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Interrelation of MicroRNAs and Transposons in Aging and Carcinogenesis

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Abstract—The dysregulation of transposable elements plays a key role in human carcinogenesis. Physiological aging in humans is also caused by the deregulation of transposons. Moreover, aging is associated with the development of cancer. We present the results of an analysis of data on the presence of common epigenetic changes during aging and carcinogenesis, associated with changes in the expression of microRNAs derived from transposons. We find that aging is characterized by changes in the expression of 21 specific transposon-derived microRNAs associated with the development of malignant neoplasms. Before us, evidence similar to ours on the relationship between the mechanisms of aging and carcinogenesis at the epigenetic level has not been presented. We hypothesize that one of the key mechanisms of aging is an imbalance in the programmed activation of mobile genetic elements, which is reflected in changes in the body's epigenetic regulation and leads to an increased risk of cancer. Since microRNA precursors can be translated with the formation of functional molecules, peptides used in gerontology can be considered as potential anticancer drugs.

Keywords: malignant neoplasms, noncoding RNA, peptides, aging, transposons, epigenetic regulation

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INTRODUCTION

Currently, there are no accurate data on the genetic mechanisms underlying the aging of human and animal organisms. Their discovery could be the basis for effective life extension. The most promising direction in this area is the study of the influence of epigenetic (EG) factors, since they are higher-order regulators. In addition, the changes they cause are reversible [6]. EG information in eukaryotic genomes is encoded as the presence or absence of histones in specific DNA sequences, DNA methylation, chromatin remodeling, structural and functional variants of histones, and the transcription of noncoding RNA (ncRNA) [42]. Aging is accompanied by global EG changes with disturbances in the expression profiles of protein-coding genes, the chromatin landscape, histone methylation (such as *H3K*4, *H3K*27, *H3K*9), and the activity of histone deacetylases (sirtuins). In this case, specific ncRNAs are expressed, such as long ncRNAs (*HOTAIR*, *PANDA*, *MALAT*-1, *GUARDIN*) and microRNAs (miRNA) [34]. EG factors play an important role in maintaining the stability of the genome by regulating the activity of transposable elements (TEs) capable of transposition to different DNA loci. The chromatin of TE sequences in the genome is enriched in nucleosomes with di- and trimethylated histone *H*3 (*H3K*9*me*2/3), which inhibits transcription [6].

During aging, the role of a decrease in DNA methylation (modification of cytosine to 5-methylcytosine), which is the most important mechanism for regulating TEs activity in vertebrates, plants, and fungi, has been proven [12]. As a result of genome hypomethylation, TE expression is increased, which leads to the increased transcription of various ncRNAs with age due to their formation from TE transcripts by processing. The origin of some miRNAs from TEs in humans has been proven in various independent studies. In 2011 T.J. Filshtein et al., a study of 208 human miRNAs showed that 191 of them arose from TEs [26]. In the same year, Z. Yuan et al. identified 226 microRNAs [67], in 2012 S. Tempel et al. revealed 235 miRNAs [57], and in 2015 S. Qin et al. found 409 microRNAs derived from TEs [44]. This substantiates the assumption that TEs are regulators of EG control of ontogenesis [1].

TEs are classified into class I: retroelements (REs), which transpose by "copy and paste"; and class II: DNA transposons that change their position in the genome by the "cut and paste" or "rolling circle" mechanism [6]. In turn, REs are subdivided into containing long terminal repeats LTR and non-LTR REs that do not contain them. Transposons can be autonomous, i.e., able to move with the help of reverse transcriptase (for RE) or transposase (for DNA-*T*) encoded by them. Nonautonomous TEs require the enzymes of autonomous transposons. At least 46% of

the human genome consists of TEs, most of which are REs. Of these, non-LTR RE *LINE*-1 (long interspersed nuclear elements), which occupy 17% of the total DNA and are represented by more than 500000 elements of about 6000 bp in size, are the most common. Of these, only the *ERE* family is characterized by a preserved ability for retrotransposition. LTR REs occupy 8% of all human DNA nucleotides. These include *HERV* (human endogenous retroviruses) 7000–9000 bp long [12]. They play an important role in the development of autoimmune diseases due to the expression of *env*, *gag*, and *pol* genes. *HERV* protein products can be recognized by toll-like receptors as a pathogen-associated molecular pattern (*PAMP*), inducing the production of type-I interferon (IFN1) [8]. Nonautonomous non-LTR REs include *SINE* (short interspersed nuclear elements), which include *Alu* elements about 300 bp long, occupying 11% of the entire human genome and representing more than 1 million copies. *Alu* are subdivided into subfamilies based on evolutionary age. The youngest of them, *Alu Ya*5 and *Alu Yb*8, are highly polymorphic among individuals, as they retain the ability to transcribe and transpose. About 0.2% of the human genome consists of complex TEs named *SVA* (*SINE-R*, *VNTR, Alu*), the average length of which is 2000 bp, and the number of copies is 2700 [12].

The displacements of TEs in evolution have made a significant contribution to the formation of the structure and function of genomes, influencing the physiological functioning of all living organisms. Unlike point mutations, TE insertions cause more radical changes. They serve as sources of many *cis*-regulatory sequences, rearranging gene networks over very short evolutionary periods. For example, the regulation of genes responsible for IFN has changed many times with the help of *ERV*, which facilitated the function of transcriptional enhancers [56]. It has been proven that TE regulatory regions have been domesticated by mammalian genomes to modulate the regulation of neighboring genes [4]. The preservation of TEs in genomes during evolution occurs in two stages: first, integration; second, selection by the host, in which harmful events are eliminated and beneficial insertions are preserved. A surprising variety of TE-integration site preferences have been found, ranging from highly specific nucleotide sequences (site-specific TEs) to characteristic chromatin domains or chromosomal regions. This is reflected in the nonrandom distribution of TEs in genomes. For example, LTR REs in *Saccharomyces cerevisiae* are detected mainly in regions encoding transfer RNAs, while non-LTR retroelements *R*1 and *R*2 are found inside rDNA units and the MLV (murine leukaemia virus) transposon is found near the protooncogene promoter [56]. TE transpositions facilitate the accumulation of regulatory sequences throughout the genome, altering gene regulation and promoting evolutionary advantage. When located in euchromatic regions, TE transcriptional silencing by histone methylation and modification causes suppression of the expression of genes located in them. In addition, small ncRNAs derived from TEs exert post-transcriptional control [4].

