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REVIEW

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MicroRNAs influence and longevity

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Abstract

Background: MiRNAs play critical roles in the regulation of cellular function, life span, and the aging process. They can affect longevity positively and negatively through different aging pathways.

Main text: MiRNAs are a group of short non-coding RNAs that regulate gene expressions at post-transcriptional levels. The different types of alterations in miRNAs biogenesis, mRNA expressions, and activities of miRNA-protein complexes can affect the regulation of normal post-transcriptional gene process, which may lead to aging, age-related diseases, and an earlier death. It seems that the influence of deregulation of miRNAs on senescence and age-related diseases occurring by targeting aging molecular pathways can be used for diagnosis and prognosis of them. Therefore, the expression and function of miRNAs should be studied more accurately with new applicable and validated experimental tools. However, the current review wishes to highlight simply a connection among miRNAs, senescence and some age-related diseases.

Conclusion: Despite several research indicating the key roles of miRNAs in aging and longevity, further investigations are still needed to elucidate the essential roles of miRNAs in controlling mRNA regulation, cell proliferation, death and/or protection during stress and health problems. Besides, more research on miRNAs will help to identify new targets for alternative strategies regarding effectively screen, treat, and prevent diseases as well as make slow the aging process.

Keywords: Aging, Cancer, Cognition, Longevity, MiRNA, Stress

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are a large class of small non-coding RNAs functioning as the important regulators of a wide range of cellular processes [1] that have been identified firstly in C. elegans in 1993 [2–4]. They act as mediators that can regulate post-transcriptional gene expressions [5–7]; therefore, they are able to control cellular behavior, balance in biological processes, development, and diseases [7, 8] by modulating gene expression [1]. The post-transcriptional gene effect of miRNAs happens by base-pair binding on their related mRNAs targeting untranslated regions (UTRs) of genes and multiple sites within a single UTR [9]. Each miRNA can target multiple mRNAs, and one mRNA can be regulated by multiple miRNAs [10, 11]. MiRNAs have been found in plants, animals, bacteria and some viruses [12] by their gene expression profiling. In animal models, miRNAs contribute into genetic networks and metabolic pathways. It seems that miRNAs play critical roles in the occurrence of pathological conditions like neurodegeneration and cancer following the alterations in the expression of specific miRNAs in the brain and/or homeostasis in the body [6, 9].

Besides, some miRNAs are related to the regulation of senescence in a variety of human cells [8]. As it is shown in Table 1, cancer, cognition, and senescence can be associated with miRNAs [2, 6, 13–17]. Until now, more than 950 miRNAs in humans have been found [18]. It has been indicated that some of miRNAs are tissue- or cell-specific and some of them are house-keeping molecules. However, a relatively small number of miRNAs have probably key functions in order to regulate the human genome and affect post-transcriptional physiological process. It seems

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Table 1 Showing the correlation of miRNAs with cancer, cognitive function and senescence

	MiRNAs	Cancer	Neurodegeneration and cognition	Senescence
1	miR-1	√	√	√
2	Let-7	√	√	√
3	Let-7b??	√	√	√
4	MiR-9	√	√	√
5	miR-17	√	√	√
6	MiR-21	√	√	√
7	MiR-26b	√	√	√
8	MiR-29a	√	√	√
9	MiR-29b	√	√	√
10	miR-30a	√	√	√
11	MiR-31	√	√	√
12	MiR-34	√	√	√
13	miR-34a	√	√	√
14	miR-71	??	??	√
15	miR-100	√	√	√
16	MiR-107	√	√	√
17	MiR-124	√	√	√
18	MiR-125b	√	√	√
19	MiR-132	√	√	??
20	MiR-137	√	√	√
21	MiR-146	√	√	√
22	MiR-146a	√	√	√
23	MiR-155	√	√	√
24	miR-199a	√	√	√
25	Mir-206	√	√	√
26	MiR-210	√	√	√
27	miR-211-5p	√	√	√
28	MiR-212	√	√	√
29	MiR-217	√	??	√
30	MiR-221	√	√	√
31	MiR-222	√	√	√
32	miR-320	√	√	√
33	MiR-340-3p	√	??	√
34	MiR-371-3	√	??	??
35	MiR-374a-5p	√	√	√
36	MiR-376c-3p	√	√	√
37	miR-483	√	??	√
38	MiR-484	√	√	√
39	MiR-567	√	√	??
41	MiR-1225-3p	√	??	√
42	MiR-5095	√	??	√

√ presence of correlation

?? there are not studies obviously indicating the correlation

that they can influence differentiation and tumor suppression in cells, which may relate to some pathological processes such as carcinogenesis or senescence [10]. Thus, miRNAs have been suggested to be used as biomarkers to evaluate many diseases and aging [9], even though it is difficult to estimate miRNAs quantification due to their small size, low copy number, interference from other small RNAs, and contamination by degradation products of mRNAs or other RNA species [2].

Despite the presence of miRNAs in tissue cells, they can also be found in the body fluids and extracellular environments such as plasma, serum, urine, saliva, seminal fluid, ascites, pleural effusions, and cerebrospinal fluid [4, 19]. They are injected to the circulation in different ways. It can happen through a passive leakage following apoptosis, necrosis, inflammation, or an active secretion by exosomes/microvesicles, lipoproteins, and RNA–protein complex. Circulating miRNAs following packing into exosomes have been found specific to a tissue or a disease, which can indicate degree of tumor progression and stage of cancer. Several studies have also shown that the abnormality of specific circulating miRNAs can be associated with the manifestation, development, invasion, and metastasis of cancer [19]. However, miRNAs-related studies will increase our understanding regarding age-related gene regulation and improve miRNA-based biomarker development for an advance in RNA-based diagnosis and therapies [9]. Thus, the aging process and age-related problems and conditions can be better monitored. In addition, further studies will help to better identify specific miRNAs and their changes related to caloric restriction, aging and age-related diseases pathways.

Biogenesis of miRNA in animals

MiRNAs are a group of small non-coding RNA [8, 14, 20, 21] with approximately 21–24 nucleotide (nt) in length [3] that are widespread and probably regulate > 50% of the human genome [22]. They are produced from precursor molecules (pri-miRNAs), which are made through transcription by RNA polymerase II from independent genes or derived from introns after splicing. Pri-miRNAs are subsequently converted to pre-miRNAs by Drosha enzyme and exported to the cytoplasm. Dicer enzyme cleaves them to the mature approximately 20-bp miRNA 5p/3p pairs. One strand of this duplex will incorporate into the miRNA-inducing silencing complex (miRISC) [3, 23–25]. The process is summarized in Fig. 1.

