REVIEWS

BIOMARKERS OF HEPATOCELLULAR CARCINOMA: STATUS AND PROSPECTS

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Hepatocellular carcinoma (HCC) also known as hepatocellular cancer is one of the most common and aggressive types of primary malignant liver neoplasms. This type of cancer accounts for up to 90% of all primary liver tumors and is the third leading cause of cancer death worldwide. Despite the advances in modern medicine, diagnostics and treatment of HCC remain challenging, especially in the later stages, when the patient's prognosis significantly worsens and treatment options are very limited. More than half a century has passed since Yu.S. Tatarinov discovered embryo-specific α-globulin in the blood of people with primary liver cancer in 1963, which was later called alpha-fetoprotein (AFP), but unfortunately, the number of specific and sensitive biomarkers for HCC remains very limited. In this regard, many scientific papers are devoted to the search and study of potential HCC biomarkers, which are essential for early diagnostics, prognosis, and development of new therapeutic strategies. Proteomic studies represent one of the promising approaches to investigate both molecular mechanisms of HCC occurrence and HCC biomarkers. Identification of specific protein profiles characteristic of tumor cells can contribute to the identification of new biomarkers that can be used not only for early detection of the disease, but also for monitoring its progression, assessing the response to therapy and predicting the clinical outcome. This review discusses current achievements in the search for potential biomarkers of HCC, as well as the prospects for their clinical use.

Keywords: hepatocellular cancer; biomarkers; protein profiles; proteoforms

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INTRODUCTION

Oncological diseases still remain one of the significant problems of modern global healthcare. According to the World Health Organization (WHO), liver cancer is the sixth most common type of cancer in the world and the third leading cause of cancer deaths [1]. The liver is one of the vital human organs responsible for many body functions, and tumors that develop in it can quickly spread and affect adjacent tissues. Among all types of liver cancer, HCC is the most frequently diagnosed primary liver cancer. According to Rosstat data, during the period from 2010 to 2022 there is a clear increase in percentage of patients with newly diagnosed liver and bile duct cancer in the Russian Federation [2]. More than 850 thousand new cases are diagnosed worldwide every year, and the number of deaths is approaching 800 thousand per year. Despite significant advances in the development of treatment methods, including targeted drugs and immunotherapy, mortality still exceeds the number of primarily registered cases, due to the fairly rapid and asymptomatic development of HCC, and, as a result, diagnostics at later stages [3].

The main factors contributing to the HCC development include genetic and epigenetic changes that gradually disrupt the normal regulation of liver cell growth and division, leading to their malignant transformation. These include chronic liver damage such as cirrhosis and/or infection with hepatitis B and C viruses [4–6], alcoholic liver disease [7, 8], metabolic disorders (non-alcoholic fatty liver disease (NAFLD) and hemochromatosis), genetic mutations and epigenetic changes [9–12]. According to statistics, the largest number of registered cases of HCC occurs in countries of the Asia-Pacific region. This is primarily due to the low standard of living, high prevalence of chronic viral hepatitis and significant contamination of food products with aflatoxin B1 [13]. In countries with a higher standard of living, there is a tendency for an increase in the HCC incidence in NAFLD patients [14–17]. As the population increases and risk factors become more prevalent, the number of cases is expected to increase by 66% by 2045 [1].

Alpha-fetoprotein (AFP) assay, traditionally used in clinical practice, is characterized by low sensitivity in the early stages of HCC (within 39–65% depending on the baseline level), and its specificity increases up to 90% only at later stages [18, 19]. Moreover, AFP levels can increase not only in HCC, but also in other conditions (ovarian and testicular tumors, pregnancy, etc.) [20–24]. Reliable and specific markers that could effectively identify HCC in the early stages and distinguish it from other liver diseases are needed [25–27]. Since tumor heterogeneity

can affect the effectiveness of individual biomarkers, HCC progression, depending on the etiological factors, can manifest itself in the form of various molecular profiles, thus complicating the development of universal biomarkers [28, 29].

One of the promising approaches for early diagnosis and effective treatment of HCC is the use of proteomics to search for biomarkers that can serve as indicators of the presence and progression of HCC. Unlike the genome, which is relatively static, the proteome, i.e. the set of all proteins in the body, is constantly changing in response to various exogenous and endogenous stimuli [30]. Proteomics is a promising tool for studying cancer, where changes at the protein level (for example, changes in the concentration or modification of proteins) can serve as key indicators of pathological processes.