The regulatory role of miRNAs at the level of transcription due to the mechanism of RNA-dependent DNA methylation has also been proven [22]. In addition, ncRNAs, such as piRNAs, which directly regulate TEs expression, can cause global changes in ontogeny and aging. Thus, gene silencing of the PIWI (P-element-induced wimpy testis) system of interacting RNAs is determined only in sterile worker termites during aging and is not detected in reproductive insects, which are characterized by a significantly longer lifespan (several decades compared to several weeks). At the same time, in worker insects, the expression of a significant number of genes associated with TE increases with aging, while in reproductive termites, gene expression patterns barely change with age [23]. For most animals, the production of piRNA is specific only for germ cells and is aimed at protecting their genomes from damage due to transpositions. Loss of PIWI proteins in mice, fruit flies, and zebrafish leads to loss of fertility due to disruption in the formation and maintenance of germline stem cells, cessation of meiosis, and other gametogenic defects [32]. An additional mechanism that allows TEs to influence genome activity during aging is the relationship between TEs and lamins [4]. It has been shown that *SIRT*7-mediated deacetylation of *H3K*18 regulates *LINE*1 expression and facilitates the interaction of this element with nuclear lamins [61]. Changes in the lifespan caused by the action of piRNA in cnidarians (*Cnidaria*), which are characterized by almost unlimited regeneration abilities and immortality, are described. Their somatic cells express piRNA and PIWI proteins, resulting in a low level of TE activity in their genomes throughout life. These properties have been proven in *Hydra vulgaris* [32]. Cnidaria also have the ability to develop germline stem cells directly from somatic cells *de novo*. These include the virtually immortal jellyfish *Podocoryne carnea*, at all stages of development of which PIWI protein homologues, called Cniwi, are found. Although the level of these proteins is highest in the gonads, their expression is also traced in differentiated somatic cells, protecting genomes from damage caused by TEs translocations [51]. Since the DNA repair systems in cnidarians do not have a specific efficiency that distinguishes them from other animals, the authors concluded that the expression of piRNAs in their organisms causes delayed aging processes. This is due to the suppression of TEs activity and prevention of genomic instability due to insertional mutations [32].

Effect of Transposons on Aging and Carcinogenesis

Pathological TEs activation is characteristic of both human aging and the development of malignant neoplasms (MN), while aging is a risk factor for most

types of cancer [42]. In this regard, it is logical to assume the presence of common EG mechanisms in these processes mediated by TEs and ncRNAs derived from them. Chromatin remodeling during aging is accompanied by REs activation. Chromatin profiles are smoothed: there is more open chromatin in the pericentromeric regions, centromeres, and REs loci (*LINE*1, *Alu*, *SVA*), while chromatin becomes less open in promoters and enhancers of active genes [18]. TEs activation during aging is observed in humans, mammals, and other animals, including *Drosophila*, *C. elegans*, as well as representatives of the plant and fungal kingdoms [12]. Of greatest interest are studies of the role of TEs in human aging in connection with the prospects of targeting them for extending life, as well as for the treatment of aging-associated pathologies, such as malignant neoplasms. It has been shown that hypomethylation of *LINE*1 and *Alu* in humans develops both with aging and with the development of cancer. Moreover, specific levels of *LINE*1 hypomethylation of extracellular DNA in peripheral blood can be used as biomarkers of human aging [24]. In healthy people, the level of *LINE*1 mRNA is higher in the skeletal muscles of the elderly than the young, which is due to genome hypomethylation. Moreover, physical exercise reduces *LINE*1 expression in the elderly [47].

Cellular aging is characterized by clear changes in cellular and nuclear architecture and function. Senescent cells acquire a secretory phenotype, with the synthesis of various *IL* and IFN that cause chronic inflammation [34]. It has been proven that this is due to transcriptional derepression of *LINE*1, which activates the IFN1 response with the help of their cytoplasmic cDNAs [19]. In an experiment on a culture of aging human lung fibroblasts, in addition to changes in the expression of genes for the inflammatory response, cytokine activity, and cell adhesion, changes in the signaling pathways of *NF*-κ*B*, beta-catenin, *TGF*-β, *SMAD*, and *BMP* were shown. In addition, aging is caused by activation not only of *LINE*1, but also of *SINE*, LTR RE, and DNA transposons [34]. When studying the mechanisms of aging in a culture of mesenchymal stem cells derived from human adipose tissue, *Alu* activation was revealed. This phenomenon caused nuclear cytotoxicity due to the formation of stable DNA damage foci and the loss of effective DNA repair in pericentromeric chromatin [62]. To determine the functional consequences of *HERV-K* (*HML*-2) expression, an age-associated analysis of the correlation of their expression at the transcriptome level using gene-set enrichment analysis (GSEA) was performed. As a result, it was found that the expression of genes strongly correlated with the expression of *HERV-K* is completely different in young (435 genes) and elderly (946 genes) people, with the highest correlation of functional neutrophil genes in the elderly [8]. The reason for aging is not just the activation of TEs with age, but the species-specific limit of programmed changes in the expression of certain TEs, after which random events of disturbances in their activity begin to predominate. Indeed, when determining the activity of 111 annotated REs in young and old *Drosophila*, both an increase in the level of 18 REs and a decrease in 18 other REs with aging were revealed [13]. That is, aging is based on violation of the optimal TE-activation pattern selected in the course of evolution, which is associated with the use of TEs as drivers of EG processes to control ontogeny. This mechanism is dynamic and modulated in the course of natural selection in favor of reaching a sexually mature state and reproduction, which is necessary for preservation of the species. Aging is associated with changes in all systems of genome regulation, including RNA interference (RNAi) with the participation of ncRNAs derived from TEs [1]. The result of this imbalance in the control of gene expression is the development of pathological processes, of which MNs are most reliably caused by TEs activation.

