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REVIEW ARTICLE

MicroRNAs, DNA damage response and ageing

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Abstract Ageing is a multifactorial and integrated gradual deterioration affecting the most of biological process of cells. MiRNAs are differentially expressed in the cellular senescence and play important role in regulating of genes expression involved in features of ageing. The perception of miRNAs functions in ageing regulation can be useful in clarifying the mechanisms underlying ageing and designing of therapeutic strategies. The preservation of genomic integrity through DNA damage response (DDR) is related to the process of cellular senescence. The recent studies have shown that miRNAs has directly regulated the expression of numerous proteins in DDR pathways. In this review study, DDR pathways, miRNA biogenesis and functions, current finding on DDR regulations, molecular biology of ageing and the role of miRNAs in these processes have been studied. Finally, a brief explanation about the therapeutic function of miRNAs in ageing regarding its regulation of DDR has been provided.

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Introduction

As a progressive inevitable process, ageing is a global problem with increasing adverse impact on society (Frenk and Houseley 2018). Despite the increasing rate of age-related diseases such as cardiovascular diseases, diabetes, osteoporosis, immunological diseases, various neurodegenerative diseases, cancer, progressive disability and loss of function, ageing has caused a dramatic increase in health care cost in public health system (Gabbianelli and Malavolta 2018). Ageing completely influences every cellular and biological function pathway. Several hallmarks are explained for ageing, including a variety of molecular, biochemical and metabolic alterations, genomic instability, telomere attrition, epigenetic alteration deregulated nutrient sensing, mitochondrial dysfunction, stem cell exhaustion, cellular senescence, loss of proteostasis and changed intercellular communication. Regarding the complex alterations occurred during the ageing process, and the known function of miRNAs in mediating complex and interlinked pathways, the key role of miRNAs has been highlighted in ageing (Jung and Suh 2014). miRNAs are a large group of non-protein coding RNAs with small size of 18–25 nucleotide long (Majidinia et al. 2018) and supposed to control the expression of 60% of all human mRNA molecules through degradation at the posttranscriptional level and/or suppression of target mRNAs translation (Majidinia and Yousefi 2016). miRNAs are also demonstrated to be involved in the regulation of various important components of DNA damage response (DDR) as an intricate network responsible to maintain the genome integrity and instability (Majidinia and Yousefi 2016). This cross-talk between DDR components and miRNAs plays critical roles in the pathogenesis of ageing and ageing-related diseases (Wan et al. 2011). Therefore, in this review article, the role of interactions between miRNAs and DDR signaling in ageing has been reviewed (Fig. 1).

Molecular biology of ageing

Ageing is driven by fundamental and fascinating processes influenced by the environmental factors such as caloric or dietary restriction (DR) that delays ageing and extends life. Indeed, extensive cross-talk exists among these processes of organisms ageing. Several major signaling pathways involved in life span have been described: Insulin/IGF-like signaling (IIS) pathway is one of the signaling pathways established as regulator ageing in worms, insects and mammals, thus any interruption or genetic down-regulation of this signaling pathway such as deletion of IGF-1 receptor (Holzenberger et al. 2003) and deletion of insulin/IGF-1 signaling intermediates can extend life span (Selman et al. 2011). Also multiplex targets of IIS pathway are Mechanistic target of rapamycin (mTOR) complexes and forkhead box O (FOXO) family of transcription factors involved in ageing. Indeed, signaling by IIS pathway that starts with binding of ligands such as insulin and insulin-like growth factor can activate the PI3K/Akt/mTOR intracellular signaling cascade and modulate ageing in mammals (Lamming 2014). mTOR is the composition of two distinct cellular multi-protein complexes (mTORC1 and mTORC2) that basically modulate all aspects of anabolic metabolism (López-Otín 2013). mTORC1 makes a response to the growth factors, energy status, and cellular stress while is severely suppressed by rapamycin. In this case, a genetic downregulation of mTORC1 kinase activity leads to longevity in both invertebrates (yeast, worm and flies) and mammals (Bjedov et al. 2010; Harrison et al. 2009). It is also reported that in mice with low values of mTORC1 activity, but with normal values of mTORC2 and in mice with defective S6K1 (which is a major mTORC1 substrate) life span is increased (López-Otín 2013). Also, it is indicated that the genetically suppress of mTORC1 in C elegans through SKN-1/Nrf and DAF-16/FoxO activate the protective genes and enhance stress resistance and life span (Robida-Stubbs et al. 2012). FOXO transcription factors are the most important effectors of IIS considered as a key regulator of life span downstream of insulin/IGF-like signaling while their function is inhibited by IIS pathway (Martins et al. 2016). AMP kinas protein and sirtuins are a nutrient sensor in a contrast performance to insulin/IGF-like signaling and mTOR, representing the nutrient deficiency and catabolism instead of