1. HCC BIOMARKERS USED IN CLINICAL PRACTICE

Modern diagnostics of HCC includes several types of studies: general blood test, serological and instrumental studies (ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI)). The main problem in HCC diagnostics is the lack of specific symptoms in the early stages and, as a result, late referral of patients; which has a significant impact on possible limitations of treatment methods. In Russian clinical practice, AFP, the only tumor-specific biomarker is used in combination with non-specific inflammation markers (for example, C-reactive protein (CRP)) (Fig. 1).

In foreign clinical practice, more specific markers are used in addition to AFP; these include the glycosylated form of AFP (AFP-L3) and des-gamma-carboxyprothrombin (DCP), which are approved biomarkers for diagnostics and monitoring the HCC progression [31]. The use of this combination of biomarkers allows achieving a sensitivity of 94% and a specificity of more than 97% (Fig. 2) [32].

1.1. Alpha-fetoprotein

Alpha-fetoprotein is a glycoprotein that is normally produced in the liver and gall sac of the fetus during intrauterine development. Normally, blood AFP concentrations in adults are low, but they increase in various pathological conditions. The relationship between AFP levels and the HCC development of was first described in 1963 by Tatarinov [33]. AFP is still actively used for screening and diagnostics of HCC, especially in patients with viral hepatitis and cirrhosis of the liver [34]. It is also used to assess evaluate remission/relapse after treatment, but its sensitivity varies between 40–68%, and the concentration may not increase in the early stages or in the presence of small tumors [35]. According to clinical guidelines, serum is used for analysis, and the AFP test result is considered as positive if the AFP level is >100 ng/ml or if it has increased by 7 ng/ml per month based on three consecutive measurements [36].

1.2. Alpha-fetoprotein-L3

AFP-L3 is one of three glycoforms of AFP; it represents the main fraction that binds to *Lens culinaris* agglutinin. Unlike total AFP, which can increase in other liver diseases such as hepatitis or cirrhosis, AFP-L3 is associated primarily with malignant tumors [37]. It demonstrates higher specificity (92–99%) and, according to various studies, the AFP-L3 levels can increase several months before the tumor becomes visible using imaging methods [37, 38].

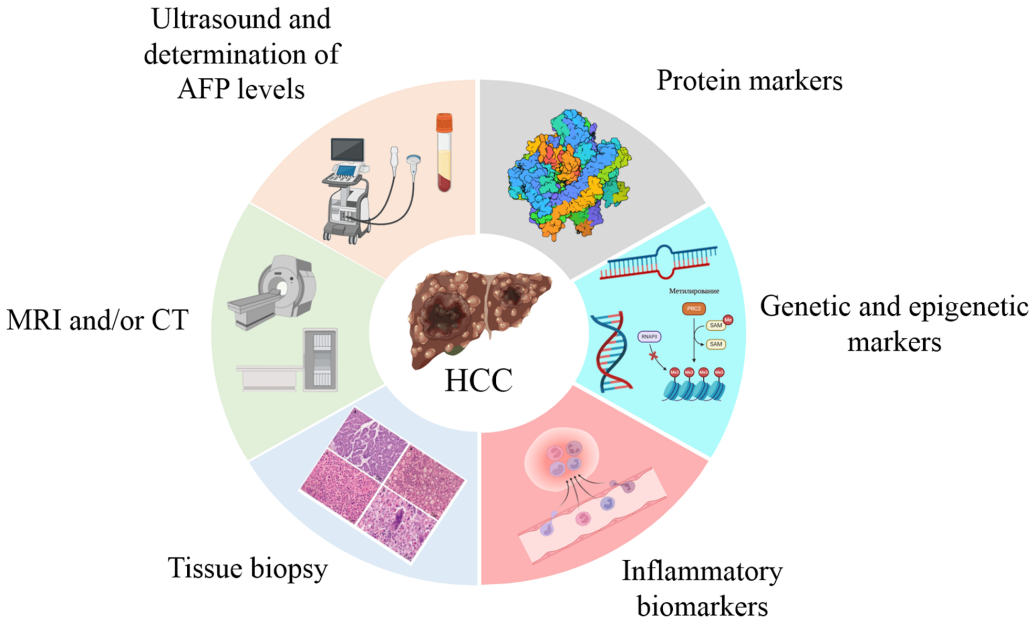

Figure 1. Graphical representation of methods used in HCC diagnostics.