Global DNA hypomethylation in the case of MNs is due to the deregulation of TEs, which cause oncogene activation, chromosome damage, and genomic instability. This leads to tumor progression [6]. About half of MNs are characterized by somatic retrotranspositions. So, in the work of B. Rodriguez-Martin et al. in the study of 2954 malignant tissue genomes, RE movements were determined in 35% of the samples. *LINE*1 integration was most frequently observed in esophageal, head and neck, and colorectal cancers. At the same time, retrotranspositions often became drivers of carcinogenesis, as they led to the loss of oncosuppressor genes and the amplification of oncogenes [48]. In addition to *LINE*1, *HERV* are also involved in carcinogenesis. For example, in breast cancer and lymphoma, an increasing level of *HERV* mRNAs has been determined. Metastatic melanoma has been associated with *HERV*-like viruses. In ovarian, colon, and testicular cancers, a high level of *HERV* envelope genes is expressed [6]. A pronounced association with the development of MN was identified for *HERV-K*, followed by *HERV-H*, *HERV-W/ syncytin* 1, and *HERV-R* in terms of the frequency of detection of transpositions. The effect of these REs has been shown for various neoplasms, including cancer of the breast, endometrium, prostate, testicle, ovary, colon, pancreas, kidney; sarcoma, melanoma, lymphoma, and leukemia. *ERV* activation during malignant growth is associated with DNA hypomethylation, which is characteristic of tumor progression [11]. At the same time, TEs highly sensitive to stress can serve as inducers of EG changes in the genome that cause hypomethylation [1], further supporting tumor development as drivers of genomic instability [48].

Relationship of miRNAs with Transposons in Carcinogenesis

An increase in the incidence of MN during aging may be due to TEs deregulation in both processes [6].

A manifestation of this is a change in the expression of small ncRNAs, since many of them are formed during the processing of human TEs transcripts [26, 44, 57, 67]. An analysis of current data on the relationship between transposons and ncRNA suggests that TEs are involved in the initial formation of most miRNA genes. The difficulty in identifying whether microRNAs belong to TEs is due to the fact that mutations accumulate in TEs loci in a series of generations [46]. An MDT (miRNAs derived from TEs) database of miRNAs derived directly from TEs has been created [64]. MicroRNAs are used to predict tumor formation and outcome. For this, appropriate bioinformatic systems are taken, such as *OncomiR*, an online resource for changes in microRNA regulation in cancer [65], the analysis of which made it possible to determine the role of microRNAs derived from TEs (according to MDT) in the development of specific cancers (Table 1). At the same time, the expression of the same miRNAs can increase in some types of tumors and decrease in others. For 94 out of 410 miRNAs presented in the MDT database [64], changes in the level in various MNs have been proven. The expression of these microRNAs changes during the development of malignant neoplasms, according to the analysis of data from *OncomiR*, which may serve as evidence for the role of TEs in carcinogenesis. One of the mechanisms of this process is the processing of miRNAs from their transcripts.

Transposon-Derived miRNAs Common to Aging and Carcinogenesis

Published data on the role of 94 identified miRNAs derived from transposons, the expression of which changes during the development of malignant neoplasms, in the mechanisms of aging were analyzed. As a result, it was found that there is evidence of changes in expression during aging for 21 out of 94 microRNAs studied (Table 2). In accordance with the results obtained, it can be assumed that the systems underlying aging may be one of the pathogenetic links of certain MNs. The discovery of common mechanisms in the physiological process of aging and the pathological mechanism of carcinogenesis can become the basis for the development of a specific targeted effect on them. It has been shown that the level of *miR*-151a in the blood of healthy people decreases significantly with aging [40], while *miR*-192 expression in the kidneys increases significantly [49]. The role of *miR*-1976 in the aging of the sinoatrial node due to its effect on *Cav*1.2 and *Cav*1.3 was revealed [72]. The comparison of centenarians with people from families with a low life expectancy revealed a significant increase in *miR*-211 expression in centenarians, which was proposed to be used as a biomarker of aging [55]. In elderly people, a significant decrease in *miR*-28 expression was shown [70]. An increase in *miR*-31 expression was found during replicative aging [20]. This microRNA is the target of histone deacetylators both during cancer and aging [15]. The level of *miR*-320*c*, which is involved in the regulation of chondrocyte renewal, decreases with aging [60]. The role of *miR*-335 in human aging and age-related neurological diseases has been shown [45]. Quantitative transcriptional analysis with reverse PCR revealed the role of *miR*-340 in aging [69]. The estrogen-sensitive microRNA *miR*-378*a* is involved in the mechanisms of aging of the human thymus, which was confirmed in experiments on mice [28]. The dysregulation of *miR*-450*b* has been shown in cellular aging caused by endogenous genotoxic stress [38], as well as the involvement of *miR*-487*b* in skeletal muscle aging [71]. *miR*-495 induces the aging of mesenchymal stem cells [37]; *miR*-511 expression changes with aging of the nervous system [73]. When *miR*-570 is inhibited, cellular aging is suppressed due to restoration of the anti-aging *Sirtuin*-1 molecule [9]. During the aging of human-blood platelets, a low level of *miR*-570-3*p* is determined along with *miR*-548*a*-3*p*, *miR*-548*x* [17], also arising from TEs.

When comparing the level of microRNA in blood-plasma exosomes in young and elderly people, *miR*-576 enrichment was revealed in the latter [31]. *miR*-487*b*, which directly interacts with the long ncRNA *MAR*1 (muscle anabolic regulator 1), can be used as a target for targeted therapy associated with aging of muscle atrophy [71]. Oxidative stress contributes to aging and the development of cardiovascular and neurodegenerative diseases. It was found that *miR*-585 regulates the *PARP*-1 (poly-(ADP-ribose)polymerase 1) gene, the product of which is involved in the repair of oxidatively damaged DNA.

