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GENETIC MECHANISMS OF HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) is the most common form of primary liver malignancy. This form of liver cancer is characterized by rapid progression and poor survival prognosis. Understanding the genetic mechanisms that underlie HCC is of great importance for developing new diagnostic and therapeutic approaches.*

The purpose was to *study the genetic factors in the development of hepatocellular carcinoma.*

Methods: *This review used various sources of literature, including scientific articles and reviews. A review of the published results of scientific and clinical studies for 2018-2023 was conducted from the PubMed, Cochrane library, Scopus and Web of Science databases, using the keywords "hepatocellular carcinoma," "genes," "genetic predictors". Inclusion of articles in the review was based on their content and relevance to the research topic.*

Results: *Various genes associated with hepatocellular carcinoma were analyzed, including genes frequently mutated in HCC, as well as genes that play a role in the regulation of cell growth, apoptosis, metastasis, and invasion. Epigenetic changes such as DNA methylation and chromatin modifications have been investigated. The roles of microRNAs, long non-coding RNAs, circulating microparticles and other biomarkers in the diagnosis and prognosis of HCC were also reviewed.*

Conclusion: *The materials and methods used in this review allowed us to cover a wide range of genes and molecular mechanisms associated with hepatocellular carcinoma. Understanding these mechanisms plays an important role in the development of new diagnostic and therapeutic approaches to combat this dangerous form of liver cancer. Further research in this area will help expand our knowledge base and lead to improved HCC treatment for patients.*

Keywords: *hepatocellular carcinoma, liver cancer, gene, risk factor.*

Introduction: Primary liver cancer, of which 75-85% of cases are hepatocellular carcinoma (HCC), is the sixth most common cancer [1, 2] and the third leading cause of cancer mortality worldwide [3, 4]. About 906,000 cases of primary liver cancer were registered in 2020 and about 830,000 people died from that disease, with an incidence-to-mortality ratio approaching 1.

The incidence of HCC is heterogeneous worldwide due to varying prevalence of major risk factors. An estimated 72% of cases occur in Asia (more than 50% in China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% in Latin America, and 0.5% in Oceania [5].

The highest incidence rates of primary liver cancer are found in Asia, where the disease is the fifth most common cancer and the second leading cause of cancer death. However, there are large differences across individual geographic regions in Asia. According to GLOBOCAN 2020, Mongolia has the highest age standardized rate (ASR) of both incidence and mortality (85.6 and 80.6/100,000), while China still accounts for the majority (62.4%) cases in Asia, followed by Japan (7.0%), India (5.3%), Thailand (4.2%), and Vietnam (4%) [6].

Among men, this cancer ranks fourth in incidence and second in cancer mortality. Men are at higher risk of developing liver cancer than women. The global incidence ratio of HCC among men and women is 2.8:1 [7].

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of HCC. In the next decade, the prevalence of NAFLD is expected to increase to 56%, which, in turn, will lead to an increase in the number of patients with HCC [8].

HCC is a serious medical problem worldwide. This tumor arising from hepatic cells (major liver cells) is characterized by rapid progression, and its treatment is limited by available methods.

HCC is an aggressive liver cancer that negatively affects the health and survival of patients. Its occurrence is due to different factors including viral infections (hepatitis B and C), NAFLD, excessive alcohol consumption, and some genetic diseases. Studies of the genetic grounds for HCC promote deeper understanding of molecular mechanisms of this tumor development and provide the basis for the development of new approaches to diagnosis, prognosis, prevention, and treatment.

HCC development is associated with many genetic abnormalities which may be involved in several pathogenic mechanisms such as cell proliferation, angiogenesis processes, metastasis and immune system suppression. In recent years, significant progress has been made in identifying and understanding genetic changes that play a key role in the development of HCC. Modern genome research methods such as DNA and RNA sequencing, allowed revealing various genetic mutations, gene

expression changes and epigenetic modifications associated with HCC.

The purpose was to study the genetic factors in the development of hepatocellular carcinoma. The paper reviews major genetic changes, such as mutations in specific oncogenes and tumor-related genes, as well as changes in signaling pathways, epigenetic modifications and other factors that may contribute to the development of HCC. Understanding these genetic changes can help develop new strategies for HCC diagnostics, prognosis, and treatment to open up prospects for improving survival and quality of life of patients.

