Review Article

MicroRNA-Based Linkage between Aging and Cancer: from Epigenetics View Point

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Abstract

Ageing is a complex process and a broad spectrum of physical, psychological, and social changes over time. Accompanying diseases and disabilities, which can interfere with cancer treatment and recovery, occur in old ages. MicroRNAs (miRNAs) are a set of small non-coding RNAs, which have considerable roles in post-transcriptional regulation at gene expression level. In this review, we attempted to summarize the current knowledge of miRNAs functions in ageing, with mainly focuses on malignancies and all underlying genetic, molecular and epigenetics mechanisms. The evidences indicated the complex and dynamic nature of miRNA-based linkage of ageing and cancer at genomics and epigenomics levels which might be generally crucial for understanding the mechanisms of age-related cancer and ageing. Recently in the field of cancer and ageing, scientists claimed that uric acid can be used to regulate reactive oxygen species (ROS), leading to cancer and ageing prevention; these findings highlight the role of miRNA-based inhibition of the SLC2A9 antioxidant pathway in cancer, as a novel way to kill malignant cells, while a patient is fighting with cancer.

Keywords: Ageing, Disability, Genomics, Longevity, MicroRNAs

Introduction

Ageing is a complex process and a broad spectrum of physical, psychological and social changes over time (1). It has been determined as one of the admitted risk factors for most of the human age-related diseases such as cancer, leading to approximately 100,000 people deaths around the world per day (2). Most of the disease and disability, which may interfere with cancer treatment and recovery, occur in old ages. Neoplasm is an undiscerning disease that can affect any part of the body of the human being. Roughly one third of the people are at risk to get cancer in their life (3). However, the incidence of cancer is greatly increased in an age-dependent manner. It is reported that around 60% of all cancers happen in people aged 65 years or above (2). Several molecular mechanisms have linked ageing and cancer together (4).

Micro-RNAs (miRNAs) are a set of small non-coding RNAs with considerable roles in post-transcriptional regulation at gene expression level. Recent studies revealed that miRNAs are involved in many important biological processes such as proliferation, differentiation, angiogenesis, and immune response. miRNAs are generally divided into two categories: the first category acts as cytoplasm mRNA inhibitory (e.g., miRNA-451, miRNA-31, and miRNA-150) and the second one targets nuclear gene transcription directly (e.g., miR-211) (5-
Thus far, numerous miRNAs have been reported to be involved in different types of malignancy, such as gastric cancer, highlighting them as potential treatment targets (8, 9).

In this review we attempted to summarize the current knowledge of miRNAs in ageing with mainly focus on malignancies and all underlying genetic, molecular and epigenetic mechanisms.

miRNAs and their biogenesis

miRNAs are highly conserved RNA molecules in the cell that regulate gene expression through an interference pathway (10). RNA interference (RNAi) is the post-transcriptional silencing mechanism in eukaryotes that induces degradation of homologous mRNA through creating double stranded RNA (11). miRNAs often bind to the 3′UTR region of the target mRNA, which directs the inhibition of its translation or degradation (12). For example, the product of Lin-4, controlling genes in Caenorhabditis elegans (C. elegans), is a 22 nucleotides RNA that is produced by a 60 nucleotides hairpin precursor, and inhibits translation of Lin-14 through interaction with the 3′UTR of this mRNA (10). Distribution of miRNA regions in the human genome is in single or cluster form. Some of these regions, at least half of them, are presented in certain transcription units, such as introns and exons (13). miRNA biogenesis takes place in the nucleus and cytoplasm, while the primary miRNAs, transcribed and polyadenylated by RNA polymerase II, are several kilo-bases (Kbs) (5). Stem-loop structure of this transcript is recognized by a 650 kDa enzyme complex that is presented in the nucleus (14). This complex contains class 2 of the RNase III enzymes, called Drosha, which is specialized to cut a double-stranded RNA, as well as a RNA binding protein named DGCR8/Pasha (15). In the cytoplasm, another RNase enzyme (called Dicer) activity leads to generation of the mature miRNAs. Functionally, Dicer cleaves the terminal loop of pri-miRNA and produces double stranded 19-22 nucleotide miRNAs (16). Usually only one strand of the mature miRNAs, known as the guide strand, enters into the micro-ribonucleoprotein complex and creates a micro-RNA-induced silencing complex (miRISC), where the sequence of this strand determine binding region at the target mRNA (17, 18). Since only one of the double strands has the ability to play the guidance role for directing the RISC to the 3′UTR region of the target mRNA, the second strand is deleted. RISC binding miRNAs pair to the 3′UTR region of the target mRNA homologous and control gene expression by inhibiting the cleavage or translation of mRNA targets (19, 20). About one-third of the human genome is considered as potential regulatory targets by the several hundred miRNAs encoded in the genome. Such regulation happens post-transcriptionally and comprises the interaction of miRNA with the mRNA target site (Fig.1).