Overexpression of this miRNA enhances DNA damage and suppresses cell survival [21]. The loss of cell functionality during aging is accompanied by a change in intercellular communication and signaling with microenvironment remodeling and proinflammatory status. The secretion of extracellular vesicles and their microRNAs in senescent human dermal fibroblasts was analyzed. Aging-specific changes in miRNAs have been identified, including a decrease in the level of *miR*-625 [58] derived from TEs [64].

When studying microRNA expression in Parkinson's disease, it was proposed to use *miR*-885 as a biomarker of human aging and cellular senescence [10]. Experiments on mice have shown the role of *miR*-450b in aging [38], as well as a decrease in *miR*-511 expression with age [73]. A study of 521 different microRNAs in six strains of mice with different life expectancy revealed the significant association of three microRNAs, including *miR*-708 [36], the expression of which changes with human cancer [65].

Table 1. Changes in the expression of microRNAs derived from TEs in malignant tumors

MicroRNA	A tumor in which miRNA expression is altered	Change in the expression	TE, miRNA source
miR-1248	*BRCA, LUSC, PRAD, UCEC*	Increase	*SINE/Alu*
	KIRC, LIHC, THCA	Decrease	
miR-1249	*BLCA, HNSC, KIRC, LUSC, PRAD, STAD, UCEC*	Increase	*LINE/L2*
	BRCA, COAD, READ, THCA	Decrease	
miR-1254	*BLCA, BRCA, ESCA, HNSC, KIRC, KIRP, LUSC, STAD, THCA, UCEC*	Increase	*SINE/Alu*
	READ	Decrease	
miR-1266	*BLCA, BRCA, CHOL, ESCA, KICH, KIRC, KIRP, LIHC, PRAD, STAD, UCEC*	Increase	*SINE/MIR*
	COAD	Decrease	
miR-1269a	*BLCA, BRCA, HNSC, LIHC, LUAD, LUSC, PRAD, STAD, THCA, UCEC*	Increase	*LTR/ERVL*
	CHOL, KICH	Decrease	
miR-1271	*BLCA, ESCA, KIRC, LUSC*	Increase	*LINE/L2*
	BRCA, COAD, KICH, LIHC, LUSC	Decrease	
miR-1293	*HNSC, LUSC*	Increase	*SINE/Alu*
miR-1296	*BLCA, ESCA, LUSC, PRAD, UCEC*	Increase	*LINE/L2*
	BRCA, COAD, KIRC, LIHC, READ, THCA	Decrease	
miR-1304	*HNSC, LIHC, LUAD, LUSC, STAD*	Increase	*SINE/Alu*
miR-151*a*	*BLCA, BRCA, CESC, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, UCEC*	Increase	*LINE/L2*
miR-1911	*ESCA, HNSC, LUSC, STAD*	Increase	*LTR/Gypsy*
miR-192	*BLCA, BRCA, COAD, KIRC, LUAD, LUSC, PRAD, READ, STAD, UCEC*	Increase	*LINE/L2*
	CHOL, KICH, KIRP, LICH, THCA	Decrease	
miR-1976	*BLCA, BRCA, CESC, HNSC, KIRC, KIRP, PRAD, STAD, UCEC*	Increase	*SINE/MIR*
	CHOL, COAD, LIHC, LUAD, LUSC, READ, THCA	Decrease	
miR-211	*KIRC, KIRP, LIHC*	Increase	*LINE/L2*
	BRCA, HNSC, LUAD	Decrease	
miR-2114	*BRCA, KIRC, LIHC*	Increase	*LINE/CR1*
miR-2115	*BRCA*	Increase	*LINE/L1*
miR-224	*CESC, ESCA, HNSC, KIRC, LIHC, LUAD, LUSC, UCEC*	Increase	*DNA/MER135*
	BRCA, KICH	Decrease	
miR-2355	*BLCA, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, UCEC*	Increase	*LINE/RTE-BovB*
	LIHC, PAAD, THCA	Decrease	
miR-28	*HNSC, KIRC, LUAD, LUSC, PRAD*	Increase	*LINE/L2*
	BRCA, CHOL, COAD, ESCA, PCPG, READ, STAD, THCA	Decrease	
miR-31	*BLCA, CESC, HNSC, KIRP, LUAD, LUSC, STAD, THCA, UCEC*	Increase	*LINE/L2*
	KICH, KIRC, PRAD	Decrease	
miR-3117	*BLCA, BRCA, ESCA, HNSC*	Increase	*L1, MIR*
	KICH, THCA	Decrease	
miR-3144	*HNSC, KICH*	Increase	*L1*

Table 1. (Contd.)