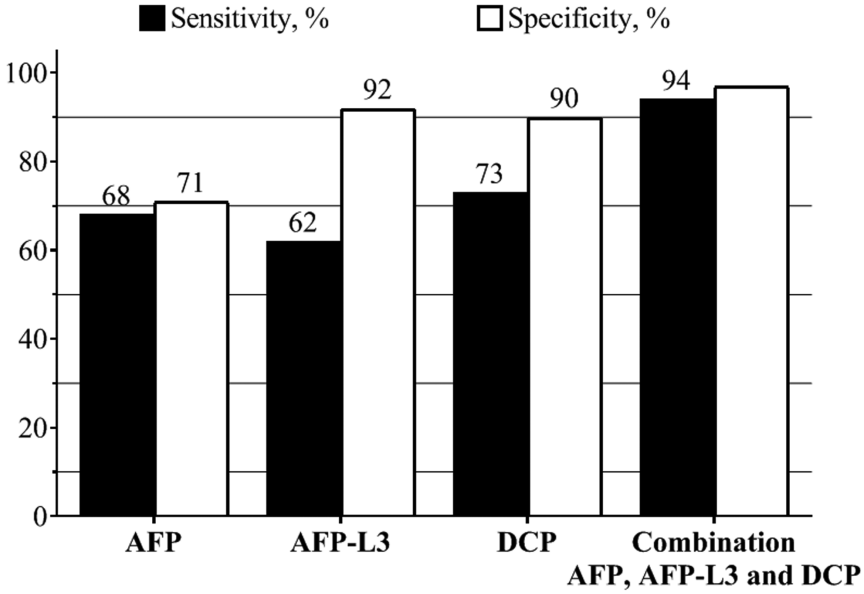

Figure 2. Graphical representation of sensitivity and specificity of HCC biomarkers used in clinical practice.

1.3. Des-gamma-carboxyprothrombin

Des-gamma-carboxyprothrombin is an abnormal form of prothrombin that occurs due to a deficiency of vitamin K-dependent carboxylation. It demonstrates high specificity for HCC, especially in comparison with benign liver diseases, and is used to monitor the response to treatment and assess the risk of recurrence after surgery or other methods of treatment [39, 40].

The levels of the above markers are determined in the blood serum of patients. According to clinical guidelines there are the following reference values: AFP less than 4.7 ng/ml, AFP-L3 less than 10% of the total AFP, DCP less than 7.5 ng/ml.

2. POTENTIAL HCC BIOMARKERS

In recent years, significant progress in molecular research has led to the identification of new potential HCC markers that can significantly improve the diagnostics and monitoring of the disease. In order to be effective in the diagnostics, prognosis and monitoring of treatment of diseases, including HCC, a marker must meet a number of strict criteria, such as high sensitivity and specificity, reproducibility, non-invasiveness, and affordability. Most of the known potential biomarkers have limitations in the context of the listed criteria, so for many decades the search and validation of potential markers has remained a relevant area of research.

If we take into consideration the etiological factors of HCC development, the potential markers can be conditionally subdivided into three main groups: protein biomarkers, genetic and epigenetic biomarkers, and inflammatory biomarkers (Table 1). Many clinical studies have been conducted for many of the listed biomarkers, thus demonstrating both their diagnostic value and the possibility of using them as a therapeutic target. For example, in April 2024, BioCity (China) began research on a new drug (antibody-drug conjugate) targeting glypican-3 (GPC3). This protein regulates cell growth and differentiation by participating in signaling through interactions with various growth factors (Wnt/β-catenin signaling pathway) and other molecules, and is also overexpressed in HCC [41]. The first stage of clinical trials is currently underway, and it is expected that GPC3 can be used for a new safe and effective method of HCC treatment [42].

One of the important tasks of modern research in the field of potential markers is the possibility of a minimally invasive method of analysis (blood serum or plasma) known as liquid biopsy. For this type of analysis, the most commonly used methods are, for example, enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), next-generation sequencing (NGS), etc. There are a number of disadvantages associated with their use, such as the lack of specific antibodies, the likelihood of false-positive results, and the high cost of research. All this leads to the need of development of new promising approaches for biomarker creation.

Among the potential markers listed in Table 1, miRNAs represent one of the promising group of is biomarkers. First of all, this is due to the fact that certain miRNAs can act as oncogenes or tumor suppressors, and, therefore, they be considered as possible therapeutic targets [87–89].

2.1. miR-21

miR-21 is an oncogenic miRNA that suppresses apoptosis and stimulates cell proliferation. Increased expression is observed in HCC and, according to various studies, expression levels correlate with the stage of the disease and metastasis [90–92].