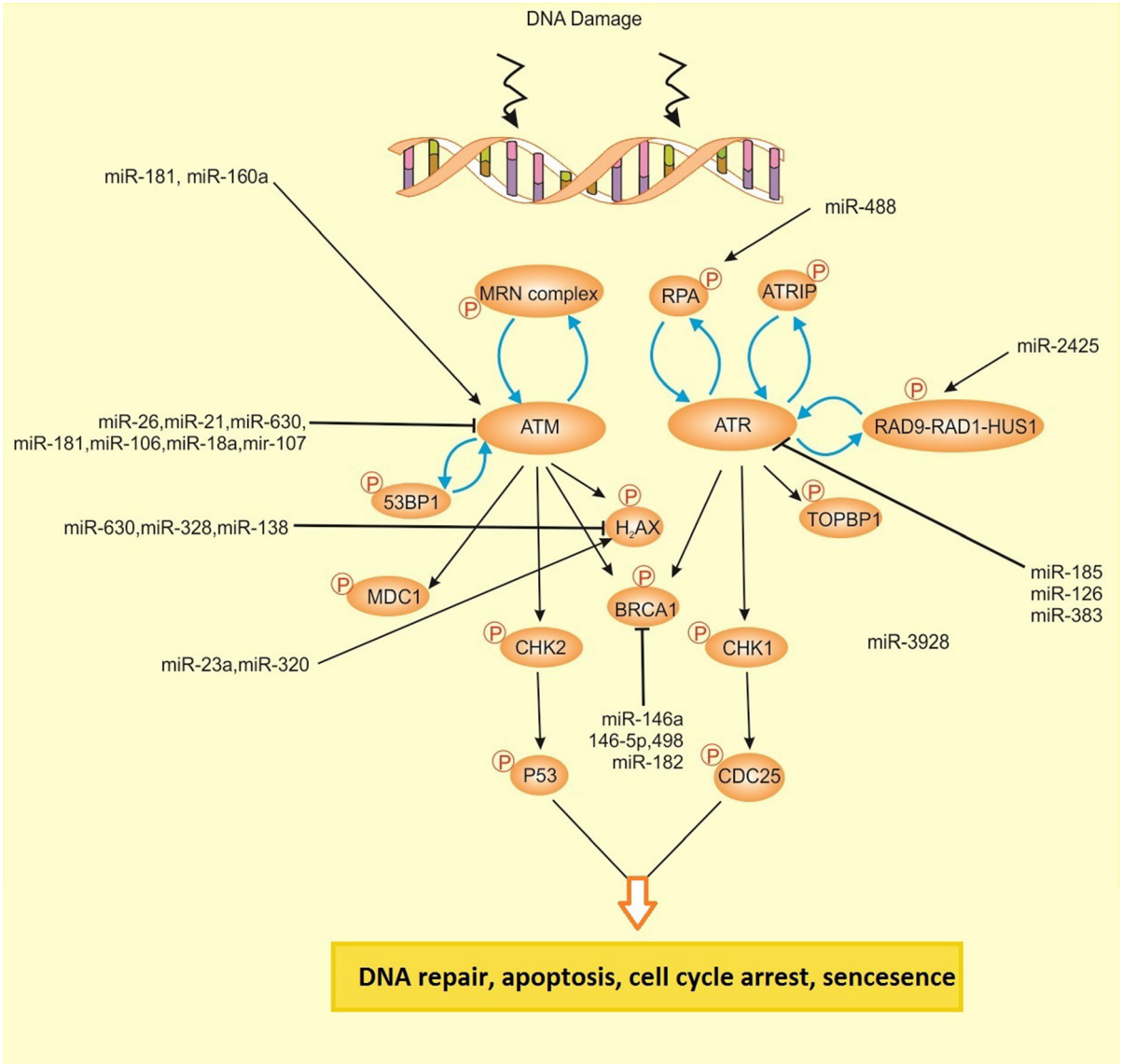

Fig. 1 The interactions between various miRNAs and key components

nutrient abundance and anabolism (López-Otín 2013). These proteins are involved in the regulation of lifespan through an integrated signaling network. AMP-activated protein kinase has several effects on metabolism indicating the substantially shuts down mTORC1 (Alers et al. 2012). Moreover, AMPK-induced activation of Fox O/DAF-16, Nrf2/SKN-1, and SIRT1 signaling pathways ameliorates the cellular stress resistance and longevity. Furthermore, AMPK suppresses the inflammatory responses by inhibition of NF-κB signaling pathway. The related studies have demonstrated that the responsiveness of AMPK signaling has clearly been decreased through ageing (Salminen and Kaarniranta 2012). Sirtuins protein family in mammalian contains seven proteins (SIRT1-SIRT7), acting in different cellular processes such as histone de-acetylation and regulation of several transcription factor. Accordingly, sirtuins have been substantially studied as a potential anti-ageing protein (Houtkooper et al. 2012). It has been reported that the increment of protein deacetylase Sir2 could extend the longevity in some lower organisms. Also, Sirt1 as the