Mammalian target of rapamycin signaling pathway

The mammalian target of rapamycin (mTOR) signaling pathway integrates inputs from both intracellular and extracellular signals to regulate different cellular processes including proliferation, growth, survival, motility, autophagy, protein synthesis and metabolism. mTOR is a downstream effector of the PI3K/AKT pathway and consists of two biochemically distinct complexes, including mTORC1 and mTORC2. mTORC1 promotes anabolism, such as cell cycle progression, and inhibits catabolism by blocking autophagy. Signaling of this complex contributes to tumorigenesis through its major downstream targets and key regulators, namely 4E-BPs. It has been demonstrated
that mTORC2 regulates cell survival, proliferation and metabolism. Furthermore, mTORC2 is responsible for phosphorylation and activating AKT, which may drive tumorigenesis (21, 22). Recent studies have revealed different roles for mTOR in modulating lifespan, considering two processes that mTOR regulates, including protein synthesis and autophagy (23). Another study reported that mTOR is increased in association with BMAL1 deficiency, a transcription factor and core component of an internal time-keeping system called circadian clock. This event eventually contributes to premature aging and reduced lifespan (24). Wide-ranging research has indicated that miRNAs-based regulation of the mTOR pathway plays a key role in cancer progression, and this pathway is a promising target by miRNAs for novel anticancer therapies (21). Jin et al. (25) in a study on the animal model identified a panel of 63 miRNAs during dermal wound healing, including miRNA-99 family (miRNA-99a, miRNA-99b, and miRNA-100). They demonstrated that miRNA-99 family members regulate AKT/mTOR signaling by targeting several genes such as IGF1R. Grundmann et al. (26) screened miRNAs involved in adaptive blood vessel growth following arterial occlusion. They showed that inhibition of miRNA-100 could be a novel approach for the modulation of mTOR-dependent processes, such as blood vessel growth. A growing body of evidences suggests that miRNAs may play a crucial role in cancer therapy and diagnosis, which mostly performed through the mTOR signaling pathway (Table 1).

miRNAs link with cellular senescence, ageing and cancer

Well understanding of the cancer molecular mechanisms pathogenesis and active targeted therapies are necessary to improve patient treatment outcomes. miRNAs act as key components in cancer progression and as the potential therapeudic agents or targets. Numerous studies have suggested that miRNAs inhibit tumor proliferation and promote cellular senescence or ageing, but its function has yet to be elucidated. Other studies reported that miRNAs repress global translation, cell proliferation and initiates premature senescence (Table 2).

miRNAs, ageing and epigenetics

Ageing is a potent predictor of survival rate in cancers, while the biological mechanisms for the variation in clinical outcome are mostly unidentified. Determining genes and pathways, which are responsible for age-related survival changes, could facilitate the chance of novel therapeutic establishments. Bozdağ et al. (38) have integrated various molecular and genetic methods to determine age-specific signatures at the genetic and epigenetic levels in glioblastoma multiforme. Ageing of higher organisms are regulated by the epigenetic variation over time. Some epigenetic changes do not follow any determined roles, suggesting that might be the outcome of epigenetics error accumulations. Thus, when this process takes place in adult stem cells, it could play an important role in ageing, through some unknown molecular mechanisms (39). Many researches have discussed various mechanism that miRNA could affect DNA methylation as an epigenetic change contributing to ageing and cancer (Table 3). Two main epigenetics components are DNA methylation, methyl marks add to a certain bases of a gene, and histone modification, combination of various molecules attached to the tails of histone proteins. Functionally, miRNAs could regulate gene expressions through two prominent mechanisms, including donation of the methyl group (40) and chromatin coiling/uncoiling (Fig. 2) (41). Wakabayashi et al. (42) revealed that there is likely a cross-talk between miRNAs and epigenetic regulators, modulating neurogenesis in the adult mammalian brain.
## Table 1: Linkage between miRNA and mTOR signaling pathway