Table 1. Some potential HCC biomarkers

Biomarker	Description	Type of biomaterial and diagnostic test	Clinical importance	References
Protein biomarkers				
Glypican-3 (GPC3)	Proteoglycan, frequently expressed in HCC cells but absent in normal liver	Blood serum / ELISA	It is used in HCC diagnostics when AFP levels are not elevated. Considered as a possible target for immunotherapy	[38, 43]
Hepatocyte growth factor (HGF)	HGF is associated with HCC progression	Blood serum / ELISA	After liver resection, elevated HGF levels are associated with poor survival prognosis	[44, 45]
Growth differentiation factor-15 (GDF-15)	A cytokine belonging to the family of transforming growth factors	Blood serum / ELISA	Can be used to assess disease severity	[46–48]
Golgi glycoprotein 73 (GP73)	Golgi membrane protein	Blood serum / ELISA	Additional diagnostic marker, more sensitive than AFP	[49, 50]
Vascular endothelial growth factor (VEGF)	Angiogenesis promoting protein	Blood serum / ELISA	Associated with aggressive disease course and poor prognosis. Can be used to assess the effectiveness of therapy	[51, 52]
Proliferation marker protein Ki-67 (Ki-67)	Protein marker of cell proliferation	Tumor bioptates / Immunohistochemical (IHC) or histologic examination	Assesses the rate of tumor growth and its aggressiveness	[53]
Annexin A2 (ANXA2)	A cell membrane associated protein involved in cell adhesion, proliferation and angiogenesis processes	Blood serum / ELISA	It is associated with more aggressive forms of the disease. Considered as a promising biomarker for prognosis and a target for targeted therapy	[54–59]
Genetic and epigenetic markers				
MicroRNA (miRNA)	Small RNA molecules regulating gene expressions: miR-21, miR-26, miR-122, miR-221/miR-222	Blood serum / PCR or NGS	Used in the diagnostics, prognosis, and evaluation of response to treatment	[60–65]
Circulating tumor DNA (ctDNA)	DNA fragments released from tumor cells into the blood circulation	Blood serum / PCR or NGS	Used for early diagnostics and monitoring of HCC recurrence	[66–71]
Beta-catenin (*CTNNB1*)	Mutations in this gene may be associated with tumor aggressiveness	Tumor tissue / PCR	It is used to identify molecular features and aggressiveness of HCC development	[72–75]
Cellular tumor antigen p53 (*TP53*)	The gene encoding the tumor suppressor protein p53	Tumor tissue / NGS	Associated with aggressive cancers and unfavorable outcomes	[76–78]
DNA methylation	Epigenetic changes in promoter regions of genes	Plasma, tumor tissue / Bisulfite PCR	Can be used for diagnostics and monitoring of HCC	[79]
Inflammation biomarkers				
C-reactive protein (CRP)	Inflammation biomarker	Blood plasma or serum / Immunochemiluminescent assay (ICLA)	Increased CRP levels are associated with inflammation and HCC progression	[80–84]
Interleukin-6 (IL-6)	Inflammatory cytokine	Blood serum / ELISA	Increased in HCC and associated with systemic inflammation and poor prognosis	[82, 84–86]

2.2. miR-122

Expression of miR-122 is specific to liver tissue. It acts as a tumor suppressor, playing an important role in the regulation of lipid and glucose metabolism in the liver [93]. A decrease in expression levels correlates with the development of HCC [94], and a number of studies have shown that it can be used as an independent prognostic factor for survival in HCC [95, 96].

2.3. miR-221/miR-222

Highly homologous miRNAs, depending on their expression levels, can act as oncogenes or tumor suppressors. In HCC, miR-221/miR-222 expression levels are significantly elevated; moreover, they correlate with a worse prognosis and increased tumor aggressiveness [97].

2.4. miR-26

miR-26 acts as a tumor suppressor in HCC. Expression levels are significantly reduced and correlate with an increase in the degree of tumor malignancy and a worse survival prognosis [98, 99].

Although the above considered markers have a significant potential in HCC diagnostics, there are a number of limitations associated with their possible use, such as specificity, sensitivity, stability, and clinical significance.