MicroRNA	A tumor in which miRNA expression is altered	Change in the expression	TE, miRNA source
miR-3189	*KIRP, LUAD*	Increase	*MIR*
miR-3194	*STAD*	Increase	*MIR*
miR-3199	*LUSC*	Increase	*L2*
	BLCA, BRCA, KIRP, LIHC, LUAD, THCA	Decrease	
miR-3200	*BLCA, BRCA, CHOL, HNSC, KIRP, LIHC, LUSC, STAD, UCEC*	Increase	*ERVL*
	KIRC	Decrease	
miR-320b	*BLCA, BRCA, CHOL, ESCA, HNSC, KIRC, LUAD, LUSC, PRAD, STAD, UCEC*	Increase	*DNA/hAT-Charlie, L2*
	COAD, KICH	Decrease	
miR-320c	*CHOL, KIRC, LUSC, STAD, UCEC*	Increase	*L1, L2*
	COAD, READ	Decrease	
miR-320d	*BRCA, KIRC, KIRP, LUAD, LUSC, READ, STAD, UCEC*	Increase	*L1*
miR-326	*BLCA, KIRC, PCPG, UCEC*	Increase	*DNA/hAT-Tip100*
	BRCA, COAD, KICH, LIHC, LUSC, READ, THCA	Decrease	
miR-335	*BLCA, COAD, ESCA, HNSC, LUAD, LUSC, PRAD, STAD, THCA, UCEC*	Increase	*MIR*
	BRCA, KICH, KIRC, LIHC	Decrease	
miR-340	*BRCA, COAD, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, UCEC*	Increase	*DNA/TcMar*
	CHOL, LIHC, PAAD	Decrease	
miR-342	*BLCA, BRCA, CESC, HNSC, KIRC, KIRP, PRAD, STAD, UCEC*	Increase	*SINE/tRNA-RTE*
	COAD, LIHC, LUAD, PAAD, READ, THCA	Decrease	
miR-3622a	*LUAD*	Decrease	*SINE/Alu*
miR-3664	*BRCA, KIRC, UCEC*	Increase	*DNA/TcMar*
miR-3667	*BRCA*	Increase	*LTR-ERVL*
miR-3678	*BRCA, KIRC, LUSC*	Increase	*LINE-L2*
miR-3680	*HNSC, STAD*	Increase	*hAT-Tip100, L2, Alu*
miR-3681	*LIHC*	Increase	*ERVL*
miR-374a	*BLCA, BRCA, COAD, KIRC, KIRP, PRAD, READ, STAD*	Increase	*L2*
	CHOL, HNSC, LUSC	Decrease	
miR-374b	*BLCA, BRCA, COAD, ESCA, HNSC, KIRC, KIRP, PRAD, STAD, UCEC*	Increase	*L2*
	THCA	Decrease	
miR-378a	*PAAD*	Increase	*MIR*
	BRCA, CHOL, COAD, HNSC, LIHC, LUAD, PAAD, PRAD, READ, STAD	Decrease	
miR-3909	*LIHC*	Increase	*L2*
miR-3912	*KIRC, KIRP*	Increase	*L1, ERVL*
	LUSC, THCA	Decrease	
miR-3913	*BLCA, BRCA, CHOL, ESCA, HNSC, KIRP, LUAD, PRAD, STAD, UCEC*	Increase	*L1*
	KICH	Decrease	
miR-3922	*BRCA, HNSC, KIRC, LIHC, LUSC, STAD*	Increase	*L2*

Table 1. (Contd.)

MicroRNA	A tumor in which miRNA expression is altered	Change in the expression	TE, miRNA source
miR-3923	*LIHC*	Increase	*MaLR, L*1
miR-3927	*LUSC*	Increase	*ERVL*
miR-3928	*BLCA, BRCA, HNSC, KIRC, LIHC, LUSC, STAD, UCEC*	Increase	*L*1
miR-3934	*BRCA, HNSC, KIRC, LUSC, STAD, UCEC*	Increase	*MIR*
miR-3937	*KIRC*	Increase	*MaLR*
miR-421	*BLCA, BRCA, ESCA, HNSC, KIRP, LIHC, LUAD, LUSC, STAD, UCEC*	Increase	*L*2
	THCA	Decrease	
miR-450b	*BLCA, BRCA, COAD, ESCA, HNSC, KIRC, LUAD, LUSC, READ, STAD, THCA*	Increase	*L*1
	CHOL, KICH, KIRP, LIHC, PRAD, UCEC	Decrease	
miR-487b	*LUAD, LUSC*	Increase	*MIR*
	BRCA, HNSC, KICH, KIRC, KIRP, LIHC, PRAD, THCA, UCEC	Decrease	
miR-493	*BRCA, ESCA, LUAD, LUSC, READ, STAD*	Increase	*L*2
	KICH, KIRC, KIRP, LIHC, PRAD	Decrease	
miR-495	*COAD, LUAD, READ*	Increase	*MaLR*
	BRCA, HNSC, KICH, KIRC, KIRP, LIHC, THCA, UCEC	Decrease	
miR-502	*BLCA, LIHC, PRAD, STAD, UCEC*	Increase	*L*2
	COAD, KIRC, KIRP, LUSC, PAAD, THCA	Decrease	
miR-511	*HNSC, PRAD, READ, STAD*	Increase	*L*1
	BRCA, CHOL, KICH, KIRP, LIHC, LUSC, PCPG,	Decrease	
miR-517*a*	*LUAD*	Decrease	*Alu*
miR-520*d*	*LIHC*	Increase	*Alu*
miR-545	*BRCA, KIRC, LIHC, READ*	Increase	*L*2
miR-548*b*	*STAD, UCEC*	Increase	*TcMar*
	CHOL, HNSC, LUSC, THCA	Decrease	
miR-548*d*	*STAD, UCEC*	Increase	*TcMar*
miR-548*e*	*KIRC, LUAD, STAD*	Increase	*L*1, *TcMar*
miR-548*f*	*HNSC, LUSC, STAD*	Increase	*TcMar, L*1
miR-548*j*	*HNSC, LIHC, LUSC*	Increase	*TcMar*
	CHOL, THCA	Decrease	
miR-548*k*	*LIHC*	Increase	*hAT-Charlie*
miR-548*o*	*BRCA, LIHC, LUAD, LUSC*	Increase	*TcMar*
miR-548*q*	*THCA*	Decrease	*TcMar*
miR-548*s*	*UCEC*	Increase	*MIR, TcMar*
miR-548*v*	*BRCA, KICH, LUAD, LUSC, STAD, THCA, UCEC*	Increase	*MIR, TcMar*
	CHOL	Decrease	
miR-548*x*	*LIHC*	Increase	*L*1, *TcMar*
miR-548*y*	*LIHC, LUAD, LUSC*	Increase	*MaLR, TcMar*
miR-551*a*	*BRCA, LUAD, LUSC, STAD*	Increase	*L*1
miR-552	*LIHC, READ, STAD*	Increase	*L*1
miR-570	*KICH, LUSC, STAD, UCEC*	Increase	*TcMar, Tigge*

Table 1. (Contd.)

