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SENSITIVE TO THE EFFECTS OF ENVIRONMENTAL FACTORS miR-638 AND COMMON DISEASES

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❀ The review provides information on environmental factors affecting the level of miR-638 in humans, potential target genes of this micro-RNA (according to "TargetScanHuman"), diseases and metabolic pathways which potentially regulated miR-638, as well as clinical and experimental data confirming the involvement of miR-638 in the developing a wide range of multifactorial diseases. The data presented in the review expand the understanding of the pathogenesis of various diseases of a multifactorial nature and determine new strategies for studying gene-environment interactions that are important for the formation of health.

❀ **Keywords:** microRNA; miR-638; common diseases.

ЧУВСТВИТЕЛЬНАЯ К ВОЗДЕЙСТВИЮ СРЕДОВЫХ ФАКТОРОВ miR-638 И МНОГОФАКТОРНЫЕ ЗАБОЛЕВАНИЯ

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❀ В обзоре представлена информация о средовых факторах, влияющих на уровень miR-638 в организме человека, потенциальных генах-мишенях данной микроРНК (по TargetScanHuman), заболеваниях и метаболических путях, для которых среди ассоциированных генов избыточно представлены гены, потенциально регулируемые miR-638, а также клинические и экспериментальные данные, подтверждающие вовлеченность miR-638 в развитие широкого спектра многофакторных заболеваний. Приведенные в обзоре сведения расширяют представления о патогенезе различных болезней многофакторной природы и определяют новые стратегии изучения ген-средовых взаимодействий, значимых для формирования здоровья.

❀ **Ключевые слова:** микроРНК; miR-638; многофакторные заболевания.

Research suggests that the development of widespread diseases is promoted by various exogenous factors, the effects of which can be depending on the genetic features of individuals. Among these genetic factors, that contribute to risk of diseases the structural diversity of the genome has been frequently studied. However, in recent years research on the epigenetic components of multifactorial diseases has also been conducted [1–5]. Changes in the spectrum and level of microRNA, as well as epigenetic modifications (including DNA methylation), are considered important components of a disease's pathophysiology, including as intermediaries of the unfavorable environmental factors that contribute to disease development [6–9]. In this context, miR-638 is of interest since it is sensitive to the exposure of different biotic and abiotic agents. The degree of change to miR-638 depends on the affecting agents, the duration of the effect, and the types of cells involved [10–17]. Low levels of miR-638 were detected in individuals exposed to chronic benzene poisoning, compared with individuals not in contact with the substance (control group) and those who had short-term contact with the substance. Concurrently, individuals experiencing short-term exposure to benzene had higher levels of miR-638 than had those in the control group [13]. Another research also registered a considerable increase in miR-638 among workers exposed to polycyclic aromatic hydrocarbons [11]. An increase in miR-638 levels was registered

during cell treatment with benzo(a)pyrene (in a dose-dependent manner) [11], whereas bidirectional effects were detected following exposure to inorganic arsenic (a decrease in the level of this microRNA in the endothelial cells of the umbilical vein, an increase in the white blood cell culture) [15, 18]. It is assumed that this microRNA can be employed as a biomarker for the assessment the effects of unfavorable environmental factors in the work place [15].

A stimulating impact on miR-638 expression was determined for a number of viruses, including the enterovirus (EV71) [16] and the chikungunya disease virus (CHIKV) [12]. However, Liu et al. [14] demonstrated that the hepatitis C virus inhibited the expression of this microRNA in the cells of human hepatoma. Furthermore, miR-638 can affect the degree of infection and, in particular, can reduce the transcription of the hepatitis B virus [19, 20]. Additionally, miR-638 is sensitive to oxidative stress [21] and temperature conditions (its level is reduced at high temperatures) [22]. Naraballobh et al. [22] assigned microRNA (including miR-638) an important regulatory role in the acute response to modified environmental conditions, which stipulates remodeling in cells and tissues. Because of the specificity in the function of microRNA, miR-638 controls the expression of many genes at a translational level. Accordingly, changes in the expression of this microRNA (including under the effect of biotic and abiotic environmental factors) can impact a range of metabolic pathways.

miR-638 is expressed in multiple tissues including brain, kidney, skin, and fat, among others. It is also expressed in more than 800 cell lines (including different types of blood cells) and in more than 500 types of tumor across multiple organs [23, 24]. A high level of miR-628 expression can be explained by the fact that it is involved in the regulation of the cell cycle [25–27].

