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ROLE OF MicroRNAs 223, 155, AND 17~92 IN THE REGULATION OF MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS) IN THE PATHOGENESIS OF OBESITY-ASSOCIATED BREAST CANCER

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ABSTRACT

Relevance: *Breast cancer (BC) is a pressing global health dilemma due to its high prevalence worldwide. According to the World Health Organization (WHO), more than 2.3 million cases of BC occur each year, and BC is the first leading cause of female cancer deaths globally. Evidence indicates that obesity increases the risk of developing BC, and myeloid-derived suppressor cells (MDSCs) play a significant role in the pathogenesis of both BC and obesity. The primary function of MDSCs is tissue repair and wound healing, which helps prevent uncontrolled inflammation and maintain homeostasis as part of the immune response. However, MDSCs can be reprogrammed by pathological processes due to long-term tissue damage caused by chronic inflammation and cancer, leading to their prolonged expansion and enhanced immunosuppressive activity. The pathological process of obesity-associated and MDSC-associated BC progression remains poorly understood at the molecular level. There is considerable interest in studying microRNAs due to their regulatory roles in various biological processes in different cell types. Recent studies have begun to unravel the crosstalk between microRNAs and MDSCs in cancer.*

The study aimed to *provide summarized data to reveal the mechanisms by which microRNAs influence the activity of MDSC and the course of obesity-associated BC.*

Methods: *We conducted a comprehensive literature search on the web and in Medline (PubMed) u Google Scholar databases until June 7, 2024, in the areas «breast cancer» and/or «obesity» and/or «MDSC» and/or «microRNA.» Based on the literature analysis, microRNA-223, -155, and -1792 were selected as the most significant objects.*

Results: *This review presents data on the expression dynamics of major signal microRNAs (microRNA-223, -155, and -17~92), focusing on their roles in the pathogenesis of BC, obesity, and MDSC regulation; we also summarized and discussed the regulation of MDSCs in the obesity-associated BC by microRNA-223, -155, and -17~92.*

Conclusion: *Based on the literature data analysis, miR-223, -155, and -17~92 may be promising diagnostic and therapeutic cancer biomarkers, including BC, associated with pathological metabolic disorders and impaired functional activity of MDSC.*

Keywords: *microRNA, breast cancer, obesity, myeloid-derived suppressor cells (MDSC).*

Introduction: Breast cancer (BC) is a pressing global health dilemma due to its high prevalence worldwide. Breast cancer ranks first in the world in terms of incidence in women, affecting women of any age after puberty, and the incidence rate increases with age. For example, during post-menopause, BC is the first leading cause of female cancer deaths globally, accounting for 23% of all cancer deaths [1]. It is also important to note that 0.5–1% of all breast cancer cases occur in male patients [2]. In addition, data obtained to date indicate that there is a risk of developing breast cancer in people diagnosed with obesity [3]. According to the World Health Organization, 2.3 million women were diagnosed with BC in 2022, with more than 670,000 deaths worldwide [2]. According to the Ministry of Health of the Republic of Kazakhstan (MoH RK), in Kazakhstan, breast cancer is diagnosed annually in an average of 5,000 patients and up to 1,200 deaths [4]. At the same time, according to statistics from the Ministry of Health of the Republic of Kazakhstan, at the beginning of 2024, more than 16 thousand people (10,392 women; 5,841 men) with a confirmed diagnosis of obesity were registered at the dispensary [5].

Breast cancer is a complex disease characterized by a high degree of heterogeneity. Its classification is based on its histological stratification, mainly depending on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (ERBB2/HER2) [6]. The pathogenesis of obesity and breast cancer involves common factors: insulin-like growth factor-I, sex hormones, and cytokines produced by adipocytes.

These factors are related to the endo- and paracrine dysregulation of adipose tissue observed in obesity. Moreover, when neoplastic cells penetrate stromal compartments rich in adipose tissue, adipocytes function as endocrine cells, forming a tolerogenic tumor microenvironment that promotes tumor development and progression. The adipocyte activity is associated with the risk of developing cancer and the percentage of deaths from it in obese people [3].

