tolerogenic microenvironment that suppresses the anti-tumor immune response. Despite numerous publications, contradictions remain in assessing AFP's functions and prognostic value, necessitating an analytical review.*

This study aimed to *summarize current data on AFP's role in tumor immune evasion mechanisms and to evaluate its potential as a target for novel immunotherapeutic approaches for HCC treatment.*

Methods: *A systematic search and analysis of publications on AFP and HCC were conducted in PubMed and Google Scholar, and several specialized medical and scientific journals (including Cancer Research) from 2017 to 2025. Keywords included: "alpha-fetoprotein", "hepatocellular carcinoma", "immunosuppression", "tumor immune evasion", "AFP immunomodulation", "immune response in HCC". Selected articles met relevance and novelty criteria.*

Results: *The review revealed that AFP plays a central role in HCC progression through its immunosuppressive effects and activation of tumor immune evasion mechanisms. Contradictions in prognostic data reflect the complexity and multilayered biological functions of AFP.*

Conclusion: *AFP is not only a key diagnostic marker for HCC but also plays an active role in establishing immune tolerance. Its ability to suppress antitumor immune response makes AFP a promising therapeutic target, especially in combined immunotherapeutic approaches aiming to improve treatment efficacy.*

Keywords: *alpha-fetoprotein (AFP), hepatocellular carcinoma (HCC), immunosuppression, AFP-mediated immunomodulation, immune response.*

Introduction: Hepatocellular carcinoma (HCC) is one of the most common and aggressive malignant liver tumors, most often developing in the context of cirrhosis and chronic viral hepatitis. HCC is characterized by high mortality, late diagnosis, and limited treatment options, making this pathology one of the most significant medical and social problems.

According to the World Health Organization, as of 2020, HCC ranked seventh in prevalence and third in mortality among oncological diseases worldwide [1]. According to official data from the oncology service of the Republic of Kazakhstan for 2023 [2], mortality from liver malignancies accounted for 4.2% of overall oncological mortality, resulting in a shift in this pathology from 10th to 9th place. At the same time, significant regional variability is noted, with the highest mortality rate recorded in the East Kazakhstan region (7.0 per 100,000) and the lowest in the Zhetysu region (1.3 per 100,000). Figure 1 presents data on mortality from malignant neoplasms of the liver per 100 thousand of the population in the regions of the Republic of Kazakhstan for 2023. The data were compiled based on official statistics from the oncology service of the Republic of Kazakhstan for 2023. These data indicate significant differences in access to healthcare, the timeliness of diagnosis, and the prevalence of risk factors that warrant further investigation.

Despite numerous studies on HCC diagnostics and treatment, the effectiveness of existing approaches remains limited. Particular attention is paid to the search for molecular markers that can serve dual roles, both as diagnostic tools and as therapeutic targets. One of these factors is alpha-fetoprotein (AFP). Traditionally, AFP is used to diagnose and monitor HCC; however, accumulating data indicate that it not only reflects tumor progression but also actively participates in pathogenesis, including the suppression of antigen-presenting cells, inhibition of cytotoxic T lymphocytes, and stimulation of signaling pathways that promote tumor growth [3]. Al-

though the number of studies examining the role of AFP in immunomodulation in HCC is constantly increasing, the existing data remain controversial. While some studies emphasize the importance of AFP in creating an immunosuppressive microenvironment, others indicate that AFP has only a limited effect on tumor progression. This underscores the need for a systematic, critical review of the literature.

This study aimed to summarize current data on AFP's role in tumor immune evasion mechanisms and to evaluate its potential as a target for novel immunotherapeutic approaches for HCC treatment.