The transcription of DNA coding for miRNAs and the related protein-coding genes occurs in a similar way. The mature miRNA directly interacts with a member of the Argonaute protein family, which results in the formation of the RNA-induced silencing complex (RISC). As a component of RISC, miRNAs direct the post-transcriptional repression. Thus, miRNAs show regulatory functions

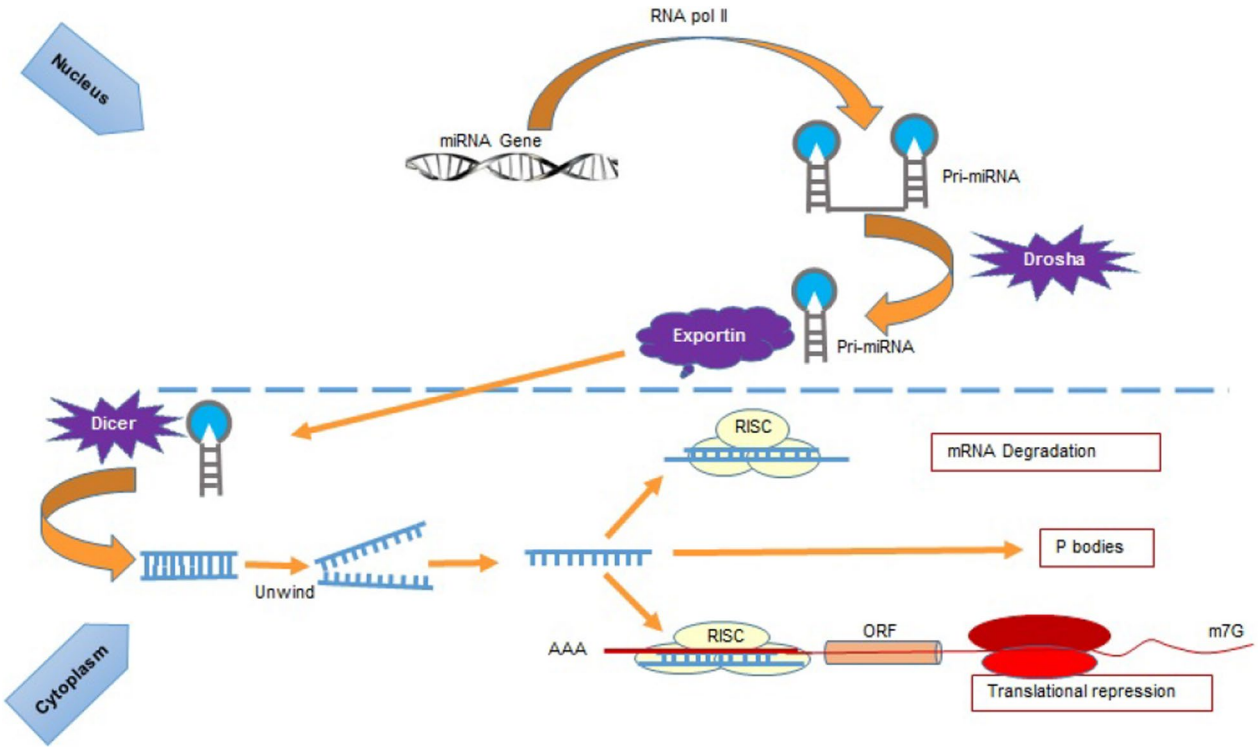

Fig. 1 Gene silencing procedure by miRNA

regarding gene expression and can play a central role in several cellular processes including cell growth, differentiation, proliferation, and apoptosis [18].

MiRNAs are potent negative regulators of gene expressions [8]. They regulate their target genes through either translational repression or mRNA degradation. Such functions happen via binding to the complementary regions of messenger transcripts [14] and targeting specific messenger RNAs (mRNAs) [21]. Each miRNA can target up to hundreds of mRNAs [8, 18, 26] and they are able to regulate the expression of more than 60% of protein-coding genes of the human genome [27]. The effect of miRNAs on the regulation of many human genes [28–30] indicates their critical roles in a variety of biological processes [8, 21].

MiRNAs are important epigenetic regulators [14] and many of them are also self-regulated epigenetically [8]. For instance, epigenetically transcriptional repression by miRNAs can be through DNA methylation and histone modifications in which to affect subsequently mostly CpG islands located in the promoter regions of genes and result in silencing of genes [31]. Moreover, miRNAs can also down-regulate mRNAs [26] by declining target mRNAs or the levels of translation into proteins [32]. The silence of target mRNAs is based on base-pairing recognition sites [8] and the interaction of miRNAs with the 3' UTR of target mRNAs. Thus, mRNA degradation and/or translational repression result in gene silencing [4, 29, 33, 34].

However, miRNAs are known as major elements that can contribute into complex functional pathways, control cellular processes [35], and the regulation of biological functions [36] such as differentiation, proliferation, apoptosis, replicative senescence [21], development, and stress responses [35] in plants and animals (Table 2).

MiRNAs are in both intracellular and extracellular regions of the body [61]. Extracellular miRNAs can be used as biomarkers in which to evaluate a variety of diseases such as liver fibrosis and hepatocellular carcinoma. Besides, miRNAs play important roles in intercellular communication. Such miRNAs can be delivered to target cells, where they have hormone-like activities and may act as autocrine, paracrine, and/or endocrine regulators. It can modulate cellular activities [4] by changing the expression of proteins following the specific inhibition of mRNA targets in cell-free miRNAs, which may originate from one cell type and acquired by another cells or other cell types [11]. In addition, miRNAs, gene expression patterns, physiology, and homeostasis in cells are related to the effects of different factors such as stress [135].