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of immature myeloid cells with an impaired ability to differentiate into monocytes, macrophages, granulocytes, and dendritic cells. MDSC are defined by the phenotype CD11b+Gr1+ and Lin-HLA-DR-CD33+ in mice and CD11b+CD14+CD33+ in humans. The primary function of MDSC is to prevent uncontrolled inflammation and maintain immune homeostasis [7]. However, MDSC reprogramming occurs through pathological processes such as long-term tissue damage caused by chronic inflammation, cancer, extensive tissue damage, or chronic infections, leading to long-term expansion and enhanced immunosuppressive function of MDSCs. Obesity induces chronic inflammation through cytokines, chemokines, and adipokines, stimulating the immunosuppressive activity of MDSCs. In addition, some of these soluble mediators contribute to the progression of malignancies [8]. In addition, MDSC is also associated with a poor prognosis of BC. The proportion of MDSC in the peripheral blood of patients with breast cancer is significantly higher compared to healthy people, and the level of MDSC positively correlates with the proportion of metastases [9].

Despite the available data, the molecular mechanisms of MDSC regulation in the pathological process of obesity-related breast cancer remain poorly understood. In this regard, there is currently significant interest in studying microRNAs due to their regulatory function in various biological processes occurring in multiple types of cells. More than 2,500 microRNAs have been identified in humans, which act as critical mediators of transcriptional and post-transcriptional gene regulation, thereby maintaining cellular balance and functional activity of cells. Over the past two decades, miRNAs have been involved in the pathogenesis of several human diseases, including breast cancer and obesity [10].

The study aimed to provide summarized data to reveal the mechanisms by which microRNAs influence the activity of MDSC and the course of obesity-associated BC.

Materials and Methods: We analyzed scientific papers in the Medline (PubMed) and Google Scholar databases to search for research results on the role of microRNAs in regulating MDSC and the pathogenesis of obesity-related breast cancer. The search terms used were "breast cancer," "obesity," "MDSC," and "microRNA." We analyzed data sources in databases – 186; other sources - 3. As a result of an analysis of the literature in three main areas, the most significant research objects were selected - microRNA-223, -155, and -17~92; data from studies on microRNA data were included in the review (n = 88). After excluding sources with duplicate data and checking the quality of studies, the evaluation included 47 sources from databases and three sources containing statistical data on the prevalence of diseases. Search is limited to June 7, 2024.

Results:

Characteristics of microRNA

MicroRNAs are characterized as small, non-coding RNA molecules that regulate gene expression by inhibiting protein translation and promoting the breakdown of messenger RNA (mRNA). Since their discovery, miRNAs have been characterized in large numbers, and advances have been made in understanding their functions and applications in research and clinical practice [10].

The biogenesis of microRNAs is generally considered a multistage process that begins in the nucleus and ends in the cytoplasm. The first stage is characterized by the transcription of microRNAs predominantly by RNA polymerase II, mapping, splicing, and polyadenylation. The result of these processes is the formation of primary microRNA molecules (pri-microRNA), characterized by one or more hairpin structures [11]. Pri-miRNA is then processed in the nucleus by RNase and its cofactor DGCR8 into microRNA precursors - pre-miRNAs, consisting of 70-100 nucleotides, which are then transported into the cytoplasm using exportin-5 through nuclear pores [12]. In the cytoplasm, RNase converts pre-microRNA into a double-stranded RNA duplex consisting of a microRNA strand and its complementary sequence. Helicase enzymes unwind this duplex into a single-stranded mature miRNA, which is then incorporated into the RNA-inducible silencing complex (RISC) containing the Ago-2 protein [13]. This inclusion directs the RISC complex to the 3' untranslated region (3'UTR) of the target mRNA, resulting in cleavage of the mRNA in the case of high sequence homology or inhibition of translation, the latter mechanism more common in mammals. Subsequently, mature miRNAs play a crucial role in post-transcriptional gene silencing by binding to RISC and partially complementary sequence motifs in target mRNAs, predominantly located in the 3'UTR region [14].

Since a single miRNA can target several hundred mRNAs, dysregulation of miRNA expression can affect multiple transcripts and significantly impact signaling pathways associated with various pathological processes. The complex incorporation of miRNAs into cellular regulatory networks may represent an Achilles' heel, where dysregulation of a small subset of miRNAs can significantly alter gene expression patterns and potentially lead to cell transformation [15].