The *MIR638* gene is localized in chromosome 19p13.2, in an intron of the *DNM2* gene (dynamin 2); polymorphic variants (primarily single nucleotide replacements) are registered in the gene of this microRNA, but they are all low polymorphic [28, 29].

This review presents data on the possible pathogenetic effects of miR-638 that are sensitive to environmental factors. For this purpose, 1) an analysis of the functional significance of genes that can be regulated by miR-638 was performed and 2) data sourced from scientific publications on the involvement of miR-638 in the pathogenesis of different diseases was integrated.

Target genes of miR-638, their involvement in metabolic pathways, and links with diseases

Genes that are regulated by miR-638 were identified using TargetScanHuman (version 7.2; updated March 2018) [30, 31]. In total, miR-638 demonstrated potential binding sites for 1,877 transcripts (a total of 2,136 binding sites). Thus, at a translational level, miR-638 can control the expression of roughly 2,000 genes.

To determine the extent to which sets of genes having target sites for miR-638 are random, enriched gene sets among genes associated with different categories of pathologies/groups of pathology (as per the Disease database) and metabolic pathways (as per the KEGG Pathway Database) was assessed using the analytical internet resource Web-Gestalt [32, 33]. Data were obtained on the basis of the hypergeometric test. The level of statistical significance was determined using allowance, as per the Benjamini–Hochberg method. As a result of the analysis of genes potentially targeting miR-638, 533 diseases/groups of pathologies and 62 metabolic pathways were detected, with a statistical significance level of $p < 0.05$. Table 1 provides examples of such diseases and metabolic pathways, the number of genes of reference genes in the category, and the statistical parameters that characterize an excess of representation for miR-638 target genes.

Genes that are potentially regulated by miR-638 are presented as statistically significantly excessive for a wide range of diseases of the central nervous system and cardiovascular system, among oncological diseases, inflammatory and autoimmune pathologies, involved in the regulation of cell cycles, and in supporting genome stability, and are indicated as being involved in metabolic pathways and disorders, in which functioning can be a reason for these pathologies. The number of metabolic pathways in which the target genes of miR-638 are represented in excess directly indicates pathological conditions (e. g., oncologic disease, amyotrophic lateral sclerosis, renal cell cancer, and small-cell lung cancer). The causes of the above diseases include smoking, unfavorable environmental exposure (pollutants and mutagens), and viruses, among others. Additionally, miR-638 is also sensitive to exposure to environmental factors at the methylation level of CpG sites, and its expression [10–13].

Genes that are studied in the context of cardiovascular disease pathogenesis are potentially regulated by miR-638. This microRNA regulates the expression of genes that are involved in blood coagulation (*F8*, *F13A1*, and *F10*), the metabolism of fats and carbohydrates (*SLC2A9*, *LDLR*, and *FADS1*), encoding calcium (*CACNA1C*) and potassium (*KCND3, KCNJ5*) channels, cardiotrophin 1 (*CTF1*), methylenetetrahydrofolate reductase (*MTHFR*), and vascular endothelial growth factor A (*VEGFA*). Additionally, miR-638 regulates the expression of oncogenes (*RAN*, *FEV*, *USP6*, *PIM1*, and *RAB36*), cell cycle genes (*CDKN2B* and *CCND1*), and the *BRCA1* gene. Moreover, miR-638 controls proteins involved in repair processes (*RFC3*, *RFC2*, *MSH3*, and *RPA1*). Thus, on the basis of this analytical approach, it appears that changes in the level of miR-638 can result in disorders of different metabolic pathways that are im-

Table 1

Examples of disease categories (as per database Disease) and metabolic pathways (as per the KEGG Pathway Database) for which genes that are potentially regulated by miR638 were determined