Table 2 Examples of miRNAs, targets and functions involved

	MiRNAs	Pathways	Functions involved	References
1	miR-1	IGF1 and HDAC4, mTORmiR1HDAC4follistatin pathway, Notch signaling pathway	Differentiation of cardiac muscle, skeletal muscle differentiation following aging, inhibit tumor growth and metastasis, cognition	[37–39]
2	Let-7	DAF-12 signaling pathway, insulin/IGF signaling (IIS) pathway, LOX-1-ROS-p38MAPK-NF-κB signaling pathway, LOX-1-ROS-PKB-eNOS pathway, TGF-β pathway, RAS and KIT signaling pathways	Senescence, age-dependent changes in the vasculature and vascular aging, tumor suppressor and oncogene, apoptosis, migration, and invasion, potential diagnostic and prognostic marker, neurodegeneration	[2, 40–44]
4	MiR-9	HIF-1α-VEGF signaling pathway, p16-Prb pathway	Neurogenesis, angiogenesis, regulation of lymphatic inflammatory and lymphangiogenic pathways, cognition, cell proliferation, migration, invasion and angiogenesis	[45, 46]
5	miR-17	the P53, ERB, and MAPK signaling pathways	Autophagy, apoptosis, growth, chemoresistance, regulated genes involved in cell cycle control and tumor development, aging, cognition	[47–49]
6	MiR-21	RasA1 signaling pathway KRAS, RAS/MEK/extracellular signal-regulated kinase (ERK) signaling pathway, PI3K/AKT pathway	Promotes cell proliferation, anti-apoptosis signaling and malignant transformation, inflammation-related miRNAs, advanced oxidation protein products (AOPP), with the presence of frailty, age-related frailty	[50–52]
7	MiR-26b	Rb1-E2F and p27(kip1) pathways, Wnt-β-catenin signaling pathway,	Cell cycle influence	[53]
8	MiR-29a	MMP2 signaling pathway, Smad4-dependent way, TGF-β signaling pathway, Wnt-β-catenin signaling pathway, PTEN/AKT/GSK3β signaling pathway, TGF-beta1/miR-29a/HDAC4 pathway, Hedgehog signaling pathway, NF-κB pathway, p42-44 MAPK pathway and Wnt-β-catenin pathway	Cell proliferation, apoptosis, angiogenesis, invasion, metastasis, drug resistance and chemotherapy resistance	[54, 55]
9	MiR-29b	PI3K-Akt signaling pathways, PTEN/AKT/β-catenin signaling pathway, AKT/GSK-3β/β-catenin signaling pathway, AKT/mTOR pathway, PTEN/AKT/GSK-3β/β-catenin signaling pathway. Wnt-β-catenin pathway	Effect on tumor suppressive genes, aggressiveness and prognosis of malignant neoplasms, cell cycle regulation, fibrosis and neuronal regulations, tumorigenesis and cellular senescence, osteogenic differentiation	[54–58]
10	miR-30a	TOR pathway, Wnt pathway, Fgf signaling pathway, Wnt/β-catenin pathway, MTDH/PTEN/Akt pathway, PI3K signaling pathway, PI3K/Akt/mTOR signaling pathway, EZH2/miR-30a/KPNB1 signaling pathway	Inhibiting proliferation, invasion, and migration, inducing apoptosis. synaptic plasticity and cognition	[2, 59, 60]
11	MiR-31	RAS/MAPK pathway, RAS/MARK pathway PI3K/AKT pathway, RB/E2F pathway, P53 pathway, Rho/ROCK pathway, NF-κB pathway, E2F pathway, WNT pathway,	Proliferation, Tumorigenesis, migration, anti-apoptosis, improving cognition	[61–64]
12	MiR-34	MEK/ERK signaling pathway, E2F pathway	Inhibits the cell cycle and cell proliferation	[65]
13	miR-34a	FoxM1/c-Myc pathway, p53 pathway, HIF-1a pathway	Cell cycle influence, response to hypoxia stress	[2, 53, 66]
14	miR-71	p38 pathway, KGB-1 on DAF-16 involved pathways, PI3K pathway, UNC-31–mediated InsR/PI3K signaling	Long-term survival	[67–69]
15	miR-100	FGFR3 pathway, HIF-1α and HIF-2α dependent pathway, mTOR pathway, MAPK pathway, PI3K pathway, PKB pathway	Subtle, maintaining cell viability, cognition	[2, 70, 71]
16	MiR-107	Wnt/β-catenin signaling pathway,	Cell cycle influence, the progression of cell growth, migration, and invasion in various cancers,	[72]
17	MiR-124	Notch signaling pathway, miR124/AMPK/mTOR pathway, miR-124-STAT3 pathway, TLR signaling pathway, JNK and p38 pathways, MiR-124-PTPN1 signaling pathway	Proliferation, differentiation, proliferation, apoptosis, and growth of cells as well as immunity	[73, 74]
18	MiR-125b	NF-kB pathway, CDKN2A pathway, p53 pathway, PI3K/Akt/mTOR pathway, ErbB2 pathway, Wnt pathway,	Proliferation, differentiation, metabolism, apoptosis, drug resistance, tumor immunity, diagnosis, prognosis and clinical treatment of tumors, neuron inflammation	[53, 75]

Table 2 (continued)