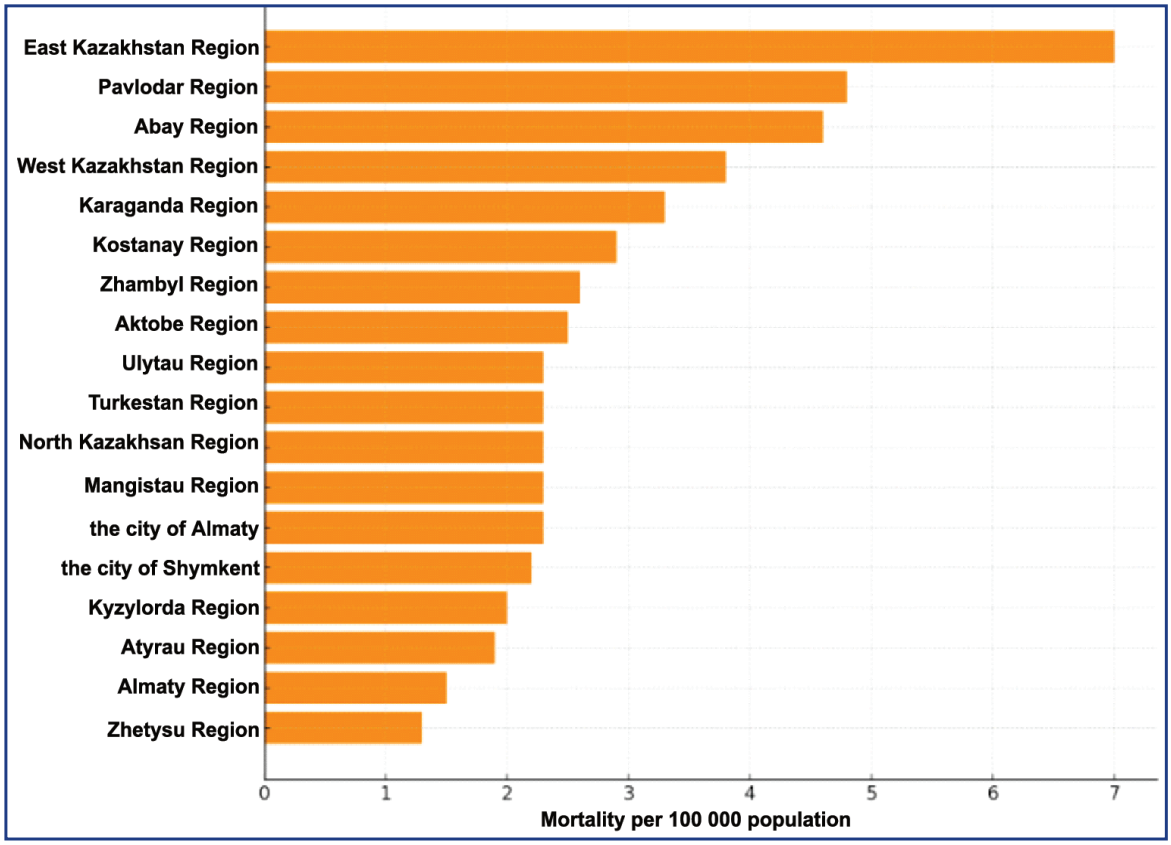

Figure 1 – Mortality from malignant neoplasms of the liver in Kazakhstan, 2023 [2]

Materials and Methods: Scientific papers from the Medline (PubMed) and Google Scholar databases were analyzed to identify available literature on the study topic. The following terms were used in the search: "alpha-fetoprotein" and/or "hepatocellular carcinoma" and/or "immunosuppression" and/or "tumor immune evasion" and/or "AFP immunomodulation" and/or "immune response in HCC". As a result, approximately 148 potentially relevant sources (articles and reviews) were identified. After removing duplicates and assessing the content, the most significant and informative works (including reviews and descriptions of original research) were selected. Selection criteria: novelty, completeness of the presented data, and the presence of unique information (works of low quality or those duplicating data from previously published studies were excluded). The final analysis comprised 50 sources, including those that provided detailed data on the mechanisms of the immune response, angiogenesis, and AFP-mediated signaling pathways, as well as two sources that contained statistical data on the disease prevalence in Kazakhstan. The search covered studies published up to and including April 2025 (Figure 2).