closest mammalian homologue Sir2 provides anti-ageing activity evidence(s) in mammals (Herranz et al. 2010). Sirt1 as a family of mammalian class III histone deacetylases are mainly a nuclear protein. It is believed that sirt1s modulates the peroxisome proliferator-activated receptor, Gamma Coactivator-1α (PGC-1α) activity and mitochondrial biogenesis (Tang 2016). Having pivotal role in apoptosis, mitochondria control a large number of different metabolic and signaling pathways (Kroemer et al. 2007). Therefore, it is highly evidenced that dysfunction of mitochondria is associated with ageing (Bratic and Larsson 2013). Also, a reduced nutrient availability could enhance the mitochondria biogenesis via the stimulation of sirtuin1 and its downstream effector such as PPARγ coactivetor-1α and AMPK (Reznick et al. 2007). Moreover, these proteins are associated with the regulation of mitochondria metabolism and longevity. As a result, the reduced nutrient availability and therapeutic strategies which keep low level energy and nutrient without malnutrition are suggested to be the main mechanism for extending longevity.

miRNAs: biogenesis and function

Since miRNAs are considered as a major regulator of all cellular pathways, their biosynthesis and their individual cellular functions must be tightly investigated (Treiber et al. 2012). miRNAs are frequently transcripted from two target genomic loci: (1) miRNA genes that are located in intergenic regions (Kim and Kim 2007), and (2) the transcripts of protein-coding genes while residing in introns (Rodriguez et al. 2004). Interestingly, the chromosome number 19,14,1 and X of human have enormous number of miRNAs in the intergenic regions (Ghorai and Ghosh 2014). Two biosynthetic pathways for miRNAs are described. Accordingly, the first step is mediated through the canonical or Drosha/Dicer-dependent biosynthesis pathway, in this pathway longer primary transcripts (pri-miRNAs) are mainly generated by RNA polymerase II or III and the origin of these miRNAs are usually in intergenic regions (Bartel 2009; Melton et al. 2010). In the second step, a special type of miRNAs known as mirtrons regulated through a non-canonical pathway and their origin are within intron of protein coding genes (Huang et al. 2013b; Rodriguez et al. 2004). The canonical pathway for miRNA biogenesis starts with the transcription of primary miRNA (pri-miRNA) through RNA polymerase II. pri-miRNAs which is folded into secondary structures comprised of base-paired stem loop can be polyadenylated and regulated through the transcription factors (Majidinia and Yousefi 2016). In nucleus, pri-miRNAs are detected by Drosha/DGCR8 enzymatic complexes containing RNase III, an endonuclease microprocessor for cutting double-strand RNA (named as DROSHA) and their protein complex DGCR8, and a double stranded RNA binding protein (named as PASHA) (Lau et al. 2001). Obviously, the function of drosha completely depends on the pasha and the specific cross-regulation between them is important for controlling of miRNA biogenesis (MacFarlane and Murphy 2010). Indeed, the absence of pasha in *Drosophila* and *Caenorhabditis elegans* has been resulted in the accumulation of pri-miRNA in cytoplasm (Lau et al. 2001). The initial processing of pri-miRNA by Drosha/DGCR8 complex has led to the production of ∼ 70 nucleotide precursor miRNA (pre-miRNA) which locally folded into the stable secondary hairpin loops with ∼ 2 nucleotide 3′-overhangs as a unique feature in RNase-III-mediated cleavage (Denli et al. 2004; Lee et al. 2004) and particularly detected by Exportin-5 and processing enzyme dicer.

The next step pre-miRNAs are exported from the nuclear envelope into cytoplasm by the nuclear export receptor Exportin-5/Ran-GTP-dependent mechanism (Terry et al. 2007). In eukaryotes, exportin-5 and Ran-GTP are similar to a carrier molecule which receive the pre-miRNA, inhibits nuclear degradation and facilitates translocation into the cytoplasm (Bohnsack et al. 2004). In cytosol, pre-miRNA is the second, processed by other RNase III enzyme (named as DICER1). Dicer1 binds the 3′ overhang of pre-miRNA through its two catalytic domains, also Transactivation responsive RNA-binding protein (TRBP) cleaves pre-miRNA into RNA duplexes of roughly ∼ 22 nucleotide length. TRBP elevates dicer1-mediated cleavage in the subset of miRNAs (Devi et al. 2017). In next step, the mature miRNA duplexes bind to argonaute (Ago 1–4) protein and led to the production of miRNA-induced silencing complex (RISC). Argonaut proteins are highly conserved involved in pathways of RNAi and miRNA. Argonaut proteins have two conserved domains with capable of binding to RNA: domain of PAZ which binds to the end of 3′ single-