	MiRNAs	Pathways	Functions involved	References
19	MiR-132	HIF-1α pathway, PTEN/AKT/FOXO3 signaling pathway, AKT signaling pathway,	Neuronal health, neuron morphogenesis and plasticity, suppresses the migration and invasion of cancer	[2, 76–79]
20	MiR-137	miR-137/Src/MAPK signaling pathway, ERK1/2 pathway	Neuroprotective effects, neural development, neoplastic transformation, act as a tumor suppressor, cell proliferation, differentiation, migration and metastasis, and induce cell cycle arrest, differentiation and apoptosis	[80, 81]
21	MiR-146	RAS pathway, NOTCH pathway, NF-κB pathway;	Cell proliferation, invasion, and metastasis, act as a tumor suppressor, inflammation	[82–84]
22	MiR-146a	NF-kB pathway, TLR4/NF-κB pathway, TNFα inflammatory pathway, IL-1α signaling pathway	Neuroinflammation, Amyloid-beta deposition, inflammation, innate immunity, and cancer, as well as to regulate mitochondrial functions, inflammation-aging, inhibition of proinflammatory pathways	[51, 53, 85, 86]
23	MiR-155	BCR pathway, Toll-like receptor (TLR) pathway, ERK pathway, c-Jun N-terminal kinase pathway (JNK), SOCS1 pathway, JAK2/STAT3 pathway, RhoA pathway, PI3K/AKT pathway	Tumor inflammation and growth, chemotherapy resistance, regulates immune system including B cells and T cells. cognition	[87–90]
24	miR-199a	HIF-1α pathway, Toll-like receptor signaling pathway, insulin signaling pathway, adipocytokine signaling pathway (KEGG), PI3K/AKT/mTOR signaling pathway, Wnt/β-catenin signaling pathway	Master regulators for cellular processes, function in immune system, potent tumor suppressor, cognition, proliferation, migration, invasion, apoptosis, autophagy and glycometabolism	[2, 91–94]
25	Mir-206	IGF1 pathway, MRFs pathway, BDNF pathway, Fstl1 pathway, MEF2 pathway, IL-17 pathway, HIF-1α pathway; WNT signaling pathway; mitochondrial apoptosis pathway;	Neuronal differentiation, brain development, functions in neuromuscular synapse development and maintenance, muscle cell proliferation; inhibits tumor cell proliferation, migration, and invasion, and induces apoptosis	[37, 95, 96]
26	MiR-210	Increased ROS pathway, protein kinase B (Akt) pathway and p53-dependent pathway, mTOR pathway, HIF-1α pathway, PI3K pathway, Akt pathway, ERK pathway, NFκB pathway, p53 pathway	Amyloid-beta deposition, mitochondrial metabolism, angiogenesis, the DNA damage response, cell proliferation, apoptosis	[53, 85, 97]
27	miR-211-5p	Ezrin/Fak/Src signaling pathway, JAK/STAT3 pathway, PERK pathway, MiR-211-5p-NUAK1 Pathway	Aging, proliferation, prognosis in various cancers, apoptosis, cell proliferation, invasion, apoptosis and immunity, cognition	[41, 98, 99]
28	MiR-212	Sirtuin signaling pathway, Hedgehog signaling pathway, Wnt/βcatenin pathway, AKT signaling pathway,	Serve as an oncogene or tumor suppressor, oncogenesis, development and metastasis of cancer, proliferation, invasion, Metastasis, cognition, life span	[76, 79, 100, 101]
29	MiR-217	Sirtuin signaling pathway, HIF-1α pathway, MAPK signaling pathway,	Hemostasis, normal growth, and maintenance of cells, proliferation, apoptosis, transcription regulation and development, invasion, drug resistance	[2, 102]
30	MiR-221	PTEN pathway, AKT pathway, JAK/STAT3 signaling pathway, PTEN-mediated PI3K/Akt pathway	Tumorigenesis and progression, chemotherapy resistance, cancer cell proliferation, invasion and metastasis, stemness promotion, cell survival, the relapse of cancer cells, cognition, life span?	[2, 49, 103–105]
31	MiR-222	PTEN pathway, p27kip1 and c-kit pathway, PTEN-mediated PI3K/Akt pathway; p53 pathway	Tumor initiation and progressions, cancer cell proliferation, invasion and metastasis, stemness promotion, cell survival, chemoresistance, the relapse of cancer cells, cognition,	[2, 48, 103, 104, 106]
32	miR-320	insulin/IGF signaling (IIS) signaling pathway, AQP1-mediated proliferative signaling pathway,	Neurodegenerative disease, tumor suppressor, to promote tumorigenesis, life span	[2, 107–109]
33	MiR-340-3p	mTOR pathway	Affecting life span, Tumoral survival, Human longevity	[48, 110, 111]
34	MiR-371–3	PLA2/PKCα signaling pathway	tumor growth and metastasis, drug resistance, overall survival	[61, 112]
35	MiR-374a-5p	mTOR signaling pathway	Proliferation, migration, invasion, chemoresistance, prognosis, life span, cognition	[113–115]

Table 2 (continued)

	MiRNAs	Pathways	Functions involved	References
36	MiR-376c-3p	Wnt/β-catenin pathway	Life span, cell cycle progression, proliferation, migration, invasion, survival and poorly response to chemotherapy, inhibits apoptosis, cognition	[55, 116–118]
37	miR-483	Wnt/β-catenin signaling pathway, glucose/OGT/miR-483-3p signaling pathway, MAPK/ERK pathway, TGF-β pathway,	Antiaging properties, inflammation, proliferation, apoptosis, promote tumor development	[51, 119]
38	MiR-484	mTOR signaling pathway, Hippo signaling pathway, estrogen signaling pathway, interferon pathway	Mitochondrial fission, synaptic transmission and regulation of synaptic plasticity, synaptic function, ATP generation, presynaptic calcium level, oncogene, tumor suppressor, negative prognostic biomarker	[120–122]
39	MiR-567	PI3K/AKT/c-Myc pathway, cMras/miR-567/PTPRG regulatory pathway;	Biological processes in the neuronal cells, neuronal differentiation and brain development, tumorigenesis and development, cell proliferation, migration and invasion, induced G1/S transition, chemoresistance, tumor suppressor;	[123–128]
40	MiR-1225-3p	mTOR/p70S6K pathway, Melatonin pathway, MMEJ pathway,	Life span, role in repairing single-strand breaks during DNA replication, uncontrolled proliferation and progression of cancer,	[129–131]
41	MiR-5095	Wnt/b-catenin signaling pathway, melatonin pathway	Life span, inhibited cell proliferation, migration and invasion of glioblastoma; esophageal tumor development and progression	[129, 132–134]

Stress

Stress is caused by different stressors and is divided into acute, chronic and several forms. It can play an important role in daily life in which to threat an individual's homeostasis, well-being, health, and/or survival. Stress is with a systemic physiological response such as inflammatory and cellular reactions, metabolic processes, and epigenetic regulation [18]. The occurrence of stress in cells may happen due to sudden or frequent changes in environmental factors. Stress can damage existing macromolecules in living cells such as proteins, mRNAs, DNA, and lipids, which in turn can increase the risk of death, metabolic imbalances [136], and chronic diseases [20] such as cognitive decline and cancer with advancing age [2].

The severity and duration of stress can affect cellular homeostasis in which to return to stable state or modify to a new state. However, responses to stress in the body can occur through several mechanisms [136] including induction of molecular chaperones [137, 138], rapid clearance of damaged macromolecules [139], activation of specific gene expressions, growth arrest [140], and cell death [20].