Results:

1. Alpha-fetoprotein (AFP)

AFP is a glycoprotein belonging to the albuminoid protein family, playing a key role in embryonic development [5]. Its structure includes three domains, each involved in the regulation of various signaling pathways [6]. Of particular significance is the interaction between domain III and PTEN, which activates the PI3K/AKT signaling cascade, thereby promoting the growth and progression of hepatocellular carcinoma (HCC). Normally, AFP levels drop sharply after birth; however, they rise again during malignant liver processes, especially in HCC [7]. To provide a broader understanding, the domain structure and functional characteristics of AFP are summarized in Table 1.

AFP is synthesized in the fetal liver and yolk sac, reaching peak levels between the 12th and 16th week of gestation [8]. In adults, its concentration is minimal. An increase in AFP levels is observed in both malignant conditions (primarily HCC and germ cell tumors) and several

benign conditions (pregnancy, chronic hepatitis, cirrhosis). In clinical practice, AFP is a key marker for early HCC diagnosis, evaluation of treatment efficacy, and monitoring for recurrence [9]. Table 2 describes the conditions associated with elevated AFP levels and their clinical significance.

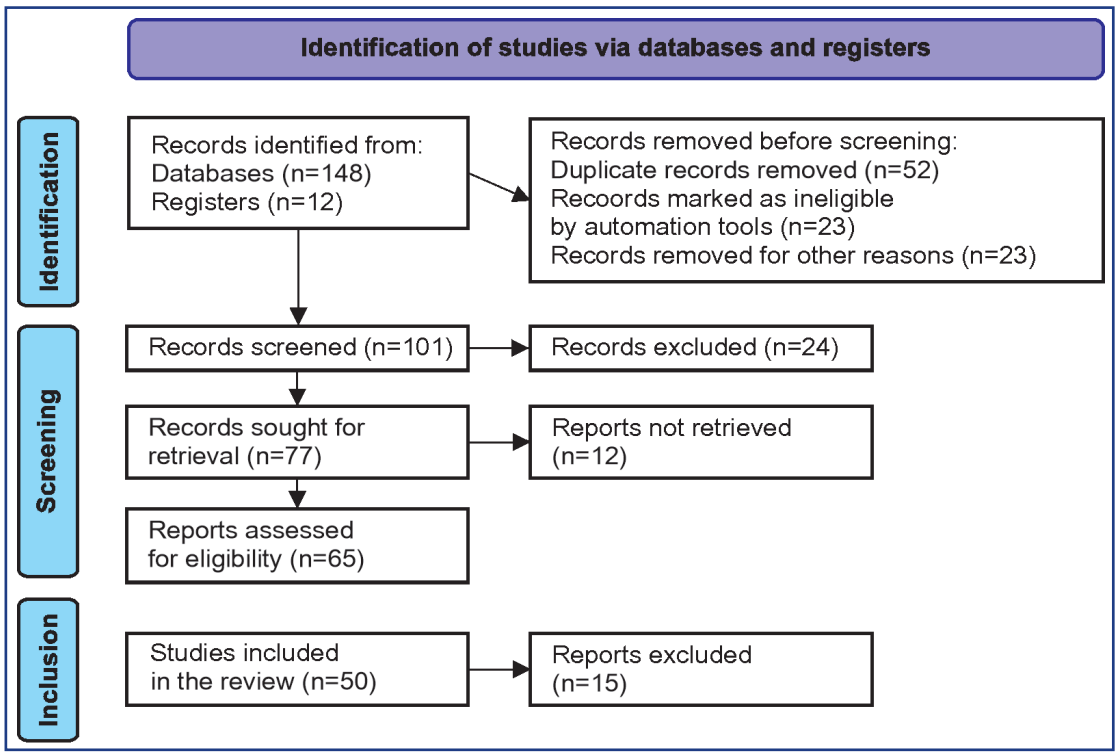

Figure 2 – PRISMA research source selection scheme [4]