MicroRNA	A tumor in which miRNA expression is altered	Change in the expression	TE, miRNA source
miR-576	*BLCA, BRCA, ESCA, HNSC, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, READ, STAD, UCEC*	Increase	*L*1
	CHOL, LIHC, THCA	Decrease	
miR-577	*BLCA, CHOL, COAD, HNSC, KICH, LUAD, LUSC, READ, STAD, UCEC*	Increase	*L*2
	KIRC, KIRP, THCA	Decrease	
miR-581	*BRCA, KIRC, KIRP, LIHC, LUSC, UCEC*	Increase	*hAT-Charlie*
miR-582	*BRCA, COAD, KICH, PRAD, READ*	Increase	*LINE/CR*1
	CHOL, HNSC, LIHC, THCA	Decrease	
miR-584	*BLCA, ESCA, HNSC, KICH, KIRC, KIRP, PRAD, STAD*	Increase	*hAT-Blackjack*
	BRCA, LUAD, THCA	Decrease	
miR-585	*BRCA, KICH, KIRC, THCA*	Decrease	*ERVL-MaLR*
miR-616	*KICH, KIRC, KIRP, LUSC, UCEC*	Increase	*L*2
	CHOL, LIHC	Decrease	
miR-625	*BLCA, CHOL, KIRC, KIRP, LUAD, LUSC, STAD, UCEC*	Increase	*L*1
	COAD, READ, THCA	Decrease	
miR-652	*BLCA, ESCA, HNSC, LIHC, STAD, THCA, UCEC*	Increase	*DNA/hAT-Tip*100
	COAD, KICH, LUAD, LUSC, THCA	Decrease	
miR-664*a*	*KICH, PRAD*	Increase	*L*1
	COAD, ESCA, HNSC, PAAD, THCA	Decrease	
miR-708	*BLCA, BRCA, CHOL, COAD, HNSC, KIRC, LUAD, LUSC, PRAD, READ, STAD*	Increase	*L*2
	KICH, THCA	Decrease	
miR-769	*BLCA, BRCA, ESCA, HNSC, KIRC, KIRP, LIHC, LUSC, PRAD, STAD, UCEC*	Increase	*LINE/CR1*
	COAD	Decrease	
miR-885	*KICH*	Increase	*SINE/MIR*
	CHOL	Decrease	
miR-887	*BRCA*	Increase	*L*2
	HNSC, KICH, KIRP, PAAD, THCA	Decrease	
miR-891*a*	*KICH, LIHC, LUAD, LUSC, STAD, UCEC*	Increase	*SINE/MIR*
	BRCA, HNSC, KIRC, KIRP	Decrease	
miR-891*b*	*KICH, LUSC, UCEC*	Increase	*SINE/MIR*
	PRAD	Decrease	
miR-942	*BLCA, CESC, ESCA, HNSC, KICH, KIRC, KIRP, LUSC, PRAD, STAD, UCEC*	Increase	*L*2
	COAD, THCA	Decrease	
miR-95	*CHOL, COAD, PRAD, READ, STAD, UCEC*	Increase	*L*2
	HNSC, KICH, PCPG, THCA	Decrease	

BLCA is urothelial bladder cancer; *BRCA* is invasive breast cancer; *CESC* is cervical squamous cell carcinoma and endocervical adenocarcinoma; *CHOL* is cholangiocarcinoma; *COAD* is colon cancer; *ESCA* is esophageal cancer; *HNSC* is head and neck squamous cell carcinoma; *KICH* is chromophobe kidney cancer; *KIRC* is renal cell carcinoma of the kidney; *KIRP* is papillary renal cancer; *LIHC* is hepatocellular liver cancer; *LUAD* is lung adenocarcinoma; *LUSC* is squamous cell lung cancer; *PAAD* is pancreatic adenocarcinoma; *PRAD* is prostate adenocarcinoma; *PCPG* is pheochromocytoma and paraganglioma; *READ* is rectal adenocarcinoma; *STAD* is gastric adenocarcinoma; *THCA* is thyroid cancer; *UCEC* is uterine endometrial carcinoma.