strand miRNA and domain of PIWI which is similar to ribonuclease H and interacts with miRNA at the end of 5′ strand miRNA (Kanellopoulou and Monticelli 2008). In mammalian, Ago 2 is the main protein in RISC complex associated with mRNA degradation or translation suppression. In continuation, only one of the mature guide miRNA strands (so-called miRNA-5p) are associated with RISC and gives complementary sequences towards the target mRNA and often finally binds to 3′ end of UTR (Majidinia and Yousefi 2016). The other strand known as passenger miRNA (called miRNA-3p, the star (*)-strand) is released from RISC and degraded (Devi et al. 2017). In noncanonical pathway, it also refers to Drosha-independent/Dicer dependent pathway (mirtrons) as a special type of miRNAs produced from bypass Drosha/DGCR8 complex and spliced introns. After exported to cytoplasm, mirtrons act like manner to miRNA that is produced from the canonical pathway (Filipowicz et al. 2008). miRNAs generally detect their mRNA targets through their different sequences called as a seed region (5′ end miRNA; 2–7 nucleotides), finally the result of these processes are "gene silencing" led to mRNAs degradation or translation repression of target mRNAs.

DNA Damage Response (DDR)

All living organisms are constantly threatened by genotoxic agents in the environment, having the potential of causing damage to genome which is led to the defects in genome replication and transcription. To overcome the challenge of maintaining the fidelity of genome, cells depend on an intricate signaling network, which systematically senses and reacts to DNA damage, and depends on multiple factors that determines the fate of cell (Jackson and Bartek 2009). Based on the type of cell-damage, DDR network is divided into two sections (1) ATM pathway which is responsible for handling DSB 1 and (2) ATR pathway which is responsible for handling single strand DNA damage. Despite the separate discussion of these two pathways, they are closely linked and act in conjunction (Awasthi et al. 2015; Maréchal and Zou 2013). The first step in DDR is sensing the damage performed by H2AX–MRN complex in ATM pathway and by RPA-RAD9-RAD1-HUS1 complex (Mirza-Aghazadeh-Attari et al. 2018; Yang et al. 2004). These sensors are activated and affected by DDR transducers, ATM, ATR, CHK1 and 2 molecules (Manic et al. 2015). The function of these transducers and their relation to sensors are further facilitated by DNA mediators. These molecules which consist of BRCA1, 53BP1, MDC, TopBP1 and Claspin are also a getaway for further interactions with other important signaling pathways involved in cellular regulation and function (Harte et al. 2014; Ibrahim et al. 2012; Mirza-Aghazadeh-Attari et al. 2018). Finally, the collective action of these mediators and transducers activate a unique set of effector molecules, which determine the fate of cell. A key effector in this regard is p^{53} and multiple downstream signaling pathways that lead to cell arrest, apoptosis, senescence, therefore, DNA repair is initiated from this molecule (Williams and Schumacher 2016). DNA repair is performed in multiple manners with the involvement of a specific set of enzymes and proteins with non-enzymatic characteristics. DNA repair methods consist of NHEJ, BER, HR and NER (Majidinia and Yousefi 2017). Further, DDR can drive cells into checkpoint arrest, which is mediated by the action of multiple cell cycle proteins such as cyclins and cyclin dependent kinases (CDKs), Wee1, CDC25 and other molecules (Alberts et al. 2002). Cell can also enter to a permanent state with no replication called senescence and mediated again by some molecules involved in cell cycle regulation and more specific molecules, such as p^{16} and p^{19} (Capparelli et al. 2012; Cascales et al. 2017). An example for DNA damage: if damage is irreparable and the sustenance of cell is distorted, apoptosis is initiated and described as the programmed death of cell. Many effector molecules are active in the process of apoptosis, while many are regulated and affected by DDR signaling (Norbury and Zhivotovsky 2004).

miRNAs mediate DDR regulation

Sensors/mediators/transducers of DDR

DNA damage sensors are the starting point of DDR, and known as the targets of multiple regulatory mechanisms including miRNAs. A study by Wang et al. has found that miRNA-138 is able to directly target the H2AX 3′-untranslated region, causing a reduced expression and foci formation and increased tolerance to DNA damage led to the instability of