Table 1 – Domain Structure and Functions of AFP

Domain	Characteristics	Primary Functions
I (N-terminal)	1-210 a.a.r.	Interaction with PTEN
II (central)	211-402 a.a.r.	Flexibility, protease-mediated cleavage
III (C-terminal)	403-609 a.a.r.	Stability, activation of PI3K/AKT

Note: a.a.r. – amino acid residues

Table 2 – Conditions Associated with Elevated AFP Levels and Their Diagnostic Significance

Condition / Disease	AFP Level (ng/mL)	Clinical Significance	Source
Normal in adults	< 10	Physiological level	Kachanov D.Yu. et al. [10]
Pregnancy (2nd trimester)	100 - 500 (may be higher)	Physiological elevation	Zakharov V.V. et al. [11]
Chronic hepatitis/cirrhosis	10 - 200	Moderate elevation requires differential diagnostics	Glowska-Ciemny J. et al. [12]
Hepatocellular carcinoma	> 400 (often > 1000)	Most specific, used for diagnostics and prognosis	Kong F. et al. [13]
Germ cell tumors (testes, ovaries)	100 - 10,000	Diagnostics, therapy monitoring	Sharma A. et al. [14]
Hepatoblastoma (in children)	> 1000	Highly diagnostic marker	Sharma A. et al. [14]
Metastatic liver tumors	50 - 500	Additional marker, less specific	Sharma A. et al. [14]

2. Mechanisms of Immune Response Suppression by Hepatocellular Carcinoma Cells.

HCC tumor cells utilize various mechanisms to evade the immune response [15]. The primary mechanisms include reduced expression of major histocompatibility complex class I (MHC-I) molecules, disruption of antigen presentation, and activation of non-classical immunosuppressive molecules [16]. Key signaling pathways involved in immune evasion in HCC are presented in Table 3 and Figure 3.

The Role of AFP in Liver Cancer Development.

Over the past decades, it has been demonstrated that AFP is not only a diagnostic marker but also actively participates in the progression of liver cancer. Elevated AFP levels (>400 ng/mL) are often associated with aggressive disease course and poorer prognosis. At the same time, changes in AFP levels during treatment allow for monitoring therapy effectiveness: a decrease in levels is associated with a positive response, while a renewed increase may indicate relapse even in the absence of signs on CT or MRI.

It is important to note that AFP affects not only prognosis but also the tumor's immune microenvironment. It suppresses the activity of key immune cells, including macrophages, dendritic cells, NK cells, and T lymphocytes. As a result, a so-called "immunosuppressive niche" forms, helping the tumor evade immune surveillance [29]. The effects of AFP on the immune microenvironment of HCC are summarized in Table 4.

Table 3 – Main Mechanisms of Impaired Antigen Presentation in HCC

Mechanism	Prevalence	Consequences for Immune Response	Source
Decreased MHC-I expression (HLA-A, HLA-B, HLA-C)	≈78% of cases	Reduced recognition by $CD8^+$ T cells	Kamilova T.A. et al. [17]
Hypermethylation of HLA promoters	Frequent	Suppression of MHC-I gene transcription	Liu H. et al. [18]
miRNA regulation (miR-148a, miR-152)	Reported in clinical samples	Inhibition of HLA translation	Bird T.G. et al. [19]
TAP1/TAP2 mutations	30-40%	Disruption of antigen transport to the ER	Bird T.G. et al. [19]
B2M mutations	25-30%	Instability of MHC-I on the membrane	Galle P.R. et al. [20]
Decreased PSMB8/PSMB9 (proteasome subunits)	–	Defective antigen processing	Yang Z. et al. [21]
Increased expression of HLA-E, HLA-G	Frequent	Suppression of NK and T cells via inhibitory receptors	Zhu M. et al. [22], Hong G.Q. et al. [23]