Usually, microRNAs act as important feedback components, ensuring the stability of essential biological processes through their buffering effect. By modulating

protein synthesis, microRNAs increase the accuracy of gene expression, ensuring the maintenance of proteins at a physiologically optimal level [15].

Although many aspects of miRNA function are not fully understood, miRNAs play critical roles in biological processes, including stem cell division, cell proliferation, cell cycle progression, apoptosis, differentiation, and metabolism. These functions are also involved in cancer pathogenesis, making miRNAs promising targets for therapy [15].

MicroRNA-223

One of the essential signaling microRNAs is microRNA-223, first discovered in 2003 using quantitative polymerase chain reaction [16]. This microRNA is located in the q12 locus of the X chromosome, is highly conserved, and is believed to play a potential role in significant physiological changes in the body [17]. The miR-223 has been shown to act as an oncogene in several cancers, including T-cell acute lymphoblastic leukemia, leukemia, breast, gastric, liver, and prostate cancers. Still, it is a tumor suppressor in acute myeloid leukemia and cervical and small-cell cancers. Lung cancer [18-21]. MicroRNA-223 plays a vital role in processes such as proliferation and invasion of cancer cells [17]. Proliferation and invasion of breast cancer cells are enhanced after the transfer of miR-223 into cells [22]. Another study showed that ectopic expression of miR-223 can inhibit the invasion, migration, growth, and proliferation of breast cancer cells [23]. In 2021, T. Du et al. found that the transcription level of miR-223 was significantly higher in breast cancer cells than in normal breast cells. In addition, they found that transfection of miR-223 inhibitor into cells significantly suppressed miR-223 expression. When miR-223 was inhibited, the carcinogenic activity of tumor cells was markedly reduced while the apoptosis rate increased. The miR-223 may be essential in breast cancer cell proliferation, metastasis, and invasion [17].

In addition to its role in carcinogenesis, miR-223 is a crucial regulator of MDSC maturation/differentiation and their functional activity [24]. It has been shown that miR-223 is predominantly expressed in hematopoietic tissues, and its expression is also bone marrow-specific. In contrast, the expression of miR-223 in bone marrow cells is limited to myeloid cell lines. MicroRNA-223 was subsequently found to be an essential modulator of myeloid differentiation in humans. In a model of granulocyte differentiation, it was shown that overexpression of miR-223 increases the number of cells transitioning to a granulocyte-specific cell lineage.

In contrast, the knockdown of miR-223 has the opposite effect. Further analysis of miR-223 expression revealed an exciting regulatory loop involving two known regulatory proteins, CCAAT enhancer binding protein (C/EBP) and nuclear factor I A (NFI-A). Notably, these two transcription factors compete for binding to the miR-223 promoter. In this case, the NFI-A factor ensures weak expression of microRNA-223 before the differentiation process begins. During differentiation, the transcription factor C/EBP, which induces higher expression of microRNA-223, replaces the transcription factor and suppresses the post-transcriptional expression of NFI-A. The microRNA-223 enters an autoregulatory feedback loop, controlling its expression and enhancing granulocyte differentiation [25].

The role of miR-223 in obesity as a regulator of developing myeloid cells into macrophages in adipose tissue is limited. The microRNA-223 regulates the polarization of adipose tissue-resident macrophages by targeting the transcription factor Pknox1, which, in turn, leads to the suppression of nuclear factor kappa B (NF-κB) and N-terminal kinase c- Jun (JNK) and stimulates the response of adipocytes to insulin stimulation [26, 27]. Increased expression of miR-223 in subcutaneous adipose tissue in obesity has also been reported. Moreover, miR-223 expression has been shown to increase in obesity not only in subcutaneous adipose tissue but also in white adipose tissue in obesity [28].

We can conclude that miR-223 plays an essential role in the pathogenesis of breast cancer and obesity and the functional activity of MDSCs. This demonstrates the importance of clinical studies of this miRNA in regulating cellular functions and metabolism.