Materials and methods: The search in PubMed, Cochrane library, Scopus, and Web of Science databases covered articles containing such keywords as "hepatocellular carcinoma," "gene," and "genetic predictors."

A total of 27 973 articles were selected using keywords; 13 628 of them were full-text open-access articles, and 5 411 sources were published in 2018-2023. Inclusion criteria: observational studies, systematic reviews and meta-analyses. Exclusion criteria: brief reports, newspaper articles, abstracts and personal communications.

Results: In recent years, genetic studies revealed a number of gene polymorphisms that promote (e.g., PNPLA3 and TM6SF2) and prevent (ego, HSD17B13) the development of NAFLD [9-11]. Among those factors, the genetic variant *PNPLA3 rs738409 I148M* replicated most consistently in Asian populations [12]. Notably, the genetic variant *PNPLA3* is more common among East Asian patients than among Caucasian and black patients. This may partly explain the relatively high prevalence of NAFLD in Asia despite less severe metabolic conditions. In some cohort studies, these gene polymorphisms were related to NAFLD and its advanced stages such as liver fibrosis and cirrhosis, which, in turn, leads to an increased risk of HCC. In a multi-center European study, they combined the *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7,* and *HSD17B13* genes to form polygene risk indicators to predict the development of HCC in patients with NAFLD and in the general population [13]. Though most of those genetic markers have been studied in the Asian population, data on HCC associated with NAFLD are largely lacking. Besides, the prevalence and functional significance of genetic markers may vary in Asian populations. I.e., the *TM6SF2 rs58542926 E167K* variant is rare in all populations, but its prevalence is similar in Caucasian and Asian patients and lower in Hispanic and African Americans [14]. The *rs641738* variant adjacent to the *MBOAT7* gene is more common in Caucasians compared to the Chinese and is less correlated with liver inflammation in patients with chronic hepatitis B (CHB) [15]. However, in a study in Hong Kong, both histological steatosis of the liver and the *rs2854116 APOC3* variant were associated with the incidence of HCC in patients with CHB [16]. The *APOC3* gene polymorphism was initially shown to be associated with NAFLD in Asian Indians.

The role of epigenetics (e.g., DNA methylation, modification of histones and non-coding RNAs) has been extensively studied with regard to HCC. Emerging data suggest that these processes are also involved in the NAFLD pathogenesis [9,10].

The next most common genetic change in HCC is the *TP53* gene mutation. The *TP53* gene plays a key role in cell cycle regulation, apoptosis, and DNA repair. Mutations of the *TP53* gene in HCC are usually associated with a more aggressive form of the tumor and a poor prognosis. Studies suggest that presence of the *TP53* gene mutations may be a predictor for survival of patients with HCC, indicating a more unfavorable outcome [17, 18]. The *TP53* gene mutations may also be associated with resistance to certain forms of HCC treatment, including chemotherapy and the drugs belonging to the inhibitors of the epithelial growth tissue factor. It is associated with the fact that the normal function of the *TP53* gene plays an important role in regulation of the cellular responsibility in cancer treatment.

Another most common genetic changes in HCC are mutations in the *CTNNB1* gene, which can cause the β-catenin activation, which in turn may contribute to abnormal activation of Wnt/β-catenin signaling. This can lead to improper regulation of cell growth and, as a result, to HCC development [19, 20].

Several studies have also found an association between *TERT* gene polymorphisms and an elevated risk for HCC development [21-23]. Polymorphisms are changes in the genetic sequence that can affect the gene function and create conditions for development of certain diseases. This makes the *TERT* gene and telomerase the potential targets for development of new methods for HCC diagnostics and treatment.

According to the researchers, mutations in the *ARID1A* gene can lead to the loss of a protein function that initiates a series of changes in the gene's expression, that support the normal cell growth and cell reproduction. As a result, conditions that contribute to the development of liver cancer may occur [24-26].

Other studies have also detected an association between changes in *AXIN1* gene expression and prognosis for patients with HCC [27, 28]. Mutations in the *AXIN1* gene play the role in activation of the Wnt/β-catenin signaling pathway. One of the most well-known links between the *AXIN1* gene and HCC is that the gene plays the tumor suppressor role. This means that the *AXIN1* gene can inhibit the tumor growth and development by regulating the Wnt/β-catenin signaling pathway. Mutations in the *AXIN1* gene can deprive it of its tumor suppressor effect and contribute to the HCC development.