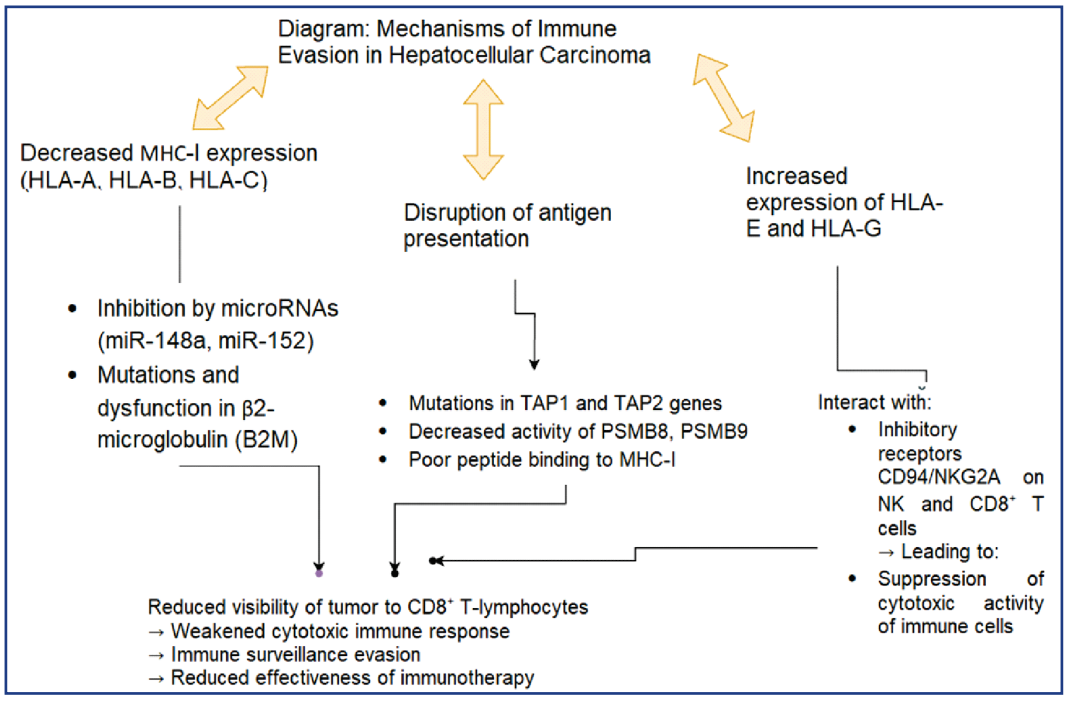

Figure 3 – Mechanisms of Immune Evasion in HCC [24-28]

Table 4 – Mechanisms of AFP Action on Target Cells

Target Cell	Mechanism of Action	Immune Consequences	Source
Macrophages	Stimulates transition to M2 phenotype via PI3K/Akt pathway	Suppression of antitumor response, support of tumor growth	Wu S. et al. [30]
Dendritic cells	Induces apoptosis, reduces CD80/CD86 expression	Impaired antigen presentation and T-lymphocyte activation	Palucka K. & Banchereau J. [31]
NK cells	Indirectly decreases activity via reduced IL-12	Reduced cytotoxic activity	Zhou Y. et al. [32]
$CD8^+$ T-lymphocytes	Inhibits the IL-2R signaling pathway	Loss of proliferation and cytotoxicity	Shang N. et al. [33]
$CD4^+$ T-lymphocytes	Reduces IL-2 and IFN-γ production	Weakened coordination of the immune response	Isyangulova A.Z. [34]
Regulatory T-cells	Stimulates differentiation via TGF-β/Smad3	Formation of a tolerogenic environment	Tian L.Y. et al. [35]
Myeloid-derived suppressor cells (MDSCs)	Enhances immunosuppressive activity	Suppression of NK and T-cell responses	Mishra R. et al. [36]
Tumor cells	Activation of NF-κB → ↑PD-L1 expression	Inhibition of T-cell activity	Ebrahimi N. et al. [37]

In addition to its impact on immunity, AFP contributes to the maintenance of liver cancer stem cells (LCSC) [38]. These cells possess self-renewal capability and are associated with recurrence and drug resistance. Studies have shown that AFP stimulates the expression of LCSC markers (CD44, CD133, EpCAM) and activates the PI3K/Akt signaling pathway, thereby enhancing tumor malignancy [39].