Diseases (groups of diseases)/metabolic path-ways	ID	Descriptive statistics of gene enrichment analysis*				
		C	O	E	R	adjP
Diseases in which the largest number of genes are potentially regulated by miR 638						
Nervous System Diseases	PA445093	694	77	29.13	2.64	$1.86 \cdot 10^{-11}$
Mental Disorders	PA447208	564	62	23.67	2.62	$5.25 \cdot 10^{-9}$
Congenital Abnormalities	PA443223	643	67	26.99	2.48	$5.64 \cdot 10^{-9}$
Brain Diseases	PA443553	411	50	17.25	2.90	$7.70 \cdot 10^{-9}$
HI virus	PA447230	755	73	31.69	2.30	$1.37 \cdot 10^{-8}$
Central Nervous System Diseases	PA443657	438	51	18.38	2.77	$1.62 \cdot 10^{-8}$
Cardiovascular Diseases	PA443635	425	48	17.84	2.69	$1.40 \cdot 10^{-7}$
Genetic Predisposition to Diseases	PA446882	808	73	33.91	2.15	$1.77 \cdot 10^{-7}$
Musculoskeletal Diseases	PA445001	462	50	19.39	2.58	$2.10 \cdot 10^{-7}$
Epilepsy	PA444065	201	30	8.44	3.56	$2.53 \cdot 10^{-7}$
Diseases of the cardiovascular system						
Heart Diseases	PA444368	366	41	15.36	2.67	$1.19 \cdot 10^{-6}$
Hypertension	PA444552	227	28	9.53	2.94	$1.63 \cdot 10^{-5}$
Atherosclerosis	PA443425	214	26	8.98	2.89	$4.67 \cdot 10^{-5}$
Arterial Occlusive Diseases	PA443423	219	26	9.19	2.83	$6.60 \cdot 10^{-5}$
Myocardial Ischemia	PA446459	261	29	10.95	2.65	$6.65 \cdot 10^{-5}$
Coronary Artery Disease	PA443796	254	28	10.66	2.63	0.0001
Aortic Diseases	PA443393	64	11	2.69	4.10	0.0009
Cardiovascular Abnormalities	PA446717	164	17	6.88	2.47	0.0050
Brain Ischemia	PA443671	09	13	4.57	2.84	0.0056
Arrhythmias, Cardiac	PA443421	107	12	4.49	2.67	0.0116
Stroke	PA447054	235	20	9.86	2.03	0.0132
Myocardial Infarction	PA445019	242	20	10.16	1.97	0.0167
Cerebellar Diseases	PA443660	133	13	5.58	2.33	0.0194
Heart Block	PA444366	49	7	2.06	3.40	0.0199
Essential Hypertension	PA447288	120	12	5.04	2.38	0.0212
Cardiomegaly	PA444369	120	12	5.04	2.38	0.0212
Aortic Aneurysm	PA446510	39	6	1.64	3.67	0.0233
Carotid Artery Diseases	PA443636	81	9	3.40	2.65	0.0272
Atrial Fibrillation	PA443459	67	8	2.81	2.85	0.0274
Aortic Aneurysm	PA443394	19	4	0.80	5.02	0.0280
Infarction	PA444613	236	18	9.90	1.82	0.0370
Heart Arrest		60	7	2.52	2.78	0.0396
Oncological diseases						
Cancer or Viral Infections	PA128407012	951	79	39.91	1.98	$8.31 \cdot 10^{-7}$
Liver Neoplasms	PA444804	242	30	10.16	2.95	$7.38 \cdot 10^{-6}$
Carcinoma, Hepatocellular	PA444447	208	26	8.73	2.98	$2.91 \cdot 10^{-5}$

Table 1 (continued)