chromosome. Further, this miRNA is able to inhibit HR causing an increased sensitivity to DNA damageing agents (Wang et al. 2011a). Similar inhibitory effects on H2AX are seen in a study by Wei et al. (when), where miRNA-328-3p increases the sensitivity to radiotherapy in small lung cancer cells (Majidinia and Yousefi 2016). Another study has found that miRNA-320 has increased the expression of γH2AX and apoptosis related proteins in glioma cells, leading to the increased sensitivity to radiation. This miRNA also shows the inhibitory effects on the function of Sirt1 (Li et al. 2018). Tsai YS has shown that miR-23a has increased γH2AX and decreased the rates of DNA double strand break in human oral fibroblasts. These effects are found to be mediated by the regulatory effect of this miRNA on FANCG (which is a Fanconi anemia susceptibility gene) (Tsai et al. 2011). Galluzzi et al. has found that a synthetic miRNA precursor (pre-miR-630) is able to block DDR cascade phosphorylation, leading to a decreased phosphorylation of ATM and H2AX and modulating the sensitivity of A549 to cisplatin (Galluzzi et al. 2010). Yang et al. (2014) has found that miR-138 is able to increase the sensitivity to ionized radiation by increasing the expression of γH2AX and inhibiting Sentrin/SUMO-specific protease 1. MRN complex is another DNA damage sensor in DSB pathway of DDR. A study by Wu et al. (2015) has found that SNPs in miRNA binding sites of each one of the components, including MRE11, NBS1 and RAD51 have significance function on the homologous recombination repair process. Some SNPs are even significantly associated with breast cancer. Farooqi et al. (2015) has found similar significant variations in 3′-UTR of NBS1 regarding prostate cancer. Moreover, miRNA-488 is reported to increase the expression of RPA and XPC, causing a net increase in nucleotide excision repair (Fang et al. 2017). Zou et al. (2016) has found that DNA replication could be halted by targeting RPA1. Further, this miRNA could induce DNA damage which is resulted from the induction of cellular checkpoints. 9–1–1 complex (RAD9-RAD1-HUS1) coupled with RAD17 is another sensor in the single strand DNA damage response pathway. A study by Tong et al. (2017) has found that miR-2425-5p is able to regulate the rate of proliferation in muscle-derived satellite cells by regulating the expression of RAD9 homolog A acted as an inhibitor of cell proliferation. Herzog et al. has studied the effects of steroids in an ischemic model and found that steroids are able to exert an anti-damage effect, mainly by modulating miRNAs. One of the target miRNAs is miR-375 targeted RAD1 and Bcl-2. Treatment with steroids inhibited post-ischemic could increase these two molecules (Herzog et al. 2017). Pandey et al. has found that the overexpression of miRNA-15a-3p downregulates RAD1 while enhancing the cell survival (Pandey et al. 2016). ATM is a DNA transducer in DSB pathway extensively regulated by miRNAs. Hoey et al. has shown that miRNA106a has increased the resistance to radiation in prostate cancer cells by upregulating ATM and downregulating lipopolysaccharide-induced TNF-α factor (Hoey et al. 2018). Similar effects are seen for miRNA-181a in promoting gastric cancer (Zhang et al. 2014b). A study by Mansour et al. has found that the overexpression of miRNA-421 resulted in the reduced amounts of ATM has caused a defective DNA repair and increased the sensitivity to radiation (Mansour et al. 2013). Similar results are shown for miRNA-26a by Guo et al. in glioblastoma cell lines and for miRNA-18a by Song et al. (2011), Guo et al. (2014). Saleh et al. (2017) has found that the administration of Ibrutinib in chronic lymphocytic leukemia has increased the expression of tumor suppressors such as ATM and PTEN by decreasing the amount of specific miRNAs such as miR-22, miR-34a, miR-146b and miR-181b. Guo et al. (2013) has found that there is a clinically important relation between the expression of ATM and the hormonal status of breast cancer. It is shown that Estrogen receptor α activates miR-18a and miR106a, which negatively regulated the expression of ATM. Fei et al. has found a function for miR-26b in promoting apoptosis in Granulosa cells. Further investigations have shown that this function is dependent on the ability of this miRNA to target ATM m-RNA at position 5555 led to a decreased ATM, and increased DNA breakage and mightily to the increased rates of apoptosis (Lin et al. 2012). Wang et al. has shown that the important signaling cascades which predispose cancer, such as Transforming growth factor-β has utilized miRNAs in order to promote malignant transformation. One of these miRNAs is miR-181 which targets ATM and interfered with its function (Wang et al. 2011b). Huang et al. has reported that miRNA-103 and miRNA-107 have similar functions in regulating ATM, and considered for increasing sensitization to chemotherapy agents in a wide range of cancer cell lines (Huang et al. 2013a). ATR is