AFP is considered a potential therapeutic target given its active role in the development of immunosuppression in HCC. The main research directions can be divided into several categories. Thus, AFP has become a target for the development of new treatment strategies given its key role in HCC progression and immunosuppression. The main approaches are presented in Table 5.

Table 5 – Potential Therapeutic Strategies Targeting AFP

Approach	Examples	Results	Limitations	Source
Restoration of antigen presentation	IFN-γ, decitabine	Increased HLA-I expression, enhanced tumor recognition	Preclinical stage only	Son C.H. et al. [40]
CAR-T cells against AFP	AFP-specific CAR-T	High efficacy in murine models	Risk of off-target toxicity, intratumoral immunosuppression	Yershov A.V. et al. [41], Gavrilina O.A. et al. [42]
Dendritic vaccines	DCs loaded with AFP	Phase I/II: safety confirmed, 20% objective response rate	The low immunogenicity of AFP requires combination with other antigens	Chekhonin I.V. et al. [43], Shardina K.Yu. et al. [44]
Signaling pathway inhibitors	Alpelisib (PI3Kα)	Tumor growth reduction in HepG2/Huh7 models	Preclinical data only; combination strategies need optimization	Semiglazov V.F. et al. [45]
Combination approaches	TACE + immunotherapy	Enhancement of local immune response	Limited clinical data	Phillips C. [46]

Discussion: Hepatocellular carcinoma (HCC) remains one of the most challenging oncological diseases due to its high mortality rate and the limited effectiveness of current therapeutic approaches [47]. The presented data confirm the key role of AFP not only as a diagnostic marker but also as an active participant in the pathogenesis of HCC. AFP creates an immunosuppressive microenvironment by modulating macrophages, dendritic cells, NK cells, and T lymphocytes. Such remodeling of the immune niche reduces the effectiveness of the antitumor immune response and promotes tumor progression. An important aspect is the influence of AFP on the population of liver cancer stem cells (LCSC), which are associated with recurrence and drug resistance. Thus, AFP plays a dual role: on the one hand, it suppresses immune surveillance; on the other, it supports LCSC and enhances tumor aggressiveness. Despite the accumulated data, certain contradictions remain: in some patients with low AFP levels, the disease still shows aggressive progression, and the mechanisms of AFP's influence on immune cells have not been fully confirmed in clinical studies. This highlights the need for further research to clarify the prognostic value of AFP and its therapeutic potential. From a therapeutic perspective, the most promising strategies are combined approaches, in which AFP is not considered a sole target but as part of a multi-antigen strategy. Current directions include AFP-targeted CAR-T cells, dendritic cell vaccines, and PI3K/Akt pathway inhibitors [48]. However, most of these methods remain limited to preclinical models or early-phase clinical trials, and their transition to widespread clinical use is hindered by the risks of off-target toxicity and the immunosuppressive tumor microenvironment. Overall, a promising direction appears to be integrating targeted and immunotherapeutic approaches with local methods (e.g., TACE), as well as monitoring AFP dynamics as a biomarker of therapeutic effectiveness.

Study Limitations: Given the retrospective design and lack of clinical outcomes data, several limitations should be considered when interpreting the results. Firstly, relapse-free survival and overall survival were not analyzed in this study, which prevents establishing a direct link between AFP, immunological changes, and actual clinical outcomes. Additionally, the effects of comorbidities and ongoing therapies (targeted and antiviral) were not accounted for, even though they may influence AFP levels and immune response parameters. Liver regeneration after surgical intervention can also affect AFP dynamics. Moreover, the limited sample size and heterogeneity in HCC stage, cirrhosis status, and viral load may reduce the analytical power and complicate the interpretation of these results.