Some studies suggest that overactivation of the *NFE2L2* gene due to mutations or deregulation may contribute to the HCC formation, and is associated with poor patient survival prognosis. Higher levels of the *NFE2L2* gene expression may also be associated with resistance to treatment and HCC chemoresistance [29].

The *HNF1A* gene mutations can lead to various pathological conditions, including genetic disorders relatable to liver [30]. The *HNF1A* gene encodes a protein that plays an important role in regulation of liver function.

Some microRNAs may exhibit lower or increased expression in liver cancer cells compared to normal cells. This indicates their possible role in regulation of processes associated with HCC. Some *MIRNA*s, e.g., miR-21, miR-221/222,

and miR-122, have been extensively studied in the context of HCC [31, 32]. These have been associated with various aspects of HCC, including disease course, tumor invasiveness, drug resistance, and regulation of tumor-related signaling pathways. The stable expression and diverse functions of microRNA in the human genome make them candidates as the diagnostic biomarkers of early cancer [33-35].

HCC is characterized not only by rapid tumor growth, but also by intensive angiogenesis, and the *VEGFA* gene is considered one of the key regulators of that process. An elevated level of *VEGFA* expression is commonly seen in the HCC tumor and is an indicator of a poor prognosis, since it is associated with more aggressive and rapidly progressing type of cancer. Some studies have already shown that the *VEGFA* inhibitors may be effective in treatment of HCC, as they were able to reduce the angiogenesis and slow down the tumor growth [29].

The specified genes and molecular mechanisms associated with them continue to be actively studied in the context of HCC. Understanding of their role and interaction could help in developing of new approaches to diagnostics, prognosis, and treatment of the disease.

Discussion: Effective diagnostic markers for HCC early diagnostics are still lacking. The review of relevant studies identified several key genes whose mutations were considered important markers for HCC. One of these genes is - *TP53*, which is responsible for regulation of the cell cycle and involved in the process of apoptosis (programmed cell death). There is a high incidence of *TP53* mutations in patients with HCC, suggesting its important role in the hepatic cancer development. However, also the TP53 gene mutation, which is a tumor suppressor gene, is found not only in HCC [36], but also in many other types of cancer, such as esophageal carcinoma [37], gastric cancer [38], colorectal cancer [39], etc.

Another gene often associated with HCC is the *CTNNB1* gene, which encodes the β-catenin protein and regulates the Wnt signaling pathway. Mutations in the *CTNNB1* gene activate this pathway in 30–50% of cases [21]. The *CTNNB1* gene mutations are detected predominantly in the early stages and in HCC associated with VHC [31]. The *CTNNB1* gene mutates most frequently; its mutations (mainly, in the promoter region) are found in up to 60% of tumors [40].

Apart from the *TP53*, *CTNNB1* and *TERT* genes, the review identified other genes that play an important role in the genetic mechanisms of HCC. Mutations in these genes or changes in their expression can contribute to the development and progression of HCC [40].

Conclusions: Genes play an important role in the development of HCC, the most common form of hepatic cancer. Researches in that area have made it possible to establish the link between certain genetic mutations and the HCC development. Genome studies permit to identify specific genetic abnormalities that elevate the risk of HCC development. Some of these mutations relate to genes that regulate the cell cycle, apoptosis, and metastasis spread, which are significant for understanding the molecular mechanisms of that type of cancer.

Mutations in the *TP53* and *NFE2L2* genes are among the key genetic mutations associated with HCC. These genes act as tumor suppressors and control cell reproduction and survival. The mutations in genes responsible for growth of new vessels (*VEGFA*) have also been identified.

Understanding the genetic characteristics of HCC allows us to develop new strategies for prevention, diagnosis and therapy, and also opens up prospects for improving survival prognosis and reducing the incidence of this type of cancer. However, further research is needed to better define the role of genes in the development of HCC and to expand our knowledge of the molecular mechanisms underlying this disease. This will increase the efficiency of diagnosis and treatment and will contribute to the development of an individual approach to each patient.