Diseases (groups of diseases)/metabolic path-ways	ID	Descriptive statistics of gene enrichment analysis*				
		C	O	E	R	adjP
Intestinal Neoplasm	PA444635	268	29	11.25	2.58	0.0001
Breast Neoplasms	PA443560	377	35	15.82	2.21	0.0002
Leukemia, Myeloid	PA444761	279	29	11.71	2.48	0.0002
Lymphoma, T-Cell	PA446309	167	21	7.01	3.00	0.0002
Adenoma	PA443269	157	20	6.59	3.04	0.0002
Colorectal Neoplasms	PA446108	260	27	10.91	2.47	0.0003
Neuroblastoma	PA445100	229	25	9.61	2.60	0.0003
Leukemia, Myeloid, Acute	PA444760	208	23	8.73	2.63	0.0004
Neoplasm of unspecified nature of digestive system	PA165108442	445	38	18.68	2.03	0.0005
Neoplasm Invasiveness	PA445057	298	29	12.51	2.32	0.0005
Carcinoma, Renal Cell	PA443624	121	16	5.08	3.15	0.0007
Neoplasm Metastasis	PA445058	315	29	13.22	2.19	0.0010
Other						
Metabolic Diseases	PA444938	612	57	25.69	2.22	$1.68 \cdot 10^{-6}$
Immune System Diseases	PA444602	680	60	28.54	2.10	$4.18 \cdot 10^{-6}$
Endocrine System Diseases	PA444037	429	43	18.00	2.39	$7.90 \cdot 10^{-6}$
Diabetes Mellitus, Type 2	PA443890	254	31	10.66	2.91	$7.07 \cdot 10^{-6}$
Chromosome Aberrations	PA443728	371	39	15.57	2.50	$8.33 \cdot 10^{-6}$
Translocation, Genetic	PA445914	431	41	18.09	2.27	$4.35 \cdot 10^{-5}$
Chromosome Deletions	PA443729	343	36	14.40	2.50	$2.18 \cdot 10^{-5}$
Chromosomal Disorders	PA447160	418	41	17.54	2.34	$2.18 \cdot 10^{-5}$
Colonic Diseases	PA443754	279	32	11.71	2.73	$1.37 \cdot 10^{-5}$
Inflammation	PA444620	435	40	18.26	2.19	0.0001
Viral Diseases	PA446038	488	43	20.48	2.10	0.0001
Autoimmune Diseases	PA443464	414	37	17.38	2.13	0.0003
Gastrointestinal Diseases	PA444256	413	37	17.33	2.13	0.0003
Lung Disease	PA444814	354	33	14.86	2.22	0.0004
Celiac Disease	PA443652	153	19	6.42	2.96	0.0004
Intestinal Diseases	PA444632	331	31	13.89	2.23	0.0005
Infections	PA444614	516	42	21.66	1.94	0.0006
Heat Stress Disorders	PA446781	39	7	1.64	4.28	0.0079
Loss of Heterozygosity	PA446859	342	24	14.35	1.67	0.0352
Metabolic pathways						
Pathways in cancer	05200	326	35	13.68	2.56	$1.95 \cdot 10^{-5}$
Cytokine–cytokine receptor interaction	04060	265	30	11.12	2.70	$2.83 \cdot 10^{-5}$
Leukocyte transendothelial migration	04670	116	15	4.87	3.08	0.0016
Wnt signaling pathway	04310	150	17	6.30	2.70	0.0028
Aldosterone-regulated sodium reabsorption	04960	42	8	1.76	4.54	0.0039
Vascular smooth muscle contraction	04270	116	13	4.87	2.67	0.0075
Glioma	05214	65	9	2.73	3.30	0.0085
Amyotrophic lateral sclerosis	05014	53	8	2.22	3.60	0.0088

Table 1 (continued)

Diseases (groups of diseases)/metabolic path-ways	ID	Descriptive statistics of gene enrichment analysis*				
		C	O	E	R	adjP
Cell cycle	04110	124	13	5.20	2.50	0.0111
JAK-STAT signaling pathway	04630	155	15	6.51	2.31	0.0113
Renal cell cancer	05211	70	9	2.94	3.06	0.0121
Small cell lung cancer	05222	85	10	3.57	2.80	0.0123
DNA replication	03030	36	6	1.51	3.97	0.0142
Systemic lupus erythematosus	05322	136	13	5.71	2.28	0.0174
Insulin signaling pathway	04910	138	13	5.79	2.24	0.0191
Basal cell carcinoma	05217	55	7	2.31	3.03	0.0255
DNA mismatch repair	03430	23	4	0.97	4.14	0.0429
Antigen processing and presentation	04612	76	8	3.19	2.51	0.0429

Notes: *Analysis was conducted using the analytical internet resource Web-Gestalt [32, 33]. ID – identification number according to Disease database for diseases and the KEGG Pathway Database for metabolic pathways. The following design indicators were provided: C, the number of reference genes in the category; O and E, respectively, observed and expected number of genes in the category, the expression of which can potentially be regulated by miR638; R = O/E, excessive representation of genes in an appropriate category in the tested selection ratio of enrichment); adjP, *p* value adjusted by the multiple test adjustment according to the Benjamini–Hochberg method.

portant to the pathogenesis of a wide range of diseases. This proposition is confirmed herein by conducting clinical and experimental studies.