To date, AFP retains its important clinical role as a diagnostic marker; however, it is not limited to that role alone. For example, AFP levels have prognostic significance, as elevated AFP is associated with more aggressive disease progression in most cases. Changes in AFP levels during treatment serve as a surrogate response indicator: a post-treatment decrease typically correlates with clinical response, whereas a renewed increase signals relapse. Current preclinical and clinical studies also suggest that AFP may act as an active immunomodulator within the tumor microenvironment, as evidenced by its effects on dendritic cell maturation and function, suppression of NK and $CD8^+$ T-lymphocyte activity, stimulation of regulatory T-cell differentiation, and enhancement of immune checkpoint molecule expression.

The conducted literature review is not limited to listing known associations between AFP and molecular phenomena in HCC. In the present study, existing data were synthesized into a single, functionally oriented model, in which AFP is considered an active immunomodulator that establishes a tolerogenic microenvironment and facilitates tumor immune evasion. Based on the comparison of preclinical and clinical studies, specific mechanisms were identified – such as its effects on dendritic cells, NK and T lymphocytes, stimulation of regulatory T lymphocytes (Tregs), activation of PI3K/AKT and NF-κB - mediated pathways, associated upregulation of PD-L1 expression, and the role of AFP in supporting the LCSC population – all presented not as isolated findings, but as an interconnected pathophysiological network contributing to HCC progression. This integrated data indicates that AFP is not just a marker of tumor burden but also a biologically active factor that alters the composition of immune cell populations and reduces the clinical efficacy of immunotherapies.

Conclusion: AFP plays a central role in the development and progression of HCC. Its ability to suppress antigen presentation, modulate immune cell activity, and maintain the stem-like properties of liver cancer stem cells (LCSC) makes AFP not only a biomarker but also an important therapeutic target [49]. Current research highlights the potential of approaches involving CAR-T cells, dendritic cell vaccines, and inhibition of the PI3K/Akt and NF-κB signaling pathways [50]. However, their clinical efficacy remains limited, underscoring the need for further preclinical and clinical studies. AFP continues to serve as an indicator for diagnostics, prognosis, and monitoring of treatment effectiveness. In the future, a comprehensive approach – combining immunotherapy, targeted agents, and local treatment methods with consideration of AFP dynamics – may become the foundation for personalized HCC therapy strategies.

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АҢДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫ КАРЦИНОМА КЕЗІНДЕ АЛЬФА-ФЕТОПРОТЕИННІҢ ІСІККЕ ҚАРСЫ ИММУНДЫҚ ЖАУАПТЫ БАСУДАҒЫ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Гепатоцелюлярлық карцинома (ГЦК) – емдеуде күрделі және иммунотерапияға жоғары төзімділігімен ерекшеленетін ең агрессивті әрі өлімге әкелетін қатерлі ісіктердің бірі. Альфа-фетопротеин (АФП) әдетте ГЦК диагнозында маркер ретінде қолданылады. Соңғы зерттеулер оның канцерогенезде және қарсы ісікке иммундық жауапты басатын төзімді микробейтарап ортаны қалыптастыруда маңызды рөл атқаратынын көрсетті. Көптеген жарияланымдарға қарамастан, АФП функциялары мен болжамдық мәнін бағалауда қайшылықтар сақталады, бұл аналитикалық шолу қажеттігін туындатады.*

Зерттеу мақсаты *– АФП-ның ісік иммундық жауаптан қашу механизміндегі ролін жинақтап, ГЦК-ны емдеуге арналған жаңа иммунотерапиялық тәсілдерді әзірлеуде АФП-ның әлеуетін бағалау.*