| Authors                      | Cell line(s)               | Type of disease       | Type of miRNA | Target* | Finding/Suggestion for miRNA                                                                 |
|------------------------------|----------------------------|-----------------------|---------------|---------|---------------------------------------------------------------------------------------------|
| Zheng et al. (27)            | SGC-7901 cell              | Gastric cancer        | miRNA-18a     | Vacuolar protein sorting-associated protein 13D | Possible therapeutic strategy against malignancy                                        |
| Wan et al. (28)              | CNE and HeLa cells         | Hypoxia-induced autophagy | miRNA-155    | Kinesin-like protein KIF1B Nuclear factor 1 A-type | A key regulator of autophagy via dysregulation of mTOR pathway                           |
| Shen and Houghton (29)       | CB17SC SCID mice           | Childhood sarcoma     | miRNA-18a     | Vacuolar protein sorting-associated protein 13D | Oncogenic growth signals may promote tumorigenesis by dampening the ATM checkpoint       |
|                             |                            |                       | miRNA-421     | Calmodulin-binding transcription activator 1 Arginine-glutamic acid dipeptide repeats protein |                                                                                           |
| Zhong et al. (30)            | Colorectal carcinoma cell  | Colorectal carcinoma  | miRNA-30a     | FUS-interacting serine-arginine-rich protein 1 | A potential therapeutic target to block CRC metastasis                                   |
|                             |                            |                       | miRNA-30b      | Kinesin-like protein KIF1B MARCKS-related protein |                                                                                           |
| Wang et al. (31)             | Mouse adult pancreatic islets | Diabetes             | miRNA-7       | Kinesin-like protein KIF1B FKBP12-rapamycin complex-associated protein | As a therapeutic target for diabetes                                                   |
| Li et al. (32)               | MG63 cells                 | Osteosarcoma          | miRNA-223     | AR DNA-binding protein 43 Msx2-interacting protein FUS-interacting serine-arginine-rich protein 1 | Could be used in anticancer therapies in osteosarcoma                                   |
| Cui et al. (33)              | Renal cell Carcinoma cell  | Renal cell carcinoma  | miRNA-99a     | Uncharacterized protein C1orf34 plasticity related gene 1 | May offer an attractive new target for diagnostic and therapeutic interventions         |
| Iwaya et al. (34)            | HT29 and CaR-1 cell        | Colorectal carcinoma  | miRNA-144     | PR domain zinc finger protein 2 Msx2-interacting protein | A meaningful prognostic marker                                                         |
| Gebeshuber and Martinez (35) | Breast cancer cell         | Breast cancer         | miRNA-100     | TAR DNA-binding protein 43 Uncharacterized protein C1 or f34 | A potential target for therapeutic approaches                                          |

*; Predicted by target scan and mTOR; Mammalian target of rapamycin.
| Authors                     | Type of disease                  | Type of miRNA | Target                          | Finding/Suggestion for miRNA                                                                 |
|-----------------------------|----------------------------------|---------------|---------------------------------|------------------------------------------------------------------------------------------------|
| Liu et al. (36)             | Ovarian carcinoma                | miRNA-506     | Calmodulin-binding transcription activator 1 Msx2-interacting protein | Inhibits proliferation while promotes senescence                                              |
| Mazan-Mamczarz et al. (37)  | Diffuse large B cell lymphoma    | miRNA-520c-3p | Kinesin-like protein KIF1B Nuclear factor 1 A-type | A key regulator of autophagy via dysregulation of mTOR pathway.                              |
| Shen and Houghton (29)      | Childhood sarcoma                | miRNA-18a     | Vacuolar protein sorting-associated protein 13D | Oncogenic growth signals may promote tumorigenesis by dampening the ATM checkpoint             |
|                            |                                  | miRNA-421     | Calmodulin-binding transcription activator 1 Arginine-glutamic acid dipeptide repeats protein |                                                                                               |
| Zhong et al. (30)           | Colorectal carcinoma             | miRNA-30a     | FUS-interacting serine-arginine-rich protein 1 | A potential therapeutic target to block CRC metastasis                                       |
|                            |                                  | miRNA-30b     | Kinesin-like protein KIF1B MARCKS-related protein |                                                                                               |
| Wang et al. (31)            | Diabetes                         | miRNA-7       | Kinesin-like protein KIF1B FKBP12-rapamycin complex-associated protein | As a therapeutic target for diabetes                                                         |
| Li et al. (32)              | Osteosarcoma                     | miRNA-223     | AR DNA-binding protein 43 Msx2-interacting protein FUS-interacting serine-arginine-rich protein 1 | Could be used in anticancer therapies in osteosarcoma                                        |
| Cui et al. (33)             | Renal cell carcinoma             | miRNA-99a     | Uncharacterized protein C1 or f34 plasticity related gene 1 | May offer an attractive new target for diagnostic and therapeutic intervention                |
| Iwaya et al. (34)           | Colorectal carcinoma             | miRNA-144     | PR domain zinc finger protein 2 Msx2-interacting protein | A meaningful prognostic marker                                                               |
| Gebeshuber and Martinez (35)| Breast cancer                    | miRNA-100     | TAR DNA-binding protein 43 Uncharacterized protein C1 or f34 | A potential target for therapeutic approaches                                                |