MicroRNA-155

MicroRNA-155 is processed from the primary transcript of the B-cell integration cluster (BIC) located on chromosome 21. It was first identified as a promoter of inflammation and activation of expressed oncogenic microRNAs in many human cancers. MicroRNA-155 is predominantly expressed in the thymus and spleen and is an essential biomarker for various diseases. T.C. Ivkovic et al. found that miR-155 overexpression regulates several cancer-related pathways involved in uncontrolled cell growth, invasion, migration, stemness, and angiogenesis [29]. MicroRNA-155 has also been shown to be one of the critical regulators of inflammation and immune response. A study by Li L. and colleagues showed that microRNA-155 is actively involved in the expansion of MDSC in both granulocyte subpopulations and monocytes. They found that high levels of microRNA-155 expression characterized bone marrow MDSCs and spleen MDSCs from tumor-inoculated mice. The effect of miR-155 on MDSCs is associated with STAT3 activation. Moreover, miR-155 deficiency in macrophages and MDSCs has been shown to promote tumor growth by enhancing the immunosuppressive functions of these cells [30].

The miR-155 was first identified as an oncogenic miRNA. The role of this miRNA in carcinogenesis and disease progression has been demonstrated in various hematological malignancies and solid tumors. For example, increased expression of microRNA-155 is characteristic of breast cancer, oral cavity, liver, lung, pancreas, and prostate cancers [31-36]. However, there is some evidence

that expression of miR-155 by cancer cells is associated with improved overall survival in patients with several types of cancer, including breast cancer, colorectal cancer, and melanomas [37–39]. Thus, conducting a retrospective analysis, J. Wang et al. showed a correlation between increased levels of microRNA-155 expression and favorable antitumor immune infiltration and prognosis of patients with breast cancer. There are conflicting reports regarding the role of miR-155 in the development and progression of breast cancer. For example, it has been demonstrated that the expression level of miR-155 in breast cancer is associated with high-grade, advanced-stage metastasis and invasion [40]. However, in a large case series of triple-negative breast cancer (TNBC), it was found that high expression of miR-155 was associated with the homologous recombination repair process by influencing the RAD51 recombinase, and, as a consequence, was associated with better overall survival of patients [37].

In addition to being identified as an oncogenic miRNA and a regulator of the immune response, miR-155 regulates the development and maintenance of obesity through its effects on adipogenic and inflammatory processes. First, miR-155 has been demonstrated to alter adipocyte differentiation toward white rather than brown adipose tissue [41]. Secondly, miR-155 has been shown to target RNAs that control lipolysis, the dysregulation of which may affect the energy storage process in adipocytes [42]. The miR-155 plays an essential role in adipose tissue accumulation by stimulating pro-inflammatory factors. E. Karkeni et al. demonstrated that overexpression of miR-155 in adipocytes leads to increased secretion of various chemokines that promote the recruitment of leukocytes into adipose tissue and the development of inflammation [43]. The effects of microRNA-155 listed above aggravate the course of obesity.

MiR-155 is a multifunctional miRNA involved in carcinogenesis, immune response, and metabolic processes associated with obesity.

MicroRNA 17~92

In 2004, a new gene called chromosome 13 open reading frame 25 (C13orf25) was discovered in cells from 70 lymphoma patients. This gene contains an 800-nucleotide transcript of the miR-17~92 cluster, encoding six microRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1. The miR-17~92 cluster and its two paralogues encode a total of 15 different miRNAs, conventionally divided based on primer sequence similarity into four families: the miR-17 family, the miR-18 family, the miR-19 family, and the miR-92 family. The miR-17 family includes 6 miRNAs: miR-17-5p, miR-20a-5p, miR-20b-5p, miR-93-5p, miR-106a-5p and miR-106b-5p based on the AAAGUG nucleotide sequence. The miRNA-18 family includes 2 microRNAs with the nucleotide sequence AAGGUG. MicroRNA-19a-3p and microRNA-19b-3p are members of the miRNA-19 family with the nucleotide sequence GUGCAA. The miR-92 family consists of three miRNAs: miR-92a-3p, miR-25-3p, and miR-363-3p, with the nucleotide sequence AUUGCA [44].