Clinical and experimental confirmation of the involvement of miR-638 in the pathogenesis of multifactorial diseases

Significant evidence was obtained regarding changes in the expression of miR-638 in different multifactorial diseases (Table 2). Changes in the level of expression of miR-638 in the tumor tissue of different organ systems (e. g., intestinal tract, breast, and lung) are recorded compared with normal tissue, and in the blood serum of patients with oncopathology, compared with healthy individuals. The majority of studies detected a reduction in the level of this microRNA in tumors and in the blood serum of patients. Contradictory results were obtained only for breast cancer, where two studies detected lower levels of miR-638 in tumor tissue [34, 35] and one study detected the reverse situation [36], where this can be linked to the clinical features of patients included in the study. Specifically, the level of expression of this microRNA was higher in patients with triple-negative breast cancer compared with that in patients with other forms of breast cancer [34]. It is also known that miR-638 expression can be affected by certain medications [11, 34].

Where patients had low levels of miR-638 in tumor tissue and blood serum prior to treatment, this was associated with a more unfavorable clinical presentation (large tumor size, later disease stage, and occurrence of metastases) [25, 26, 35, 40, 42–44], as well as negative survival forecasts (general and remote relapse free) [27, 35, 38, 40, 42, 43]. These situations were observed for tumors in different organ systems (Table 1) except for nasopharyngeal carcinoma, where a reduction in survival was demonstrated for people with higher levels of miR-638 [38].

Table 2

Level of expression of miR-638 in different pathological conditions

Pathology, source	Level of miR-638 and its value
Non-small cell lung cancer [11, 37]	Reduction of expression was observed in 68% of tumor tissues. For patients with increased levels of miR-638 in their blood serum after chemotherapy, longer survival was typical than for those with a reduction in levels of miR-638. At a high level of miR-638 expression in blood serum after chemotherapy, the risk of metastasis in lymphatic nodes was lower
Nasopharyngeal carcinoma [38]	Individuals with a high level of miR-638 in their blood serum had poorer over-all survival and distant metastasis-free survival

Table 2 (continued)

Pathology, source	Level of miR-638 and its value
Stomach cancer [25, 26]	Level of miR-638 was lower in tumor tissue and in the cell lines of tumors than in adjacent normal tissues, and in normal lines of stomach epithelial cells. Low levels of miR-638 was linked to poor differentiation of tumors, tumor size, lymph node metastasis, and more severe stages of TNM
Colon cancer [39]	Level of miR-638 was significantly reduced in the serum exosomes of patients when compared with that of healthy individuals. The reduction was more obvious at the later stages of TNM and among patients with metastasis in the liver. At low levels of miR-638, lower overall and disease-free survival was registered
Colorectal cancer [40]	The level of miR-638 was lower in the serum exosomes of patients than in healthy individuals. A lower level of miR-638 was associated with increased risk of liver metastasis and later TNM
Colorectal cancer [27]	A lower level of miR-638 in tumor tissue than in noncancerous tissue. A low level of miR-638 in tumor tissue is linked with an unfavorable disease forecast
Hepatocellular carcinoma [41–43]	In the serum exosomes, in tumor tissue (as well as in cell lines), miR-638 level was lower than in the serum of healthy individuals and normal liver tissue. Low levels miR-638 is associated with tumor size, metastasis, vascular invasion, later TNM stage, and low postoperative survival
Cervical cancer [44]	Expression of miR-638 was lower in cancer-invaded tissue (cell lines) in comparison with that in normal tissue (cell lines). Low expression was associated with later stages, as per the International Federation of Gynecology and Obstetrics (FIGO) classification, with metastasis in lymphatic nods, vascular invasion, and low overall and progression-free survival
Breast cancer [35]	In tumor tissue (cell lines), lower levels of miR-638 expression was in compared with those in normal tissue (cell lines). Low expression correlated with lymph node metastasis and later stages as per TNM, with shorter overall survival
Invasive ductal carcinoma [34]	In tumor tissue samples, miR-638 expression was lower than that in normal tissues. Low miR-638 levels were more often registered in patients with non-basal-like breast cancer, compared with that in patients with a diagnosis of triple-negative breast cancer
Breast cancer and esophageal squamous cell carcinoma [36]	Higher miR-638 expression in tumor tissue than in normal tissue
Osteosarcoma [45]	In osteosarcoma tissue, miR-638 level was reduced compared with that healthy tissue. Ectopic expression of miR-638 inhibited cell growth of osteosarcoma *in vitro*
Ewing sarcoma [46]	miR-638 was significantly down-regulated in tumor cells. Overexpression of miR-638 suppressed cell growth, induced cell apoptosis, and inhibited tubule formation *in vitro*.
Glioma [47]	Experimental studies show inhibition of miR-638 restore proliferation and invasion of glioma cells
Stenosis of carotid arteries [48]	Compared with that for individuals without carotid artery atherosclerosis, the level of miR-638 in blood serum was significantly lower for patients with carotid artery stenosis undergone carotid endarterectomy, particularly in the sub-group patients who had experienced stroke. Lower levels were registered in individuals experiencing an impact on both carotid arteries, stroke, coronary artery disease, high risk of fibroatheroma, and among smokers
Behcet's disease [49]	Level of miR-638 in blood mononuclear were reduced in patients with in comparison with healthy controls
COPD of smokers [50]	A higher level of miR-638 expression was observed in lung tissue at severe invasion areas
Polycystic ovary syndrome [51]	Increased level of circulated miR-638 among patients compared with that among healthy women
Celiac disease [52]	In the duodenal mucosa of patients with celiac disease that exhibited classic clinical symptoms, and with hypoferric anemia following a gluten-free diet, the level of miR-638 was higher than that in individuals with normal duodenal mucous. The level of miR-638 was higher in patients with hypoferric anemia, compared with that in those with classic symptoms of celiac disease
Sporadic amyotrophic lateral sclerosis [53]	Increased level of miR-638 expression in samples of leucocytes among patients compared with among those without pathology
Systemic sclerosis [54]	Increased level of circulating miR-638. Level of miR-638 was slightly reduced in an anti-Scl-70-positive group of patients compared with that in an anti-Scl-70-negative group