*; Predicted by target scan and mTOR; Mammalian target of rapamycin.
**Table 3: miRNA affects DNA methylation as an epigenetic change contributing to ageing and cancer**

| Authors         | Type of disease                        | Type of miRNA       | Target                                                                 | Finding/Suggestion for miRNA                                                                 |
|-----------------|----------------------------------------|---------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Ng et al. (43)  | Acute promyelocytic leukaemia          | miRNA-34a           | Kelch-like protein 17 (Actinfilin) Calmodulin-binding transcription    | Methylation of miRNA-34b/c may contribute to APL leukaemogenesis                           |
|                 |                                        | miRNA-34b           | Kelch-like protein 17 (Actinfilin) Tumor protein p73 (p53-related protein) |                                                                              |
|                 |                                        | miRNA-34c           | Kelch-like protein 17 (Actinfilin) PR domain zinc finger protein 16    |                                                                              |
| Xie et al. (44) | Hepatocellular carcinoma cancer        | miRNA-34a           | Kelch-like protein 17 (Actinfilin) Calmodulin-binding transcription    | DNA methylation might be involved in the inactivation of miRNA-34b in HCC                |
|                 |                                        | miRNA-34b           | Kelch-like protein 17 (Actinfilin) Tumor protein p73 (p53-related protein) |                                                                              |
| Ko et al. (3)   | Acute myeloid leukemia                 | miRNA-let-7a        | Basement membrane-specific heparan sulfate proteoglycan core protein  | let-7a-3 methylation is a positive prognosticator for AML patients                       |
|                 |                                        | miRNA-203           | Msx2-interacting protein Macoilin AT-rich interactive domain-containing protein 1A | miRNA-203 methylation Level might represent a marker for the patients with endometrioid cancers |
| Huang et al. (45)| Endometrial cancers                    | miRNA-124a-2        | Arginine-glutamic acid dipeptide repeats protein retinoblastoma-associated factor 600 | DNA methylation of miRNA-124-2 on HPV-test-positive self-samples is non-inferior to cytology triage in the detection of CIN2 |
| Li et al. (47)  | Non-small cell lung cancer cells (NSCLC)| miRNA-503           | Protein kinase C zeta type Vacuolar protein sorting-associated protein 13D | Epigenetic silencing of microRNA-503 regulates FANCA expression in non-small lung cancer cell |
| Ben Gacem et al. (48)| Breast cancer             | miRNA-124a-1        | Arginine-glutamic acid dipeptide repeats protein retinoblastoma-associated factor 600 | DNA methylation of miRNA-124a-1, miRNA-124a-2 and miR-124a-3 in breast cancer play a role in tumor growth and aggressiveness |
| Wang et al. (49) | Chronic lymphocytic leukemia (CLL)     | miRNA-9-3           | Nuclear inhibitor of protein phosphatase 1 Eyes absent homolog 3 Zinc finger MYM-type protein 6 | miRNA-9-3 is a tumor suppressor miRNA frequently methylated, and hence is silenced in CLL |
miRNA therapeutic applications

miRNA detection has opened a new window in our current perception of the gene expression regulation. Similar to protein-coding genes, several investigations have been performing to determine the expression level of these small RNAs in vitro or in vivo. Hence, miRNAs might undergo gain of function (GOF) or loss of function (LOF). This event could play an important role in various diseases-like protein-coding genes. Different mechanisms including genomic rearrangement, point mutation, and altering the pattern of promoter region methylation could be involved in regulation of miRNA expressions. Besides, this type of RNA plays an important role in expression and regulation of signaling pathways. It is necessary to evaluate the relationship between aberrant miRNA, like miRNA-128 and miRNA-30, expression levels and notch signaling in glioma and angiogenesis, respectively (55).