It has been previously demonstrated that miRNA-17-5p and miRNA-20a regulate the suppressive potential of MDSCs by regulating STAT3 expression. Moreover, transfection with miRNA-17-5p or miRNA-20a significantly reduces the production of reactive oxygen species (ROS) and H2O2, which STAT3 regulates. A decrease in the expression of these miRNAs under the influence of tumor-associated factors and suppression of antigen-specific CD4+ and CD8+ T-cell response as a result of ectopic expression of miRNA-17-5p or miRNA-20a in MDSCs were also shown [45]. In addition to regulating the immune response, the miRNA-17~92 cluster plays a significant role in oncogenic processes. Amplification of the genomic locus miRNA-17~92 is observed in malignant neoplasms of the hematopoiesis: breast cancer, lung cancer, colon cancer, prostate cancer, pancreas cancer, thyroid cancer, bladder cancer, stomach cancer, liver cancer, and lymphoma [44, 46]. Members of the miRNA-17~92 cluster with different maturation levels play various roles in cancer pathogenesis [44]. High levels of expression of mature miRNA-20a are characteristic of leukemia and breast cancer cells. Moreover, increased expression of miRNA-17~92 is observed in TNBC, while decreased expression of this cluster is described in estrogen receptor-positive breast cancer (ERBC) [47]. It was also shown that ectopic expression of miRNA-17~92 suppresses cell proliferation in ERBC while it promotes tumor cell growth and invasion in TNBC [44].

Few studies describe the role of the microRNA-17~92 cluster in the pathogenesis of obesity. To date, limited data have been obtained on the role of microRNA-18a in the development of fatty tissue. However, miR-18a has been shown to play a significant role in the polarization of macrophages toward the pro-inflammatory M1 lineage in adipose tissue. Overexpression of this miRNA in obesity may promote increased production of pro-inflammatory cytokines (e.g., interleukins 1β and 6) and exacerbate adipose tissue dysfunction despite adequate estrogen levels. Interestingly, microRNA-18a also affects the regulation of ER1 expression in tumor cells [48]. It was also previously shown that high levels of expression of this microRNA are associated with increased proliferation and worse prognosis in ERBC. A significant correlation between ER1 mRNA levels and miR-18a concentrations in subcutaneous adipose tissue was found only in premenopausal women, suggesting that miRNAs may partially mediate menopause-associated changes in adipose tissue [49]. The microRNA-17~92 cluster plays a multifaceted role in immune regulation, tumorigenesis, and possibly metabolic processes.

Discussion: Inflammation associated with obesity is known to contribute not only to the initiation but also to the progression and angiogenesis of breast cancer. The

inflammatory process that occurs due to current or progressive obesity leads to disturbances in cellular metabolism and hormonal metabolism. All these processes are widely regulated by the action of microRNAs, which may represent potential biomarkers influencing the pathogenesis of breast cancer [3]. In breast cancer, there is also an abnormality in the expression profiles of microRNAs that are involved in disease progression. In breast cancer, tumor and tumor-infiltrating cells secrete abundant amounts of microRNAs through the extracellular transport of vesicles, which act as messengers between cells in the tumor microenvironment and other organs and tissues [17]. However, a complete picture of the influence of these microRNAs on the pathological process of obesity-associated breast cancer is still missing.

We summarized the available literature data on the role of miR-223, -155, and the miR-17~92 cluster in the pathogenesis of breast cancer and obesity. These microRNAs regulate a wide range of biological processes in various cell types. They are involved in oncogenesis and progression of multiple types of cancer, including breast cancer. In particular, miR-155 and miR-223 regulate multiple processes in cancer cells, such as proliferation, invasion, stemness, and angiogenesis [17-23, 31-40]. The expression level of these miRNAs may be associated with various characteristics of cancer, such as the grade of malignancy and the presence of metastases. The microRNA-17~92 cluster also plays a vital role in cancer pathogenesis. Multiple members of this cluster, including microRNA-18a, influence pro-inflammatory processes and the regulation of gene expression in cancer cells. The expression of miR-17~92 may have different effects depending on the cancer type, highlighting the importance of studying the specific mechanisms of action of miRNAs in other tumor types [44–47]. In addition, there is evidence that microRNA-223, -155, and the microRNA-17~92 cluster also affect the development of adipose tissue and are involved in the aggravation of obesity-induced inflammation [28, 43, 48].