Table 2 (continued)

Pathology, source	Level of miR-638 and its value
Lupus nephritis [55]	Compared with that in control samples, lupus nephritis patients had lower glomerular expression of miR-638, but higher tubulointerstitial expression of this MicroRNA Tubulointerstitial miR-638 expression was significantly correlated with proteinuria and disease activity score
Lupus nephritis [56]	In liver biopsy slides of patients, the level of miR-638 was higher than that in control samples
Lupus nephritis [57]	In peripheral blood mononuclear cell lines obtained from patients with lupus nephritis, the expression of miR-638 was higher than in control samples (shown for Caucasians and African Americans)
Nephropathy at DM2 [58]	Patients with diabetic nephropathy had higher levels of miR-638 in urine exosomes than had patients with DM2 without nephropathy and healthy individuals
Nephrotic syndrome [59]	In healthy individuals, the level of miR-638 in urine was significantly lower than that in patients with different types of nephrotic syndromes (diabetic glomerulosclerosis, nephropathy with minimum disorders, focal glomerulosclerosis, and membrane nephropathy)
Hypertension [60]	Level of miR-638 in the renal medulla of patients with hypertonia was lower compared with those with normal arterial pressure
Age-related cataracts [61]	miR-638 was included in the top 10 expressed microRNAs in the normal human eye lens, but not in lenses affected by cataracts

Notes. COPD, chronic obstructive pulmonary disease; DM2, diabetes mellitus type 2; FIGO, International Federation of Gynecology and Obstetrics; TNM (**T**umor, **N**odus, and **M**etastasis), international classification of stages of a malignant tumor.