MiRNAs play critical roles in main cellular processes. Their identifying helps to understand the cellular stress responses and the occurrence of senescence associated with environmental changes [20]. Nowadays, there is a better understanding regarding the miRNAs involving in physiological reactions and reaction pathways as well as their regulatory roles. For instance, the alteration of miRNAs concentration such as miR-21 has been detected in some stress-related pathological conditions and diseases such as psychiatric diseases [18]. MiRNAs have shown regulatory role in the control of specific mRNA translation. It leads to a gene-specific control over protein translation, which reversibly and rapidly can regulate cellular landscape and also enables survival during periods of extreme stress with efficient utilization of ATP turnover [12]. Responses of cells to stresses are in the form of restoring or reprogramming of gene expression patterns mediated by miRNA functions, the amounts of miRNAs, the amount of mRNA targets, and the activity of miRNA-protein complexes. The levels of cells reactions can determine specificity, time, and concentration of genes related to products expressed at each stress situation [20].

Several studies indicate that miRNAs can have a major regulatory influence over a number of cellular processes in which to play essential roles in prolonged environmental stress survival [12]. For instance, several miRNAs are involved in the regulation of psychological stress effects on the genesis and maintenance of many diseases [18]. In addition, stress regulates both transcription and the biogenesis of miRNAs, which results in the accumulation of pre-miRNAs, the reduction of mature miRNAs, or facilitating the processing of some miRNAs. Such regulatory effect happens by mediating of some important factors such as SMADs, p53 and breast cancer 1 (BRCA1) protein [24]. Besides, psychological stress results in oxidative stress by induction of the sympathetic-adrenal-medullary (SAM) and later the hypothalamic–pituitary–adrenal (HPA) axis, which in turn can cause protein damages and induce specific cellular stress response pathways [18].

Such connections between several miRNAs and pathways in the body can probably explain the effect of stress on aging and age-related changes. For example, there is an association between the expression of some miRNAs (miR-217, miR-100, miR-34a, miR-199a, and miR-132) and different factors of sirtuin 1 (SIRT1) protein, chemokine production, and hypoxia-inducible factor-1 alpha (HIF-1α). It seems that such relation can affect hemostasis, normal growth, and maintenance of cells in the body [2]. The effect of miRNAs happens through recognizing partly complementary sequences in their own mRNA targets and inhibition of their expression by translational repression or degradation of the target mRNAs. As follows, it results in controlling protein synthesis in cells, which in turn plays an important role in regulating cell proliferation, development, and aging [135].

Aging

Aging is due to the accumulation of genetically and environmentally damages [8, 141, 142] accompanied with the unregulated repair systems of DNA [8]. The accumulations of cellular and molecular damages can cause aging and the functional decline of organs, which results in the increased risk of susceptibility to diseases and mortality [21, 143].

The nine hallmarks indicating aging are genomic instability, telomere reduction, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Besides, further studies show the presence of other hallmarks such as dysregulation of the extracellular matrix in aging, for example aging lung [144].

The senescent cell phenotype is under the combination effects of cell changes in morphology, behavior, structure, and functions. These changes occur due to alterations probably happening in gene expressions [145], protein secretions [146], and inducibility of apoptosis, which may increase in senescent fibroblasts [147] and decrease in endothelial cells [148].

The harmful altered senescent cells functions may accelerate senescence and/or loss of cells within tissues, resulting in the age-associated decline of body function and the increased rate of age-associated diseases [8].

It has been indicated that tissue micro-environment changes happening due to the age-related accumulation of senescent cells can promote age-related phenotypes, cancer [149–151], and neurological disorders [8]. However, changes in patterns of gene expression in cells following the effects of non-coding RNAs, particularly miRNAs can lead to different functions in senescent cells [8].

As it has been noted, miRNAs play key roles in the regulation of development, apoptosis and metabolism in the body; therefore, they regulate aging and processes responsible for life span determination in vertebrates [152]. Studies on aging in animal models have supported the major roles of miRNAs in modulating life span and the aging process [2]. Age-related diseases can also be associated with changes in the expression of circulating miRNAs in the body fluids including serum and plasma. Such miRNAs are released during tissue injury or shed from the plasma membranes of various cell types. They are remarkably stable as well as resistant to heat, pH changes, long time storage, and repeated freeze and thaw cycles. Despite these findings, exact molecular pathways underlying aging are not yet well understood [8] and also little is known about the role of circulating miRNAs related to aging in humans [21].

Some of factors and pathways involved in the aging process are insulin/insulin-like growth factor (IGF)-1, phosphoinositide 3-kinase (PI3K), target of rapamycin (TOR), mitogen-activated protein kinase (MAPK), AMP-dependent protein kinase (AMPK), protein kinase C signaling pathway (PKC), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb), transforming growth factor beta (TGF-β), WNT signaling pathway (wingless-related integration site), Notch signaling pathway, receptor tyrosine kinase (c-Kit), and H2A histone family member X (H2AX). It seems that miRNAs affect the aging process by targeting these mentioned pathways including insulin/IGF-1 pathway [2, 153]. For example, miR-100, miR-30a, and miR-34a contribute into TOR pathway (miR-100, miR-30a) and aging signaling pathway (miR-34a) as the common pathways affecting life span and aging. It has also been found that changes in miRNAs expression with age are opposite to mRNAs expression [2]. However, miRNAs have roles in the regulating aging and age-related specific phenotypes of tissue and cell type with up-regulation, down-regulation and targeting the genes involved in aging pathways during cellular senescence. Various miRNAs expressions involved in aging process can be associated with specificity of tissue and the tissue-specific functions of aging signaling pathways. Despite the up-regulation of some of miRNAs, such as miR-34 and miR-71 with aging, the vast majority of C. elegans miRNAs expression is down-regulated with aging. Such differences in their expression can be due to the globality or specificity of those miRNAs related to a tissue or differences found among plants, animals and viruses. Thus, it is important to find various factors that can actively affect up- or down-regulation of miRNAs with aging [153].

Recent studies have shown miRNAs effects on aging and age-related diseases. For instance, miRNAs can regulate all related aspects of cutaneous biogenesis, functionality, and aging. It has been found that some miRNAs, such as let-7, miR-17, and miR-34, were down-regulated in long-lived individuals. Such conserved miRNAs in humans, known as longevity-related miRNAs, presumably promote life span prolongation. Conversely, miRNA let-7, miR-17, and miR-34 are up-regulated in some age-related diseases such as cancers [48] and cardiovascular diseases [154]. Therefore, further investigations are needed to elucidate the relation between miRNAs and healthy aging.