MicroRNAs secreted in adipose tissue influence the development and progression of obesity-induced breast cancer and may also influence MDSC activity. The role of MDSCs in the development of obesity-mediated breast cancer has previously been demonstrated [50]. Obesity, the number of MDSCs, and their immunosuppressive activity significantly increase, which, in turn, contributes to the progression of cancer [50]. MicroRNAs-223, -155, and -17~92 are involved in the expansion of the MDSC pool, and an increase in their functional activity is a crucial regulator of MDSC maturation/differentiation [24, 30, 45].

We assume that miR-223, -155, and -17~92 can be classified not only as new candidates for the role of diagnostic and prognostic indicators but also as potential therapeutic targets in new treatment strategies, especially for clinically aggressive breast cancer associated with obesity. Modulating the expression of microRNA-223, -155, and -17~92 by inhibiting their transcription or a direct blockade can be a promising method for treating and preventing breast cancer combined with obesity.

Conclusion: This review summarizes data indicating that miR-223, -155, and -1792 may be promising targets for developing new approaches to treating and preventing breast cancer associated with obesity. Further studies of microRNAs in the pathogenesis of breast cancer associated with pathological metabolic disorders and regulation of the functional activity of immune suppressor cells are necessary. Understanding the role of signaling microRNAs in tumorigenesis and other pathological processes may open new perspectives for personalized medicine and the development of innovative therapeutic strategies.

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АҢДАТПА

СЕМІЗДІКПЕН БАЙЛАНЫСТЫ СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ПАТОГЕНЕЗІНДЕГІ МИЕЛОИДТЫ СУПРЕССОРЛЫҚ ЖАСУШАЛАРДЫҢ (MDSC) БЕЛСЕНДІЛІГІН РЕТТЕУДЕГІ 223, 155 ЖӘНЕ 17~92 МИКРОРНҚ-ЛАРДЫҢ РӨЛІ

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Өзектілігі: *Сүт безінің қатерлі ісігі (СБІ) бүкіл әлемде таралуының жоғары болуына байланысты өзекті жаһандық денсаулық мәселесі болып табылады. Дүниежүзілік денсаулық сақтау ұйымының (ДДСҰ) мәліметтері бойынша, жыл сайын 2,3 миллионнан астам адамнан СБІ анықталады, сондай-ақ бүкіл әлемде әйелдердің қатерлі ісік ауруымен өлімінің басты себепшісі болып табылады. Семіздік сүт безі қатерлі ісігінің даму қаупін арттыратыны белгілі және миелоидты супрессорлық жасушалар (MDSC) сүт безі қатерлі ісігінің де, семіздіктің де патогенезінде маңызды рөл атқарады. MDSC-тің негізгі функциясы тіндерді қалпына келтіру және жараларды емдеу болып табылады, ол бақыланбайтын қабынудың алдын алуға және иммундық гомеостазды сақтауға көмектеседі. Дегенмен, созылмалы қабынудың ұзаруы MDSC-дің кеңеюіне және иммуносупрессиялық белсенділігінің жоғарылауына әкеледі. Семіздік кезіндегі сүт безі қатерлі ісігінің дамуының патологиялық процесі және осы процесте индукцияланған MDSC рөлі молекулалық деңгейде әлі де аз зерттелген. Соңғы жылдары дүниежүзілік ғылыми қоғамдастықта микроРНҚ-ны зерттеуге олардың әртүрлі жасуша типтерінің әртүрлі биологиялық процестеріндегі реттеуші рөліне байланысты үлкен қызығушылық пайда болды. Соңғы онжылдықта жүргізілген зерттеулер онкологиялық аурулардағы микроРНҚ және MDSC арасында өзара байланыстың болуын көрсетті.*

Зерттеудің мақсаты *– семіздікпен байланысты сүт безі қатерлі ісігінің даумуына және MDSC белсенділігіне микроРНҚ әсер ету механизмдерін ашу үшін мәліметтерді жинақтау.*

Әдістері: *Бұл жұмыс бойынша 2024 жылдың 7 маусымына дейінгі интернетте, Medline (PubMed) және Google Scholar дерекқорларындағы мәліметтерден «сүт безі ісігі» және/немесе «семіздік» және/немесе «MDSC» және/немесе «микроРНҚ» салаларындағы әдебиеттерге жан-жақтылы іздеу жүргіздік. Әдебиеттерді талдау нәтижесінде ең маңызды нысандар ретінде микроРНҚ-223, -155 және -17~92 таңдалды.*