Әдістері: *PubMed және Google Scholar мәліметтер базаларында, сондай-ақ профильді медициналық және ғылыми журналдарда (оның ішінде Cancer Research) 2017-2025 жылдар аралығында АФП және ГЦК тақырыбындағы жарияланымдар жүйелі түрде ізделіп, талданды. Іздеу кілт сөздері: «альфа-фетопротеин», «гепатоцелюлярлық карцинома», «иммуносупрессия», «ісік иммундық жауаптан қашу», «АФП иммундық модуляциясы», «ГЦК иммундық жауабы». Таңдалған мақалалар өзектілік пен жаңалық талаптарына сай болды.*

Нәтижелері: *Шолу барысында АФП иммуносупрессивті әсерлері және ісіктің иммундық бақылаудан қашу механизмдерін белсендіріп, ГЦК прогрессиясында орталық рөл атқаратыны анықталды. Болжамдық мәліметтердегі қайшылықтар АФП-ның көпқырлы биологиялық қызметінің күрделілігін көрсетеді.*

Қорытынды: *АФП тек ГЦК-ның маңызды диагностикалық маркері ғана емес, сонымен қатар иммундық төзімділіктің қалыптасуында белсенді қатысушы. Оның қарсы ісік иммундық жауаптарын басу қабілеті емдеу тиімділігін арттыруға арналған кешенді иммунотерапиялық тәсілдерде перспективалы терапевтік мақсат болып табылады.*

Түйінді сөздер: *льфа-фетопротеин (АФП), гепатоцелюлярлық карцинома (ГЦК), иммуносупрессия, АФП-бақыланатын иммундық модуляция, иммундық жауап.*

АННОТАЦИЯ

РОЛЬ АЛЬФА-ФЕТОПРОТЕИНА В ПОДАВЛЕНИИ ПРОТИВООПУХОЛЕВОГО ИММУННОГО ОТВЕТА ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) – один из самых агрессивных и смертельно опасных типов злокачественных новообразований, который характеризуется сложностью в лечении и высокой устойчивостью к иммунотерапии. Альфа-фетопротеин (АФП) традиционно используется в качестве маркера для диагностики ГЦК. Кроме этого последние исследования показывают, что он также играет важную роль в канцерогенезе и в формировании толерогенного микроокружения, подавляющего противоопухолевый иммунный ответ. Несмотря на значительное число публикаций, остаются противоречия в оценке функций и прогностической ценности АФП, что обусловливает необходимость проведения аналитического обзора.*

Цель исследования *– обобщить современные данные о роли АФП в механизмах уклонения опухоли от иммунного ответа и оценить потенциал АФП как мишени для разработки новых иммунотерапевтических подходов лечения ГЦК.*

Методы: *Проведен систематический поиск и анализ публикаций по теме α-фетопротеина и ГЦК в базах данных PubMed и Google Scholar, а также в ряде профильных медицинских и научных журналов (в том числе Cancer Research) за период с 2017 по 2025 год. Для поиска использовались ключевые слова: «альфа-фетопротеин», «гепатоцеллюлярная карцинома», «иммуносупрессия», «иммунное уклонение опухоли», «иммуномодуляция АФП», «иммунный ответ при ГЦК». Отобранные статьи соответствовали критериям релевантности и новизны.*

Результаты: *Обзор показал, что АФП играет центральную роль в прогрессировании ГЦК за счёт иммуносупрессивных эффектов и активации механизмов уклонения опухоли от иммунного надзора. Кроме того, выявлены противоречия в данных о его прогностическом значении, что отражает сложность и многоуровневость биологических функций АФП.*

Заключение: *АФП является не только ключевым диагностическим маркером ГЦК, но и активным участником формирования иммунной толерантности. Его способность подавлять противоопухолевый иммунный ответ делает АФП перспективной терапевтической мишенью, особенно в контексте комбинированных иммунотерапевтических подходов, направленных на повышение эффективности лечения.*

Ключевые слова: *альфа-фетопротеин (АФП), гепатоцеллюлярная карцинома (ГЦК), иммуносупрессия, АФП-опосредованная иммуномодуляция, иммунный ответ.*

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