Table 2. *TE*-derived miRNAs associated with aging and carcinogenesis

MiRNA	Tumor	TE source	Bibliographic link on the role of miRNAs in aging
miR-1248	*BRCA, LUSC, PRAD, UCEC, KIRC, LIHC, THCA*	*SINE/Alu*	[40]
miR-151*a*	*BLCA, BRCA, CESC, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, UCEC*	*LINE/L2*	[40]
miR-192	*BLCA, BRCA, COAD, KIRC, LUAD, LUSC, PRAD, READ, STAD, UCEC, CHOL, KICH, KIRP, LICH, THCA*	*LINE/L2*	[49]
miR-1976	*BLCA, BRCA, CESC, HNSC, KIRC, KIRP, PRAD, STAD, UCEC, CHOL, COAD, LIHC, LUAD, LUSC, READ, THCA*	*SINE/MIR*	[72]
miR-211	*KIRC, KIRP, LIHC, BRCA, HNSC, LUAD*	*LINE/L2*	[55]
miR-28	*HNSC, KIRC, LUAD, LUSC, PRAD, BRCA, CHOL, COAD, ESCA, PCPG, READ, STAD, THCA*	*LINE/L2*	[70]
miR-31	*BLCA, CESC, HNSC, KIRP, LUAD, LUSC, STAD, THCA, UCEC, KICH, KIRC, PRAD*	*LINE/L2*	[15, 20]
miR-320*c*	*CHOL, KIRC, LUSC, STAD, UCEC, COAD, READ*	*LINE/L1, L2*	[60]
miR-335	*BLCA, COAD, ESCA, HNSC, LUAD, LUSC, PRAD, STAD, THCA, UCEC, BRCA, KICH, KIRC, LIHC*	*SINE/MIR*	[45]
miR-340	*BRCA, COAD, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, UCEC, CHOL, LIHC, PAAD*	*DNA/TcMar-Mariner*	[69]
miR-378*a*	*PAAD, BRCA, CHOL, COAD, HNSC, LIHC, LUAD, PAAD, PRAD, READ, STAD*	*SINE/MIR*	[28]
miR-450*b*	*BLCA, BRCA, COAD, ESCA, HNSC, KIRC, LUAD, LUSC, READ, STAD, THCA, CHOL, KICH, KIRP, LIHC, PRAD, UCEC*	*LINE/L1*	[38]
miR-487*b*	*LUAD, LUSC, BRCA, HNSC, KICH, KIRC, KIRP, LIHC, PRAD, THCA, UCEC*	*SINE/MIR*	[71]
miR-495	*COAD, LUAD, READ, BRCA, HNSC, KICH, KIRC, KIRP, LIHC, THCA, UCEC*	*ERVL-MaLR*	[37]
miR-511	*HNSC, PRAD, READ, STAD, BRCA, CHOL, KICH, KIRP, LIHC, LUSC, PCPG*	*LINE/L1*	[73]
miR-570	*KICH, LUSC, STAD, UCEC*	*TcMar-Mariner*	[9]
miR-576	*BLCA, BRCA, ESCA, HNSC, KICH, KIRC, KIRP, LUAD, LUSC, PRAD, READ, STAD, UCEC, CHOL, LIHC, THCA*	*LINE/L1*	[31]
miR-585	*BRCA, KICH, KIRC, THCA*	*ERVL-MaLR*	[21]
miR-625	*BLCA, CHOL, KIRC, KIRP, LUAD, LUSC, STAD, UCEC, COAD, READ, THCA*	*LINE/L1*	[58]
miR-708	*BLCA, BRCA, CHOL, COAD, HNSC, KIRC, LUAD, LUSC, PRAD, READ, STAD, KICH, THCA*	*LINE/L2*	[36]
miR-885	*KICH, CHOL*	*SINE/MIR*	[10]

Relationship between Peptides and Transposons during Aging and Carcinogenesis

The role of TEs in the origin of miRNAs [26, 44, 57, 67], along with TEs dysregulation during aging [8, 12, 18, 19, 24, 34, 42, 47, 62] and the development of malignant neoplasms [6, 11, 48] indicates the possibility of finding ways to specifically influence these processes. Peptides used in gerontology, the protective role of which in relation to carcinogenesis has been shown in experiments on animals, may become the most promising tools for this [2, 3]. Indeed, according to recent data, the possibility of the translation of pri-miRNAs with the formation of functional peptides, which are designated as *miPEP* [63], has been proven due to the presence of small open reading frames (*smORF*) that interact with ribosomes. *miPEP* can regulate the expression of specific protein-coding genes, as well as the genes of their own microRNAs. This property has been proven. Moreover, such peptides are

used in agriculture to increase the yield of plants. For example, *miPEP*172*c* stimulates the level of *miR*172 and is used to stimulate the formation of nodules in the root system of soybeans, which are involved in symbiosis with rhizobia [16].

In humans, various peptides that are formed during the translation of long ncRNAs, circular RNAs, microRNAs and play an important role in the development and progression of malignant neoplasms have been identified [63]. For example, a conserved peptide consisting of 53 amino acids is formed from the long ncRNA *HOXB-AS*3 and suppresses the development of colon cancer by regulating the alternative splicing of pyruvate kinase-M and reprogramming tumor metabolism [30]. Micropeptides *miPEP*-200*a* (187 amino acids) and *miPEP*-200*b* (54 amino acids), which are encoded in *miR*-200*a* and *miR*-200*b* pri-miRNAs, inhibit the migration of prostate cancer cells by suppressing the process of epithelial-mesenchymal transition. The mechanism of action of *miPEP*-200*a* and *miPEP*-200*b* is associated with suppression of the expression of vimentin, E-cadherin, and beta-catenin [25]. Interestingly, some *miPEP* are encoded in pri-miRNAs annotated as long ncRNAs due to their lack of long reading frames. Recent ribosome profiling and proteomic database studies have identified 48 different human pri-miRNAs that potentially encode *miPEP*. Like plant micropeptides translated from pri-miRNAs [16], some *miPEP* (*miPEP*133) are characterized by positive self-regulation.

Although no such feature was found for *miPEP*-200*a* and *miPEP*-200*b* [43], miRNAs from which they are translated are also involved in the regulation of carcinogenesis [74], including the same pathways (epithelial-mesenchymal transition) as their *miPEP* [27]. Similar properties were also found for other micropeptides. For example, *miPEP*-155 suppresses autoimmune inflammation in humans by inhibiting antigen transport and presentation in antigen-presenting cells [39]. At the same time, *miR*-155 is involved in innate and acquired immunity, and also has oncogenic properties in acute myeloid leukemia and lymphoma [59]. The potential of *miPEP* use is associated with their oncosuppressive effect. For example, *miPEP*-133, which is translated from *pri-miRNA*-34*a*, enhances *p*53 transcription by altering mitochondrial functions. At the same time, *p*53 serves as a transcription factor for the *pri-miR*-34*a* gene [33].