Нәтижелері: *Шолуда негізгі сигналдық микроРНҚ-лардың (микроРНҚ-223, -155 және -17~92) экспрессиясының динамикасы, сондай-ақ олардың сүт безі қатерлі ісігінің, семіздіктің патогенезіндегі және MDSC белсенділігін реттеудегі рөлі туралы қазіргі уақытта қолда бар деректер ұсынылды. Сондай-ақ, микроРНҚ деректері арқылы семіздікпен байланысты сүт безі ісігі кезінде MDSC жасушасының екі бағытты реттелуі бойнша мәліметтер қортыланды.*

Қорытынды: *Әдебиет деректерін талдау нәтижелері бойынша микроРНҚ -223, -155 және -17~92 патологиялық метаболикалық бұзылулармен және MDSC функционалдық белсенділігінің бұзылуымен байланысты қатерлі ісіктің оның ішінде сүт безі ісігінің перспективалы диагностикалық және емдік биомаркерлері болуы мүмкін.*

Түйінді сөздер: *микроРНҚ, сүт безі қатерлі ісігі, семіздік, миелоидты супрессорлық жасушалар.*

ABSTRACT

РОЛЬ МИКРОРНК 223, 155 И 17~92 В РЕГУЛЯЦИИ АКТИВНОСТИ МИЕЛОИДНЫХ СУПРЕССОРНЫХ КЛЕТОК (MDSC) В ПАТОГЕНЕЗЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ, СВЯЗАННОМ С ОЖИРЕНИЕМ

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Актуальность: *Рак молочной железы (РМЖ) является глобальной проблемой здравоохранения из-за его высокой распространенности во всем мире. По данным Всемирной организации здравоохранения, ежегодно регистрируется более 2,3 миллиона случаев РМЖ, который является главной причиной смертности женщин от рака во всем мире. Известно, что ожирение увеличивает риск развития РМЖ, а миелоидные супрессорные клетки (MDSC) играют значительную роль в патогенезе как РМЖ, так и ожирения. Основная функция MDSC – восстановление тканей и заживление ран, что помогает предотвратить неконтролируемое воспаление и поддерживать иммунный гомеостаз. Однако хроническое воспаление и рост неопластических клеток приводят к длительной экспансии и усилению иммуносупрессорной активности MDSC. Патологический процесс прогрессии РМЖ при ожирении и роль индуцированных MDSC на молекулярном уровне в этом процессе остается малоизученными. В последние*

годы в мировом научном сообществе существует значительный интерес к изучению микроРНК в связи с их регуляторной ролью в различных биологических процессах различных типов клеток. Исследования, проведенные за последнюю декаду, показали наличие взаимодействия между микроРНК и MDSC при онкологических заболеваниях.

***Цель исследования** – обобщение имеющихся данных для раскрытия механизмов влияния микроРНК на активность MDSC и на течение РМЖ, связанного с ожирением.*

***Методы:** Проведен комплексный поиск литературы в интернете и в базах данных Medline (PubMed) и Google Scholar до 7 июня 2024 г. по направлениям «рак молочной железы» и/или «ожирение» и/или «MDSC» и/или «микроРНК». По результатам анализа были выбраны наиболее значимые объекты исследования – микроРНК-223, -155 и -17~92.*

***Результаты:** В обзоре представлены имеющиеся на сегодняшний день данные о динамике экспрессии основных сигнальных микроРНК (микроРНК-223, -155 и -17~92) и их роли в патогенезе РМЖ, ожирении и регуляции активности MDSC, а также двунаправленной регуляции MDSC при РМЖ, связанном с ожирением, посредствам данных микроРНК.*

***Заключение:** Основываясь на результатах анализа литературных данных, микроРНК-223, -155 и -17~92 могут быть многообещающими диагностическими и терапевтическими биомаркерами онкологических заболеваний, в том числе и РМЖ, связанных с патологическими метаболическими нарушениями и нарушением функциональной активности MDSC.*

***Ключевые слова:** микроРНК, рак молочной железы, ожирение, миелоидные супрессорные клетки (MDSC).*

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