3. PROSPECTS

3.1. Diagnostic Models and Algorithms for HCC Diagnostics

Since new HCC biomarkers have been introduced into clinical practice for a long time, one of the promising approaches is the development of diagnostic algorithms that use existing data on the levels of known clinical markers. In 2014 for HCC diagnostics, Johnson et al. [100] proposed the GALAD (Gender, Age, AFP-L3, AFP, and Des-carboxy-prothrombin) model based on a combination of AFP, AFP-L3, and DCP, including data on gender and age. The study involved 670 patients: 331 HCC patients and 339 patients with chronic liver diseases without signs of oncology as a control. In this groups of patients the model after optimization of sensitivity and specificity showed a prediction accuracy (Area Under Curve, AUC) of 0.88 (95% confidence interval (CI), 0.85–0.91) regardless of the stage of the disease [100].

In 2016, in order to improve the accuracy of HCC diagnostics, the Doylestown Algorithm (DA) using logistic regression was proposed. It includes logarithmically transformed AFP values, as well as age, gender, alkaline phosphatase (ALP), and alanine aminotransferase (ALT) levels [101]. The study was conducted on the basis of electronic data of 360 patients with liver cirrhosis or HCC that developed in cirrhotic patients. The results have shown that DA increases the overall diagnostic efficiency by 10% as compared to the use of AFP alone. In independent testing performed in three different centers using 2700 patients, the algorithm improved the HCC detection rate from 4% to 20% as compared to AFP alone [101]. This model was later shown to have serious limitations associated with AFP levels below 20.0 ng/ml, and was therefore refined and named as Doylestown Plus. It includes three more potential HCC markers, namely fucosylated alpha-1-antitrypsin (A1AT), fucosylated kininogen (KNG1), and Golgi glycoprotein 73 (GP73). It was shown that DA with the addition of only one marker, KNG1, yielded better results (AUC 0.83) in the overall cohort, but inclusion of GP73 increased the overall individual performance (AUC 0.87) [102].

Based on the GALAD model, Yang et al. [103] proposed an improved version of this model known as GALADUS. It includes not only the GALAD model but also results of ultrasound examination [103]. The use of this model made it possible to achieve an AUC of 0.98 (95% CI, 0.96–0.99), and also to increase the sensitivity and specificity of HCC detection to 95% and 91%, respectively [103].

In 2022, for subsequent assessment of the accuracy of the above algorithms, the data obtained were analyzed in a prospective cohort of patients with Child-Pugh class A or B cirrhosis (408 patients) who were included in the HCC surveillance program between 2004 and 2006. Patient follow-up was terminated if one of the following events occurred: diagnosed HCC, liver transplantation, death, or study discontinuation [104]. Both Doylestown Plus and GALAD algorithms demonstrated higher sensitivity (79% and 72%, respectively) compared to the sensitivity of AFP alone (95% CI, 33.3–90.0). However, it should be noted that this study is limited by small sample sizes and wide CI and requires further investigation [104].

3.2. Development of Test Panels for HCC Diagnostics

Proteomic studies of proteins that determine the proteomic profile for each disease represent a relevant approach to search for potential biomarkers. The human proteome, characterized by heterogeneity and complex composition, consists of polypeptides with or without a certain set of modifications, which are known as protein species or proteoforms [79, 80, 86]. Information on specific fragments of the profile, the so-called protein signatures and the proteoforms that comprise them, can significantly facilitate the search for promising biomarkers. This approach can be used both to search for highly specific proteins secreted by the tumor in small quantities and to develop a panel of several proteins.

To date, there is no standardized panel for HCC screening. The main studies are focused on measuring serum AFP levels and instrumental methods. Therefore, already known HCC markers and their diagnostic improvements are actively studied. The most frequently studied combination of markers includes AFP, AFP-L3, and DCP [105–109]. At the same time, the possibilities of combination with other markers to increase diagnostic sensitivity are also separately considered [50, 110–113].

3.3. Proteoforms as a Source of Biomarkers

In addition to the development of panels of known biomarkers, proteoforms are also actively studied as they can represent highly specific markers of diseases. Proteoforms are formed due to single nucleotide polymorphism (SNP) or alternative splicing or post-translational modifications (PTM). This in turn leads to proteoform diversity and, as a consequence, to diversity of protein functions, their localization, activity, stability and interaction with other molecules. Many PTMs, such as glycosylation, phosphorylation, ubiquitination, etc., are known to be associated with various diseases [114]. A characteristic feature of cancer cells is aberrant glycosylation, which affects different stages of tumor progression. In the case of HCC, the most striking example of a proteoform that has been introduced into clinical practice is the glycosylated form of AFP (AFP-L3) [37].