One of the mechanisms that regulates the expression of microRNA is the methylation of its gene promoter. Hypermethylation of the host gene of miR-638 (*DNM2*) was registered in colorectal cancer tissue [62]. Zhang et al. demonstrated that the CpG island in the area of the miR-638 promoter in colorectal cancer tissue was hypermethylated. Therefore, a lower level of this microRNA expression was observed, and weakening of the methylation level was sufficient for the recovery of miR-638 expression in tumor cells [27]. When miR-638 expression increased, inhibition of proliferation was observed, as well as the invasion of cancer cells and arrest of the cell cycle in the G1 phase, whereas repression of miR-638 resulted in contrasting effects [27]. Similar results were obtained in experimental studies by other authors [25, 35, 42, 45–47]. This explains a more favorable forecast for patients who had increased levels of miR-638 following treatment. For example, patients with non-small lung cancer cells after cisplatin chemotherapy showed an increase in serum miR-638, longer survival than had patients with a reduced level of this microRNA [37]. The high level of expression of miR-638 stipulated an elevated sensitivity of tumor cells to cisplatin, which ultimately resulted in a reduction of the tumor cells' viability in response to chemotherapy [63]. The same authors determined that high expression of miR-638 affected the recovery processes of damaged DNA by means of suppressing the expression of γ*H2AX* [63]. miR-638 also reduced the ability of repair DNA damage in triple-negative breast cancer cells that had been impacted by ultraviolet irradiation and cisplatin [34]. These conflicting results indicate the different physiological effects of microRNA (miR-638 in particular) under different conditions.

The fact that in the majority of cases, a lower level of miR-638 was registered in tumor cells compared with normal cells, allows microRNA to be considered as a tumor suppressor (e. g., for Ewing's sarcoma, cervical cancer, breast cancer, and stomach cancer) [25, 27, 35, 44–46] and as an independent prognostic factor for different oncological diseases (regardless of the disease stage TNM and occurrence of metastases) [27]. However, single studies will be noted herein in which miR-638 served as an oncogene contributing to cell proliferation, migration, and invasion (for esophageal squamous cell cancer and breast cancer) [36]. According to the analysis of enrichment (Table 1), changes in the expression in oncological diseases are significantly correlated with data related to an excess of genes regulated by miR-638, among genes associated with pathologies and metabolic pathways.

Low expression of miR-638 in blood serum or affected tissue has been registered for other diseases such as atherosclerosis of the carotid artery, Behcet's disease, hypertension, and nephrotic syndrome (Table 2). Interestingly, patients with cardiovascular disease, as in the case of those with oncological disease, demonstrated lower levels of miR-638. Furthermore, much lower levels of this microRNA were typical for patients with severe clinical presentation [48]. One study determined that the level of this microRNA was lower in smokers compared with that in non-smokers, which correlates with data regarding an increase in the level of methylation of the CpG sites of this miR-638 for smokers [10]. It is known that miR-638 is highly expressed in smooth muscle cells of human aorta and is involved in the regulation of proliferation and migration in these

cells [64]. This microRNA also affects the proliferation and migration of smooth muscle cells in the respiratory tract (hyper-expression inhibits proliferation and migration), which indicates the potential of miR-638 in asthma pathogenesis [17].

For the above-noted diseases, miR-638 is considered a diagnostic marker, as well as a therapeutic target. The level of miR-638 in blood serum is proposed for use as an invasive biomarker for plaque vulnerability and the probability of ischemic stroke, particularly among individuals at risk of cardiovascular complications [48]. It has been stated that changing the level of miR-638 in vascular smooth muscle cells may be useful in the treatment of proliferative vascular diseases [64]. miR-638 can also serve as a new therapeutic target for the prevention of hyperplasia of smooth muscle cells in the respiratory tract in asthma [17].

A reduction in the expression of miR-638 was not observed for all pathologies. A number of diseases demonstrated an increase in the level of this microRNA in the blood serum of patients or in affected tissue (Table 2). This situation was detected for esophageal squamous cell cancer, polycystic ovary syndrome, and celiac disease. For example, an increase in the expression of miR-638 was registered in the blood serum of patients with sporadic amyotrophic lateral sclerosis [53]. However, contradictory results have been obtained for this disease in different studies [53]. Development of this disease can be promoted by a wide range of environmental factors (e. g., heavy metals, pesticides, smoking, and viral infections) [65]. Accordingly, conflicting results from different studies regarding changes in the expression of miR-638 in the case of amyotrophic lateral sclerosis can be explained in a number of ways. On the one hand, sporadic amyotrophic lateral sclerosis can differ on the basis of etiological factors. On the other hand, the focus of changes to the level of this microRNA can differ in response to exogenous stimulants. Specifically, it was demonstrated that infectious agents can result in an increase in the expression of miR-638 [12, 16, 17]. This means that the same pathological phenotype can result from different pathophysiological pathways, which can be explained by the presence of different genetic components (genes and their structural and functional features), even in the presence of the common *intermediate* between environmental factors and genes (e. g., microRNA).