Longevity

The solution of longevity and how to have a healthy aging is one of the principal challenges in biology and medicine. The improvement of lifestyle and reduction of environmental hazards can prevent diseases and increase health in general population. Besides, the genetic assessment of exceptional individuals can provide important biological insights regarding the basis of healthy aging and human longevity [155]. However, genetics in aging is investigated in which to evaluate life span, longevity, exceptional longevity, and healthy aging. Longevity is defined as a specific advanced age or older, which is often considered 100 years or above. Besides, healthy aging states a combination of old age and health. It indicates the absence of certain diseases, disabilities, and health problems such as cognitive impairment and mobility disorders in older people. It is probably because such people live much healthier [155]. Several studies indicated that life span can be associated with miRNAs expression changes [21]; therefore, the identification of miRNAs roles in the induction and maintenance of senescence [20] will clarify the mechanisms associated with age-related diseases [8]. Thus, miRNAs can be good biomarkers used in order to facilitate predicting individuals' longevity [21] or treat premature aging and age-related diseases such as cognitive function in the future [156].

Different investigations have shown that changes in the expression of some miRNAs such as let-7, miR-17, and miR-34 have been involved in life span prolongation among long-lived individuals as well as age-related diseases such as cancers [48] and cardiovascular diseases [154]. Further studies suggested the expression profiles

of miRNAs miR-211-5p, miR-374a-5p, miR-340-3p, miR-376c-3p, miR-5095, miR-1225-3p [129], miR-146a, miR-21, and miR-483 can be used as useful biomarkers for predicting and evaluating aging and age-related diseases. It has been suggested that miRNAs with the decreased production of melatonin, the increased levels of inflammatory and ROS markers [51], and their association with mRNA and epigenetic factors can affect aging and age-related diseases [154] like neurodegenerative and cognitive disorders [157].

Cognition

Neurodegenerative diseases are progressive disorders of the nervous system [6]. There are many cognitive disorders such as Alzheimer, Parkinson, Schizophrenia, Huntington's diseases, and Autism spectrum disorders [157]. Their pathogenesis is complex and involves the alterations of multiple basic cellular pathways and non-coding RNAs [6]. Non-coding RNAs like miRNAs [6] play key roles in a wide range of physiological processes in the body [158, 159]. For example, miRNAs can regulate the neuronal activity, which contributes into neurogenesis, neurodegeneration, and cognition [6, 160, 161]. Several studies showed that the genetic deletion of dicer and the disruption of miRNAs expressions can affect development, differentiation, morphogenesis, and signaling in neurons [158, 159].

Alzheimer disease is one of neurodegenerative diseases that is the most common cause of dementia. It is mostly related to the aging process [162]. Many cases of dementia have been progressed from mild cognitive impairment (MCI), which is a transitional phase between the cognitive changes of normal aging and senile dementia. It presents with memory or cognitive impairment without significant effect on daily living. The conversion rate of MCI to dementia is approximately 10–15% each year. As many people suffer from dementia; therefore, early and effective diagnosis and intervention of MCI can have a great effect to reduce or delay the progression of dementia [163, 164].

MiRNAs are one of the main regulators of homeostasis in neurons. Their dysregulation can result in pathological conditions in the brain; therefore, their regulatory functions may have great impact on neurodegenerative diseases [128]. Thus, using miRNAs especially multiple miRNAs and serum-based miRNA assays suggested as a method with a high sensitivity and specificity can be used in which to diagnose cognitive impairment [163]. For instance, miR-206 and miR-567 (hsa-mir-567) have been introduced as good biomarkers that can be used to evaluate MCI and the earliest stages of dementia due to their effects on the involved genes in the biological processes in neuronal cells and their crucial roles in the neuronal differentiation and brain development [128]. Many of miRNAs are specific for cells and tissues [165–168]. For example, axons, dendrites and synapses have their own miRNAs and various expressions of miRNAs in neurons in neurodegenerative diseases such as Alzheimer disease (AD) [14] are probably associated with dendritogenesis and axonal path [169].

AD damages are started in the hippocampus and spread progressively throughout the brain. Although pathological hallmarks of AD are intracellular neurofibrillary tangles, the abnormal deposition of tau protein, and the accumulation of extracellular plaques of β-Amyloid (Aβ) peptides [6], miRNAs network (Fig. 2), and changes such as alterations in miRNAs targeting APP (miR-29a, miR-29b) can also affect the process of this disease [54].

Deregulation of miRNAs can lead to the Aβ-accumulation, which occurs probably due to the activation of several pathogenic cascades. MiRNAs play important roles in homeostasis and pathogenesis of diseases in the brain by targeting 3'-UTRs mRNA that are related to several important proteins such as amyloid-beta precursor protein (APP), transforming growth factor-beta-induced protein (TGFBI), Tripartite Motif Containing protein 2 (TRIM2), SIRT1, and BTB domain containing protein 3 (BTBD3) [6, 170]. For instance, miRNAs let-7 and miR-320 can affect cognition through DAF-12 signaling and insulin/IGF signaling (IIS) pathways, respectively [2].

Further studies showed that several miRNAs such as miR-34, miR-9, miR-124 [171], miR-137 [157], miR-132, and miR-212 play important roles in cognition and memory function. Besides, miRNAs reactions to the higher expression of SIRT1 (miR-132 and miR-212) [76], NF-kB protein complex (mir-125b and mir-146a), cell cycle proteins (mir-26b, mir-107, mir-125b, mir-107, and mir-34a) [53], mitochondrial fission, synaptic function, ATP generation, presynaptic calcium level (miR-484) [120], and the increased production of ROS (mir-210 and mir-146a) can lead to a possible explanation regarding the induction of aging and aging-related diseases. Such correlations may result in releasing factors including IL6, altered genes function such as p53 and/or altered Wnt signaling, which in turn may affect cell cycle control, apoptosis, DNA, and cellular senescence [53]. It is now necessary to obtain consistent knowledge about the role of miRNAs in the brain for the maintenance of cognitive function or the appearance of cognitive deficits. A variety of miRNAs and their combinatorial effects may mediate their roles in pathological disorders in the brain. Several studies suggest that miRNAs-based therapy can be an alternative in the future for diagnosis and treatment of diseases such as neurodegenerative diseases [157, 172] and cancers [19].