In the case of other diseases, for example, neurodegenerative ones, the role of beta-amyloid peptide (Aβ), associated with the rapid progression of Alzheimer's disease (AD), is actively studied. It is known that Aβ hyperphosphorylation, leading to the formation of amyloid plaques, contributes to the development of AD. A recent study has shown that there are 33 proteoforms of Aβ associated with rapid progression of AD [115].

In the case of Parkinson's disease (PD), the promising diagnostic and prognostic biomarkers are proteoforms of alpha-synuclein, a protein encoded by the *SNCAB* gene. Common PTMs of α-synuclein include phosphorylation of Ser129, eight glycosylated Thr residues (positions 33, 44, 54, 59, 64, 72, 75, 81), and Ser87 [116, 117].

3.4. Bioinformatics Studies

In recent decades, bioinformatics analysis methods have become one of the key links in the search for potential biomarkers. In the context of the rapid growth of data volumes obtained due to modern technologies such as NGS, transcriptomics, proteomics, and metabolomics, bioinformatics research methods represent an effective tool for the systematic analysis of the obtained data. The use of bioinformatics methods allows integrating and analyzing data arrays, identification of new promising markers at various levels of biological organization. Modern databases (e.g., TCGA or GEO) contain information on genomic, transcriptomic, and proteomic profiles of tumors. Using bioinformatics methods it is possible to analyze these data sets and identify differences in gene/protein expression levels between normal and tumor tissues. This will allow creating a more extensive database of promising HCC markers, which in turn can significantly accelerate the identification of hidden patterns and relationships to create more accurate and personalized approaches to the treatment of malignant tumors [118–120].

CONCLUSIONS

Biomarkers play an important role in the fight against HCC, providing new opportunities for early detection, prognosis and development of targeted therapies. Despite significant progress in the study of HCC biomarkers, many issues remain unresolved. The search for HCC biomarkers is an important direction in improving the diagnostics, prognosis, and disease monitoring. Currently, traditional markers, such as AFP, have their limitations; this emphasizes the need to search for new markers with better diagnostic and prognostic characteristics. Potential biomarkers such as microRNA, changes in DNA methylation, specific protein expression, show significant potential in the early diagnostics of HCC. Such markers can provide a more detailed understanding of the molecular mechanisms of the disease and improve a personalized approach to its treatment. In addition, the introduction of bioinformatics and machine learning methods opens new horizons for data integration and personalization of the treatment. However, despite the promising results of preliminary studies, additional clinical trials are needed to test their reliability and practical value, as well as to develop combined approaches using several markers to improve diagnostic accuracy and prognosis. It is especially important to integrate new biomarkers into existing diagnostic and therapeutic regimens, which may ultimately lead to improved treatment and reduced mortality from this type of cancer.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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БИОМАРКЕРЫ ГЕПАТОЦЕЛЛЮЛЯРНОГО РАКА: СОСТОЯНИЕ И ПЕРСПЕКТИВЫ

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Гепатоцеллюлярная карцинома или гепатоцеллюлярный рак (ГЦР) представляет собой один из наиболее распространённых и агрессивных видов первичных злокачественных новообразований печени. Этот вид рака составляет до 90% всех первичных опухолей печени и занимает третье место среди причин смертности от онкологических заболеваний в мире. Несмотря на достижения современной медицины, диагностика и лечение ГЦР остаются сложными задачами, особенно на поздних стадиях, когда прогноз для пациента значительно ухудшается, а вариант выбора лечения весьма ограничен. С момента обнаружения Ю.С. Татариновым в 1963 году эмбрионспецифического α-глобулина в крови людей, болеющих первичным раком печени, впоследствии получившего название альфа-фетопротеин (АФП), прошло более половины столетия, но, к сожалению, количество специфичных и чувствительных биомаркеров для ГЦР остаётся весьма ограниченным. В связи с этим, многие научные работы посвящены поиску и изучению потенциальных биомаркеров ГЦР, имеющих существенное значение для ранней диагностики, прогноза и разработки новых терапевтических стратегий. Одним из перспективных подходов к изучению молекулярных механизмов возникновения ГЦР и поиску биомаркеров являются протеомные исследования. Выявление специфических белковых профилей, характерных для опухолевых клеток, может способствовать идентификации новых биомаркеров, которые могут быть использованы не только для раннего выявления заболевания, но и для мониторинга его прогрессирования, оценки ответа на терапию и предсказания клинического исхода. В данном обзоре рассмотрены современные достижения по поиску потенциальных биомаркеров ГЦР, а также перспективы их клинического использования.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: гепатоцеллюлярный рак; биомаркеры; белковые профили; протеоформы

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