Several studies have shown that expression or inhibition of miRNAs can change the pattern of tumorigenesis or cancer progression (56-59). It has been demonstrated that expression of several miRNAs (e.g. miRNA-17, miRNA-155) might have oncogenic properties, while the others (e.g. miRNA-34, miRNA-16 and let-7) function as tumor suppressor (60, 61). Here, we suggest that oncogenic or inhibitory effect of miRNAs could raise a distinctive point to compare the normal cells with different types of cancer. Thus, analysis of miRNA expressions, as a molecular bio-marker, could help diagnose the patient’s disorder stage. For example, over-expression of miRNA-155 and down-regulation of let-7 indicated low survival chance in the patients with lung cancer (62, 63). Curiously, the expression pattern of some miRNAs is associated with different stages of tumorigenesis or metas-
MiR-Linkage between Aging and Cancer

Discussion

Currently, there are several types of synthetically made miRNA. Antagomir is an example of this type of artificially made miRNAs. These RNA molecules are designed to inhibit miRNAs. The precise mechanism that antagomir could inhibit miRNAs is not clear yet, although this mechanism might possibly be performed where these molecules could irreversibly bind to miRNAs. miRNA-based therapeutics could be applied through two approaches; in the first approach, miRNA antagonist applications (e.g. antagomir, anti-miRNA and LNA) contribute through GOF. In the second strategy, using inhibitory miRNAs (e.g. tumor inhibitors) could lead to LOF, compensating lack of natural intracellular miRNAs function. This strategy is similar to transferring protein-coding genes into cells during gene therapy, with even less limitations due to the small size of transferred DNA. Thus, it can easily be transferred into the cells using chemicals without any vector, like inhibitory RNA delivery. In addition, the nature of miRNA function is the other benefit which is mostly influenced by multiple oncogenic paths. Delivery of tumor suppressor miRNAs is mainly done by viral vectors. Another inhibitory transmission approaches, direct miRNAs to the target organ using plasmids, transposons and cationicliposome, as monoclonal antibodies embedded on their surface, epigenetic modifying drugs such as DNA methyltransferase inhibitors (including 5-aza-2′-deoxycytidine), histone deacetylase inhibitors (including 4-phenylbutyric acid) increase the expression of miRNA by reducing DNA methylation and increasing histone acetylation level, as well as inhibiting cell proliferation through reversing the tumor suppressor effect of miRNA (67). Thus far, several miRNA inhibitors have been introduced to preclinical studies in animal models, one of the most prominent of which is let-7 (68-70). The expression of this miRNA inhibitor is reduced in some cancers, leading to inhibitory effects on the RAS protein family. Furthermore, reduction or loss of activity of this miRNA inhibitor leads to increase in the expression of these proto-oncogenes (71).

These miRNAs also affect other targets such as MYC, cyclin D and HMG2A, indicating the importance of such miRNAs in controlling several pathways related to cancer (72). miRNA-34a, as a target of P53, is another small RNA that prevents the growth of cancer cells by controlling the cell cycle (73). In addition to these direct applications of miRNA in cancer therapy, adjuvant administrations have been discovered for these RNAs. For example, it has been shown that transferring and expressing miRNA-302 in breast cancer cells enhances the sensitivity of these cells to radiotherapy (74). However, the important point, regarding miRNAs replacement therapy, is the risk of cellular toxicity. As demonstrated, miRNAs are required to be proceeded by the RISC. Transferring high amounts of miRNAs to the cells can, in contrast, decrease or omit the other natural miRNAs processing by this complex, which could negatively affect the cell survival. Recently in the field of cancer and ageing, scientists claimed that uric acid can be used to regulate ROS, preventing cancer and ageing. These findings highlight the role of miRNA-based inhibiting the SLC2A9 antioxidant pathway in cancer as a novel approach to kill malignant cells while a patient is fighting with the cancer (75).

Conclusion

The aforementioned evidences illustrate the complexity and the dynamic nature of miRNA-based linkage of ageing and cancer at genomics and epigenetics levels that might be crucial for the understanding of the age-related cancer mechanisms and ageing, in general.

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