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АНДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫҚ КАРЦИНОМАНЫҢ ГЕНЕТИКАЛЫҚ МЕХАНИЗМДЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Гепатоцеллюлярлық карцинома (ГЦК) - бауырдың біріншілік қатерлі ісігінің ең көп таралған түрі. Бауыр ісігінің бұл түрі тез прогрессиямен және нашар өмір сүру болжамымен сипатталады. ГЦК негізінде жатқан генетикалық механизмдерді түсіну диагностикалық және емдеудің жаңа тәсілдерін дамыту үшін үлкен маңызға ие.*

Зерттеудің мақсаты *– гепатоцеллюлярлық карциноманың дамуындағы генетикалық факторларды зерттеу.*

Материалдар мен әдістері: *Бұл шолуда әртүрлі әдебиет көздері, соның ішінде ғылыми мақалалар мен шолулар пайдаланылды. Әдебиеттерді іздеу PubMed, Cochrane кітапханасы, Scopus және Web of Science дерекқорларында «гепатоцеллюлярлық карцинома»,*

«гендер» түйінді сөздері арқылы жүргізілді. Мақалаларды шолуға қосу олардың мазмұны мен зерттеу тақырыбына сәйкестігіне негізделді. Іздеу тереңдігі 5 жыл (2018-2023) болды.

Нәтижелері: *Гепатоцеллюлярлық карциномамен байланысты әртүрлі гендер, соның ішінде ГЦК жиі мутацияланған гендер, сондай-ақ жасуша өсуін, апоптозды, метастазды және инвазияны реттеуде рөл атқаратын гендер талданды. ДНҚ метилденуі және хроматин модификациялары сияқты эпигенетикалық өзгерістер зерттелді. Сондай-ақ микроРНҚ-лардың, ұзақ кодталмаған РНҚ-лардың, айналымдағы микробөлшектердің және ГЦК диагностикасы мен болжамындағы басқа биомаркерлердің рөлдері қарастырылды.*

Қорытынды: *Осы шолуда қолданылған материалдар мен әдістер гепатоцеллюлярлық карциномамен байланысты гендер мен молекулалық механизмдердің кең ауқымын қамтуға мүмкіндік берді. Бұл механизмдерді түсіну бауыр ісігінің осы қауіпті түрімен күресудің жаңа диагностикалық және емдік тәсілдерін әзірлеуде маңызды рөл атқарады. Осы саладағы әрі қарай зерттеулер біздің білім қорымызды кеңейтуге көмектеседі және пациенттер үшін ГЦК емдеудің жақсаруына әкеледі.*

Түйінді сөздер: *гепатоллюлярлық карцинома, бауыр ісігі, ген, қауіп факторы.*

АННОТАЦИЯ

ГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЫ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) представляет собой наиболее распространенную форму первичного злокачественного опухолевого процесса в печени. Эта форма рака печени характеризуется быстрым прогрессированием и плохим прогнозом выживаемости. Понимание генетических механизмов, которые лежат в основе ГЦК, имеет большое значение для разработки новых диагностических и терапевтических подходов.*

Цель исследования *– изучение генетических факторов развития гепатоцеллюлярной карциномы.*

Материалы и методы: *В данном обзоре были использованы различные источники, включая научные статьи и обзоры. Был проведен обзор результатов научных и клинических исследований, опубликованных за 2018-2023 годы и индексированных в базах данных PubMed, Cochrane library, Scopus и Web of Science, использовались ключевые слова «гепатоцеллюлярная карцинома», «гены», «генетические предикторы». Включение статей в обзор происходило на основе их содержания и релевантности для темы исследования.*

Результаты: *В ходе исследования был проведен анализ различных генов, связанных с ГЦК, включая гены, часто мутированные при ГЦК, а также гены, играющие роль в регуляции клеточного роста, апоптозе, метастазировании и инвазии. Несмотря на более раннее выявление влияния генов, основные исследования были проведены в последние годы. Были исследованы эпигенетические изменения, такие как метилирование ДНК и модификации хроматина. Также были рассмотрены роли микроРНК, длинных некодирующих РНК, циркулирующих микрочастиц и других биомаркеров в диагностике и прогнозировании ГЦК.*

Заключение: *Материалы и методы, использованные в данном обзоре, позволили охватить широкий спектр генов и молекулярных механизмов, связанных с ГЦК. Понимание этих механизмов играет важную роль в разработке новых диагностических и терапевтических подходов для борьбы с этой опасной формой рака печени. Дальнейшие исследования в этой области помогут расширить нашу базу знаний и привести к улучшению лечения ГЦК.*

Ключевые слова: *гепатоцеллюлярная карцинома (ГЦК), рак печени, ген, факторы риска.*

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