the counterpart of ATM in a single strand DNA damage, and likewise, is in part regulated by miRNAs. In an study by Wang et al. (when), miR-185 has negatively regulated ATR expression, which resulted in the inhibition of proliferation and increased rates of apoptosis (Wang et al. 2013). Chang et al. has also found that miRNA-3928 activates ATR by affecting Dicer (Chang et al. 2012). Indeed, ATR has numerous interactions with multiple molecules of DDR, including polo-like kinases-4. A study by has shown that miRNA-126 inhibits the functions of polo-like kinases-4 including its interactions with ATR. This miRNA inhibits the PLK-4/ATR/CHEK1 axis which promoted proliferation in cancer cells (Bao et al. 2018). miRNAs can also be the means to regulate ATR by other signaling pathways. STAT3 regulates ATR by microRNA-383 shown in a study by liao et al. also miRNA-383 decreases the level of ATR and promotes an anti-apoptotic phenotype (Liao et al. 2015). The Next major group of molecules involved in DDR with links to miRNAs is DDR mediators. BRCA1 is probably the most important mediator with wide functions in multiple human pathologies, most notably cancer (Mersch et al. 2015). Studies have shown that the expression of BRCA1 is linked to multiple regulators including miRNAs (Shariati-Kohbanani et al. 2016). It is known that over 100 miRNAs are linked to BRCA1 function, such as miRNA-146a, miRNA-146-5p and miRNA-498 which repress BRCA1 with important functions in the formation of triple negative breast cancer cell lines (Garcia et al. 2011; Matamala et al. 2016; Petrovic et al. 2017). Moreover, miRNAs namely miRNA-206 can determine how cell could coup with deficiency of BRCA1 (Wronski et al. 2016). Heyn et al. has found that miRNA-335 has an important regulatory role on BRCA1 by effecting its upstream signaling molecules due to a direct relation between the expression of this miRNA and transcription of BRCA1 (Heyn et al. 2011). Targeting of BRCA1 has been shown to have potential clinical interests by Moskwa et al. showing that miRNA-182 downregulates BRCA1, and sensitizes cells to PARP inhibitors. Antagonizing the effects of this miRNA has caused cancer cells to experience a rapid gain of resistance to PARP inhibitors (Moskwa et al. 2011) (Table 1).

Effectors of DNA repair

DNA repair is regulated by multiple agents as miRNA. A study by Zhang et al. has found that miRNA205 is a determinant of radio-sensitivity, which exerted its effects by inhibiting DNA repair via targeting zinc finger E-box binding homeobox 1 and Ubc13 (Zhang et al. 2014a). Mueller et al. has found that miRNA-99 regulates DDR and DNA repair by targeting SNF2H that reduces DNA damage repair by abrogating the function of BRCA1 (Mueller et al. 2013). Another study by Di Francesco et al. has investigated that miR-27a affects the rejoining kinetics of DSB in A549 cells undergoing radiation (Di Francesco et al. 2013). Also, miRNA-346 has a pro-cancer effect, increasing proliferation and metastasis by downregulating XPC and negatively affecting XPC/ERK/Snail/E-cadherin signaling (Sun et al. 2016). Xie et al. has shown that miRNA-192 inhibits NER by targeting two important effectors as ERCC3 and ERCC4, resulting that the carcinogenesis of hepatitis B could be mediated by upregulating of this miRNA (Xie et al. 2011). Studies have shown that SNPs in the miRNA binding domains of genes and effective in NER can have significant effects on DNA repair capacity and can be linked to conditions such as age related cataracts and colorectal cancer (Gu et al. 2016; Naccarati et al. 2012). BER is another DNA repair method, which miRNAs have regulatory functions on. It is shown that like other repair pathways, SNPs in miRNA binding regions play an important role in regulating BER, thus having significant effects on progression of cancer (Pardini et al. 2013). A study by Wang et al. found that miRNA-149 targets DNA polymerase β in esophageal cancer cell lines resulted in increased sensitivity to cisplatin (Wang et al. 2018b). Further, Wang et al. has found that miRNA-499 has the similar effect (Wang et al. 2015). HR is also affected by miRNAs. One important function of miRNAs in physiologic processes is the inhibition of HR during G1 phase of cell cycle. miRNA-98-5p affects HR by targeting RAD51 as a key mediator which is performed by the mediatory effect of another miRNA (miRNA-152 that directly regulated RAD51). MiRNA-98-5p has a global inhibitory effect on other miRNAs, and contributed to resistance toward chemotherapy by platinum agents (Choi et al. 2014; Wang et al. 2018a). Cortez et al. has found that miRNA-34a has increased the sensitivity of lung cancer cells to radiation by targeting RAD51 and