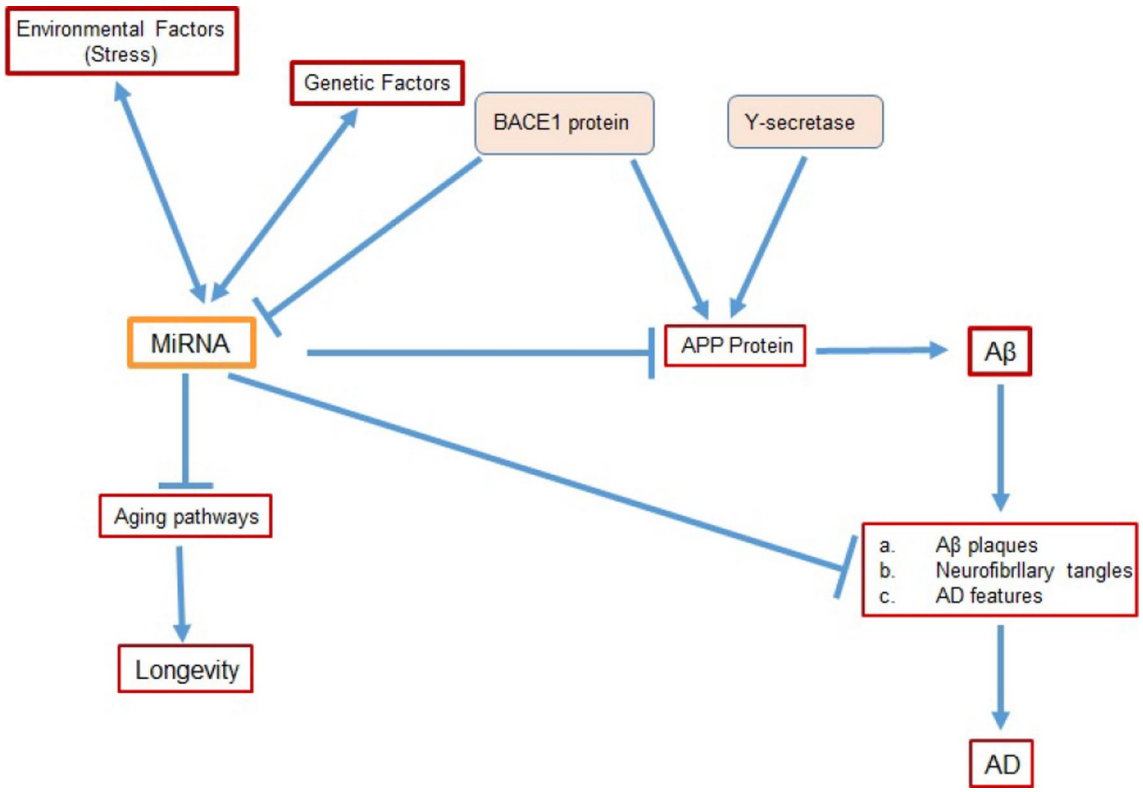

Fig. 2 Alzheimer's disease (AD) formation, longevity and miRNA

Cancer

MiRNAs are key molecular components of cells and play important roles in both normal and pathologic states in the body [173]; hence, changes in their expression can lead to human diseases such as cancers [61, 174, 175]. They act as regulators for controlling a wide range of biological functions including apoptosis, tumor cell proliferation, differentiation, cell cycle progression, invasion, and metastasis [61, 175, 176].

Cancers are a group of age-related diseases. The initiation and progression of cancers can be related to miRNAs deregulation in a cause-effect manner [8] as it has been indicated in Table 3. Thus, miRNAs can be good biomarkers [8] for diagnosis, prognosis, and prediction of tumors. Several investigations have identified specific miRNAs related to solid tumors and hematological malignancies [176, 178] and their actions and effects vary among cancers [61]. For instance, let-7 miRNA and miR-146 act in cancers through their corresponding pathways, namely RAS and KIT, respectively [82]. The effects of miRNAs on proliferation, invasion and cell survival in prostate and pancreatic cancers occur by targeting cyclin

Table 3 Examples of some miRNAs and indicating their roles in cancer

	Mechanism	MiRNAs
1	Growth signals	let-7 family, miR-21
2	Antigrowth signals	miR-17–92 cluster, miR-195
3	Apoptosis relation	miR-34a, miR-185, miR-15, miR-16, mir-125b
4	Angiogenesis	miR-210, miR-26, miR-15b, miR-155
5	Invasion and metastases	miR-10b, miR-31, miR-200 family, miR-21, miR-15b
6	EVADING IMMUNE DESTRUCTION	miR-124, miR-155, miR-17–92
7	TUMOR-PROMOTING INFLAMMATION	miR-23b, miR-155, let-7d
8	GENOMIC INSTABILITY	miR-21, miR-155, miR-15b

Reference [177]

D1 (CCND1), Wnt family member 3A (WNT3A), and B-cell lymphoma 2 (BCL2). MiRNAs can regulate metabolism and energy production in oral cancers by targeting NAD-dependent deacetylase SIRT3 (miR-31). Tumor formation and metastasis in germ cell tumors and gastric cancer can be promoted by miRNAs, which happens through targeting tumor suppressor gene TOB1 (transducer of ERBB2. 1) (miR-371-3) [61]. More than half of miRNAs-related genes in cancers are located in either cancer-associated genomic regions leading to amplification, loss of heterozygosity, and breakpoints, or fragile sites [176, 178]. As shown in Fig. 3, miRNAs play important roles in cancers as oncogenes or tumor suppressors [35, 61]. The expressions of tissue-specific miRNAs may lead to malignant transformation changes as tumor formation and growth by repressing tumor suppressor genes or increasing oncogene expressions. Thus, miRNAs can be good biomarkers in order to evaluate cancers and their classifications [61]. Changes of miRNAs function as tumor suppressors may mediate suppression of normal cells functions, which may result in initiation of malignant transformation in cells. Alterations such as mutations, genomic deletions, epigenetic silencing, and miRNA processing alterations can change the function of miRNAs in the regulation of normal cell proliferations. The oncogenic role of miRNAs can also happen by triggering mRNAs, which may encode tumor suppressor proteins. Moreover, miRNAs affect the progression of tumor by influencing the inflammation system, the components of the innate immune system [175, 176], and the modulation of apoptosis [5].

MiRNAs abnormal expression and their effects on inflammation and cell proliferation [179, 180] in cancers [35, 181, 182] can be due to various factors such as defect in miRNA biogenesis machinery, activity changes in drosha, dicer [183], and transcription factors [184], as well as epigenetic changes such as DNA methylation, and histone modifications (histone methylation, and histone acetylation) [35]; therefore, the controlling mechanism of miRNAs expression is almost same to protein-coding genes [182]. As miRNAs play important roles in the regulation of many cancer-related genes, identification of specific ones of them may act as powerful tools to aid in diagnosis and treatment of tumors [82].