During comparison of miR-638 expression in the samples of affected tissues, a number of cases indicated conflicting results, which can be explained by tissue-specific differences. Lu et al. [55] determined bidirectional changes in the level of miR-638 in different areas of the kidney among patients with lupus nephritis (i. e., low levels in glomeruli and higher levels in tubulointerstitial tissue) compared with control samples (Table 2). However, two other studies detected an increase in the level of this microRNA in patients with lupus nephritis (in kidney biopsies and in peripheral blood mononuclear cells) [56, 57].

A change in the level of miR-638 during pathologies also influenced a change in the expression level of a number of proteins. For example, it was shown that a change in miR-638 expression had an effect: with Ewing sarcoma at the level of VEGFA protein [46], with osteosarcoma at the level of proto-oncogen PIM1 [45], with hepatocellular carcinoma and gastric cancer at the level of transcription factor SOX2 [22, 43], in colorectal carcinoma at the level of the cell surface protein TSPAN1 [27], in gastric cancer at the level of the methyl-CpG-binding protein 2 [26], in breast cancer at the level of BRCA1 [34], and in emphysema at the level of TOMM40 [50].

This microRNA also affected the expression of *CCND1* (G1/S-specific cyclin-D1) and transcriptional activator NR4A3 (*NOR1*), which are required for cell proliferation, migration [17], and activation of the Wnt/β-catenin signaling pathway [44], disturbances to which can result in the formation of different pathologies including oncological diseases, metabolic and neurodegenerative disorders, and cardiovascular and endocrine system diseases. Individuals with hypertension demonstrated a reduction in the level of miR-638 in kidney tissue, and an increase in the expression of *NR4A3* and *RENBP* when compared with individuals with normal arterial pressure [60]. According to TargetScanHuman, all genes coding the above-mentioned proteins had targets for miR-638. However, the range of genes regulated by miR-638 may be more widespread than forecasted by bioinformatic methods [50, 60].

The sensitivity of microRNA to environmental effects and the control of the expression of protein-coding genes may depend on the genetic features of the individual. Genetic polymorphic variants (SNP) in the miRNA binding sites can change the expression of genes regulated by appropriate miRNA.

So, on the one hand, the prevalence of allelic frequencies for rs799917 of the *BRCA1* gene and rs334348 of the *TGFR1* gene is significantly different among populations with different risks of developing breast cancer, and on the other, depending on the genetic characteristics of tumor cells according to the above polymorphic variants specificity in the regulatory potential of miR-638 and miR-628–5p for the *BRCA1* and *TGFR1* genes has been established [66].

Genetic variants in microRNA genes (particularly in the areas of target binding) can impact the expression of target genes. *MIR638* gene includes a large number of polymorphic variants (SNP, insertions, and deletions, though low level of the polymorphisms are typical) [29], which can also modify the regulatory potential of this microRNA.

Genetic components are also involved in the regulation of DNA methylation. For example, one study demonstrated that smoking affected methylation in some areas of DNA in the blood leucocytes of native Hawaiians, but this was not the case in Europeans, Japanese, or Americans [67]. DNA methylation in fat tissue depended on the SNP associated with smoking [68], and etc. It was shown that DNA methylation was affected by exogenous and endogenous factors (in particular, smoking and obesity), as well as additive genetic factors [69]. This indicates the importance to take into account the genetic characteristics of the examined individuals during analysis of different epigenetic aspects (e. g., DNA methylation and the regulatory potential of microRNA).

The data presented in this review allow miR-638 to be considered as a sensitive to environmental effects marker that is in a wide range of diseases of a multifactorial nature. First, overlap was observed between diseases/groups of pathologies and metabolic pathways for which the potential target genes of microRNA were present in abundance (Table 1) and for the list of diseases where a change in the level of microRNA was detected in the affected tissue or blood serum of patients during clinical studies (Table 2). Second, data were accumulated to demonstrate that biotic and abiotic factors in the environment (including those serving as risk factors for multifactorial diseases) can affect the level of expression of miR-638. One of the mechanisms by which the level of expression of this microRNA can be changed is the methylation of CpG sites. Third, a number of cases showed that the level of miR-638 can affect expression and protein levels. The information provided in this review expands our perceptions on the pathogenesis of different multifactorial diseases and can help to determine new examination strategies for gene–environment interactions.

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