Table 1 miRNAs involved in the highly coordinated network of DDR

MicroRNA	miRNA targets	Function in DDR	References
miR-138 miR-328-3p	H2AX	Reduced expression, foci formation, and increased tolerance to DNA damage. Also inhibit HR causing an increased sensitivity to DNA damageing	Bao et al. (2018), Gao et al. (2017)
miR-320	γH2AX, Sirtuin Type 1	Increased the γH2AX, inhibitory effects on the function of Sirt1	Garcia et al. (2011)
miR-23a	γH2AX	Increased the γH2AX and decreased rates of DNA double strand break	Gasparini et al. (2014)
pre-miR-630	ATM and H2AX	Block DDR cascade phosphorylation, decreased phosphorylation of ATM and H2AX	Ghorai and Ghosh (2014)
miR-138	γH2AX	Increasing the expression of γ-H2AX and inhibiting Sentrin/SUMO-specific protease 1	Gu et al. (2016)
miR-488	RPA and XPC	Causing a net increase in nucleotide excision repair	Harrison et al. (2009)
miR-2425-5p	RAD9 homolog A	Inhibitor of cell proliferation	Herranz et al. (2010)
miR-375	RAD1 and Bcl-2	Increasing the expression of RAD1 and Bcl-2, exert an anti-damage effect	Herzog et al. (2017)
miR-15a-3p	RAD1, GTSE1, NR2C1, FKBP9 and UBE2I	Elevated in stress response, downregulates GTSE1 and RAD1 at the protein level and improves cell survival	Heyn et al. (2011)
miR-106a miR-181a	ATM	Upregulating ATM, decreased double strand break	Hoey et al. (2018), Holzenberger et al. (2003)
miR-421 miR-26a miR-26a miR-107 miR-103 miR-181 miR-18a miR106a miR-26b	ATM	Downregulating ATM, increased double strand break	Houtkooper et al. (2012), Hu et al. (2017), Hu et al. (2014), Huang et al. (2013b), Huertas and Jackson (2009), Hühn et al. (2015), Ibrahim et al. (2012)
miR-185	ATR	Upregulating ATM, decreased double strand break	Jackson and Bartek (2009)
miR-3928	ATR	Activated ATR, decreased double strand break	Joaquin and Watson (2003)
miR-383	ATR	Decreased the level of ATR	Jung and Suh (2014)

inhibiting HR (Cortez et al. 2015). Furthermore, Liu et al. has suggested that miRNA-506 has the same effect (Liu et al. 2015). Besides, Liu et al. has reported that the regulatory effect of miRNA-590 is exerted via the miR-590/Acvr2a axis, which directly affects Rad51b. This axis has important applications in preserving stabilization in embryonic stem cells (Liu et al. 2014). Wang et al. has suggested that miRNA-96 downregulates the expression of REV1 and RAD51 led to the decreased efficacy of HR and increased sensitivity to PARP inhibitors and cisplatin (Wang et al. 2012). Gasparini et al. has found that miRNA-155 has a protective role against radiation in breast cancer by regulating RAD51, and patients could be classified based on their levels of this miRNA to be treated with radiation (Gasparini et al. 2014). Patel

et al. has also said that miRNA-15a and miRNA-16 downregulates B-lymphoma Moloney murine leukemia virus insertion region-1as a key molecule in the process of HR. The elevated levels of these miRNA has caused a growing sensitivity to chemotherapy agents and increased apoptosis in cancer cells (Patel et al. 2017). CtIP is a molecule involved in DSB resection in S/G2 which promotes HR (Huertas and Jackson 2009). Hühn et al. has found that miRNA19 targets CtIP and reduces the amount of HR in a p53 dependent manner (Hühn et al. 2015). XRCC2 is another molecule associated with HR and targeted by miRNAs. Xu et al. has shown that miRNA-7 targets this molecule and has anti-cancer effects by increasing the expression of p21, caspase-3 and Bax. This miRNA is downregulated in colorectal cancer specimens (Xu et al. 2014). MDC1 is a DNA damage mediator with functional characteristics in HR. Lee et al. has noticed that miRNA-22 suppressed DNA repair by targeting this molecule which is led to the increased DNA damage accumulation and genome instability (Lee et al. 2015). NHEJ is also affected by miRNAs. A study by Hu et al. has found that miRNA-21 mediates the radio resistance in specimens of human cancer cells. This miRNA targets GSK3B, which subsequently altered the function of CRY2/PP5 signaling and led to the increased rates of NHEJ and HR (Hu et al. 2017).

Effectors of apoptosis and cell cycle checkpoint

As mentioned before, two important end points of DDR are apoptosis and cell cycle arrest, which play important roles in preventing cancer progression. Various molecules are involved in upholding the cell cycle checkpoints including E2F family of proteins (Ren et al. 2002). A study by Lu et al. has found that miRNA-136 targets E2F1 by NF-KB signaling, promoting apoptosis and sensitivity to radiation (Lu et al. 2018). Qin et al. has preformed a study on multiple myeloma cells and studied the effects of silencing miRNA-137, finding that this inhibition is led to a reduced sensitivity to chemotherapy agents. This effect has been mediated by silencing of miRNA-137 functions promoted cell cycle arrest by increasing the expression of p53, and p21 (Qin et al. 2017). One important signaling cascade which is effective in preventing apoptosis and cell cycle arrest is c-Myc. A study has found that miRNA-34c acted as a downstream molecule in p38 MAPK/MK2 signaling, and regulates the expression and function of c-Myc. The inhibition of this miRNA resulted in abrogated S phase arrest has led to an increased genomic instability (Cannell et al. 2010). MiRNAs also affect apoptosis, which is an important cellular function involved in multiple physiologic and pathologic processes. Also, miRNAs regulate apoptosis mediators such as caspase molecules, XIAP, death receptor proteins such as Fas and DR4,5, regulating other signaling pathways which are closely linked to apoptosis such as NF-KB and Smad signaling (Su et al. 2015). Rane et al. (2009) has shown that these numerous interactions between miRNAs and apoptosis proteins have significant clinical applications due to their involvement in resistance to anti-cancer medications (Lima et al. 2011).