One of miRNAs is MiR-34a that can be used as an important diagnostic and therapeutic miRNA in many cancers due to its general expression. MiRNAs can also be used in order to evaluate chemotherapy resistance in cancers such as lung cancer and breast cancer. Despite this, miRNAs expression among different cancer types varies in a wide range, as it has been shown for miR-155, miR-221, and miR-222 expression [61].

It has been noted that miRNAs can be associated with the risk of recurrence and the chance of relapse-free survival in cancers. For example, the overexpression of miR-210 in breast cancer is with a higher risk of relapsing and lower chance of survival [22]. On the other hand, some miRNAs such as miR-34 and miR-1 contribute into several biological processes of tumor cells, including differentiation, proliferation, and apoptosis through their down-regulation [185]. Besides, miRNAs can affect drug resistance of tumor cells, which may happen by targeting drug resistance-related genes and/or influencing genes that are related to cell proliferation, cell cycle, and apoptosis [103]. Thus, further research are required in order to understand the exact roles of miRNAs in the development [82], diagnosis, prognosis, treatment [5], and survival [13] of cancers.

Accordingly, gene therapy using miRNAs might be used in the future in which to block the progression of cancers [175] by inhibiting the overexpression of oncogenic miRNAs or replacing those that are effective on

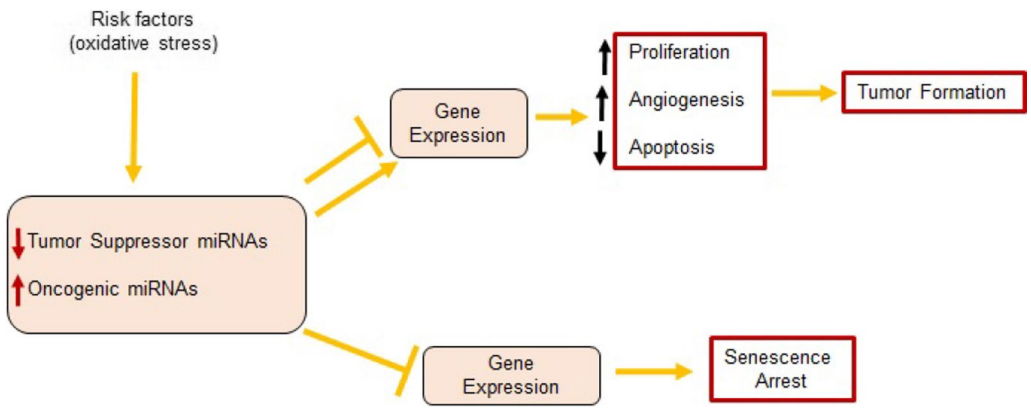

Fig. 3 Correlation of miRNA with tumor formation

tumor suppressive genes [176]. As present cancer-related biomarkers are not specific for tissues and have poor early diagnosis and prognostic value; therefore, they cannot be used as targeted therapy for cancers. Thus, miRNAs sound to be good non-invasive cellular and molecular biomarkers that can be replaced in order to early diagnosis, prognosis, and treatment of cancers [19]. However, further studies are needed for increasing the related knowledge in order to cope with challenges such as miRNAs stability, delivery drug systems, and the control of target effects [176] in which to use the miRNA-based therapeutic approaches in cancers [19]. Despite several therapeutic miRNA delivery systems such as virus-based delivery, non-viral delivery (lipid-based, polymer-based, or chemical structures), and the emerged extracellular vesicle (EV)-based delivery, miRNA-based therapeutic approach is still one of the great challenges. However, it seems that further improvements in techniques such as the targeted-therapeutic miRNA delivery in miRNAs-therapy for the treatment of different cancers will happen in the future [61].

Limitations

However, there are some limitations that can restrict miRNA investigations. Identification of specific miRNAs and their own targets in different diseases such as cancers and dementia is difficult and it limits the use of the miRNA-based therapeutic approaches. MiRNA and the related targeted mRNA must express at the same time in which to change gene expression, protein and biological function. It would be even more complex, when a single miRNA can target hundreds of mRNAs and vice versa. Therefore, it is crucial to identify and validate miRNA/mRNA target pairs and verify their interactions. In addition, technical limitations and delivery problems should be considered as extra factors that can confine such related studies.

Conclusion

This review highlights some relationships among miRNAs, senescence, cancer, and cognitive decline. Different investigations have shown that the actions and biological roles of miRNAs vary in various biological conditions. As noted in the review, further studies are needed to understand better the roles of miRNAs in the development and death of cells in aging and age-related diseases. Such new investigations can help to identify new targets for alternative strategies in order to treat or prevent diseases such as cancers and cognitive decline. The discovery of specific miRNAs will lead to find new biomarkers for screening and diagnosis of diseases as well as exploring of new therapeutic applications in numerous diseases in the future.

Abbreviations

miRNAs: MicroRNAs; UTRs: MRNAs targeting untranslated regions; miRISC: MiRNA-inducing silencing complex; RISC: RNA-induced silencing complex; mRNAs: Messenger RNAs; ATP: Adenosine Triphosphate; ROS: Reactive oxygen species; SAM: Sympathetic-adrenal-medullary; HPA: Hypothalamic–pituitary–adrenal; HIF-1α: Hypoxia-inducible factor-1 alpha; IGF-1: Insulin/insulin-like growth factor; PI3K: Phosphoinositide 3-kinase; TOR: Target of rapamycin; MAPK: Mitogen-activated protein kinase; AMPK: AMP-dependent protein kinase; PKC: Protein kinase C signaling pathway; NF-κb: Nuclear factor kappa-light-chain-enhancer of activated B cells; TGF-β: Transforming growth factor beta; wingless-related integration site: WNT signaling pathway; c-Kit: Notch signaling pathway, receptor tyrosine kinase; H2AX: H2A histone family member X; MCI: Mild cognitive impairment; Aβ peptides: β-Amyloid; APP: Amyloid-beta precursor protein; TGFBI: Transforming growth factor-beta-induced protein; TRIM2: Tripartite Motif Containing protein 2; BTBD3: BTB domain containing protein 3; CCND1: Cyclin D1; WNT3A: Wnt family member 3A; BCL2: B-cell lymphoma 2.

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Consent for publication

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