Thus, the use of both peptides and mature miRNAs formed from mRNAs encoding them is promising in oncology. Currently, various peptides that have potential applications or are already being used for the treatment of malignant neoplasms and their diagnosis have been described. For example, the peptide ^{99m}*TC-HYNIC-*$(Ser)_3$*-LTVPWY* specifically accumulates in glioblastoma and is therefore used as a marker to detect this type of tumor [52]. Quantum dot (QD) nanoparticles with the *RGD* peptide (QDs *RGD*), which specifically bind to the cell surface αvβ3 integrin, inhibiting the proliferation, migration, and invasion of cancer cells, are of significant potential for the diagnosis and therapy of pancreatic cancer [53]. A promising target for antitumor therapy in prostate cancer is the gastrin-releasing peptide receptor (GRPr). A high level of tumor uptake of [177*Lu*]*Lu-RM*2 (GRPr antagonist) was demonstrated during targeted radiation therapy [35]. A promising direction for the development of cancer treatment methods is the use of RNA interference (RNAi) components. Small interfering RNAs (siRNAs) have been developed that suppress *ROR*1 (an oncoembryonic gene overexpressed in many cancers). For their delivery to breast-cancer cells, gold nanoparticles coated with the *TAT* peptide of the human immunodeficiency virus-1 are used [5]. Patch-1-interacting peptide, an inhibitor of Hedgehog signals, has been shown to inhibit the proliferation and migration of fibroblasts and tumor cells in pancreatic ductal adenocarcinoma (PDAC), reduce the formation of extracellular matrix and transforming growth factor β1 in fibroblasts, and enhance *HLA-ABC* expression in PDAC cells and IFN in lymphocytes. This peptide is promising for the treatment of adenocarcinoma resistant to immunotherapy [41].

The study of the role of TEs in the mechanisms of aging can become the basis for the development of antitumor therapy. For example, the induction of an interferon response in response to REs activation contributes to the progression of aging and associated inflammatory diseases [19]. This property of *HERV* is used as an internal trigger for MN sensitization to immunotherapy. This is due to the reactivation of *HERV* expression in carcinogenesis due to EG dysregulation during malignant transformation. The interferon response is caused by "viral mimicry" of *HERV*, which act as internal adjuvants and are identified by cytotoxic CD8+ T lymphocytes, resulting in cancer-cell recognition. The combination of "viral mimicry" and T-cell response can provide a powerful antitumor effect in the treatment of cancer [7]. An effective direction in this area is DNA vaccination against *HERV*-encoding genes such as *ENV*, which elicits an antigen-specific antitumor *CD*8+ T-cell response. The most promising approach is the use of therapeutic vaccines based on an adenoviral vector, the application of which stimulates the response of not only *CD*8+, but also *CD*4+ T-lymphocytes and *B*-cells [11].

Nucleoside reverse-transcriptase inhibitors (NRTIs) have been found to counteract the IFN1 response induced by *LINE*1 cDNA. Experimental exposure of mice to lamivudine suppressed IFN1 activation and aging-induced inflammation in tissues. This approach is expected to be used to treat aging-related diseases in humans [19]. The rejuvenating effect of NRTI was confirmed in another experiment on mice deficient in *SIRT*6, which was also associated with the suppression of IFN1 production [54]. Since the accumulation of *Alu* in the *NLRP*3 inflammosome leads to death of the

retinal pigment epithelium in senile macular degeneration, lamivudine has been proposed for the treatment of this pathology in humans. In a culture of human retinal pigment epithelium cells, lamivudine reduced the levels of *IL*-18 and *IL*-1β compared with the control, which showed promise of its use in clinical practice [66]. However, such approaches should take into account that aging is caused not so much by the pathological activation of ERs, but by an imbalance in their transcription. A unilateral approach to *L*1 suppression can lead to serious complications, such as an increased risk of cardiovascular disease and thrombosis, since platelets normally contain endogenous *LINE*1 reverse transcriptase, which is used as a regulator of their activation [50]. Indeed, in relation to the use of *NRTI* in clinical practice, despite their effectiveness in the experiment [19, 54, 66], these drugs can cause the opposite effect depending on the cell type. Thus, it has been shown that *NRTI* cause the increased production of ROS and mitochondrial dysfunction, which leads to premature aging of the vascular endothelium [14]. Highly active antiretroviral therapy is used in HIV therapy, but this does not increase the life expectancy of patients compared to the general population. Moreover, *NRTI* have been shown to cause chronic pain due to spinal-cord inflammation by increasing the production of proinflammatory cytokines such as *TNF*-α and *IL*-1β, as well as inducing *Wnt*5a [68].

Therefore, it is promising to influence strictly specific RE, the imbalance of which is most pronounced during aging. For example, the enzyme telomerase is needed to lengthen telomeres, preventing cell aging. At the same time, it belongs to reverse transcriptases, i.e., specific products of REs genes. It has been shown that ROS reduce the activity of telomerase, while antioxidants (*N*-acetylcysteine) suppress its nuclear export, increasing the concentration of telomerase and preventing cellular senescence [29]. An experiment on a culture of senescent human cells showed the effectiveness of lentivirus-mediated depletion of *Alu*-transcripts to restore stem-cell self-renewal [62]. A specific approach is needed to modulate TEs activity during aging. In this case, microRNAs and peptides that can act on strictly defined protein-coding genes along with genes of transposons and long ncRNAs can become the most promising target molecules. To accurately identify specific microRNAs in order to slow down aging and prevent cancer, it is necessary to create databases with the distribution of microRNAs in accordance with origin (directly from the transcripts of certain TEs, from long ncRNAs formed through evolution from *T* genes), as well as to design gene networks for the targets of each individual microRNA taking into account the cascade of reactions caused by this microRNA. The use of this approach could become a promising basis for the selection of optimal microRNAs as tools for targeting the aging process and treating malignant neoplasms.

CONCLUSIONS

The role of epigenetic factors and transposons in the development of aging and carcinogenesis has been proven. To determine the link between these processes, an analysis of the *OncomiR* databases on the role of specific microRNAs in carcinogenesis, MDT on the origin of microRNAs from transposons, and an analysis of publications of original studies on the effect of specific microRNAs on aging were carried out. As a result, 94 different transposon-derived miRNAs, the expression of which changes in certain malignant neoplasms, were found. Moreover, for 21 of these 94 miRNAs, the role in the mechanisms of human aging is described in original works. The results obtained are described for the first time and may be of interest for further research due to the prospects of using miRNAs and peptides that regulate the expression of specific genes and TEs for the development of antitumor therapy and slowing down the mechanisms of aging in the body.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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