Modulation of microRNA expression in DNA damage response

Evidence has shown that DDR and its many transducers and mediators have important effects on miRNA regulation. One important transducer regarding miRNA regulation is ATM. After DSB, ATM is activated and phosphorylates multiple substrates including KH-type splicing regulatory protein (KSRP), which after phosphorylation promotes the processing of pre-miRNAs by Drosha-DGCR8 complex (Liu and Liu 2011). Furthermore, it is suggested that mutations in ATM has resulted a dysregulation of miRNAs (Zhang et al. 2011). Wan et al. has shown another role for ATM in regulating pre-miRNAs by its interaction with AKT. It is shown that the phosphorylation of AKT by ATM is resulted in the phosphorylation of Nup153 and its increased interaction with Exportin-5 has caused an increase in the release of pre-miRNAs from the nucleus (Wan et al. 2013). It is suggested that ATM utilizes miRNAs in order to regulate DNA repair. Martin et al. has elicited that CREB-miR-335-CtIP axis, which is downstream to ATM signaling, plays an important role in the selection of HR for certain lesions (Martin et al. 2013). ATR signaling is also important in mi-RNA regulation. Tamminga et al. has shown that exposure to radiation has caused an activation of ATR/ Rfx1 which increased the amounts of miR-709. This miRNA targets Brother of Regulator of Imprinted

Sites (BORIS), a protein involved in DNA methylation regulation (Tamminga et al. 2008). BRCA1 is to effect the transcription of miRNAs. A study by Kawai et al. has found that this is in part mediated by the effect of BRCA1 on DROSHA microprocessor complex and Smad3/p53/DHX9 signaling (Kawai and Amano 2012). A study by Tanic et al. has shown that BRCA1 regulates its effects in part by regulating the amounts of miRNAs which has important roles to affect NF-KB and TRAF2 signaling (Tanic et al. 2012). A study by Kumaraswamy et al. has found that BRCA1 has increased the amount of miRNA-146a attenuated EGFR expression. Further, the expressional status of this miRNA has prognostic value, because lower amounts are associated with positive lymph node involvement and lower survival (Kumaraswamy et al. 2015). Gao et al. has suggested that BRCA1 has negatively regulated specific miRNAs which has pro-oncotic functions. They found that the amount of miRNA-155 which is commonly upregulated in breast cancer has dependent on a negative regulatory effect of FOXP3 on BRCA1, and there is a direct relation between FOXP3 function and miRNA-155 amounts (Gao et al. 2017). Chang et al. has shown that different variants of BRCA1 has been resulted in significantly different levels of miRNA-155 (Chang and Sharan 2012; Chang et al. 2011).

miRNA in the pathogenesis of ageing

Though alterations of multiple miRNA have been linked to pathogenesis of ageing and its biology, the role of miRNAs in ageing is under question. However, Accumulating data has shown that miRNA can affect pathways involved in life span (Chen et al. 2010). One of common themes seen with senescence is changes in miRNA expression similar to the mouse embryo fibroblasts. It has been shown that miR-290 can induce SA-beta-gal(+) cells and p16 that are the markers of culture senescence (Pitto et al. 2009). DNA damage response-induced senescence is mainly controlled by p53 pathway. miRNAs stimulates the expression of p53 or their downstream targets the control cellular senescence. One of the p53 induced miRNA is miR-34a which upregulated in accompaniment with p53 in replicatively senescent fibroblasts (Chen et al. 2010). Also, miR-34a can elevate senescence in hepatocellular carcinoma cells through targeting c-Myc and FoxM1 that both are associated with the activation of telomerase reverse transcriptase (hTERT) transcription as a catalytic subunit of enzyme telomerase to avoid senescence (Xu et al. 2015). It has been found that the overexpression of miR138 can be directly induced a decrease in hTERT protein expression through targeting 3′-untranslated region. Indeed, in some of cancer cell lines such as anaplastic thyroid carcinoma (ATC), loss of miR138 expression may have slightly role in hTERT protein expression (Mitomo et al. 2008). Specific miRNAs have been associated with Alzheimer's disease and other neurodegenerative disease. miR-144 is one of the important miRNA which is involved in the ageing progression. This miRNA is selectively increased in the ageing brain compared to healthy aged brain (Persengiev et al. 2011). A number of miRNAs are associated with liver function and ageing. The use of miRNA microarrays to detect specific miRNA expression in the livers of Ames dwarf mice, showing that miR-27a represses the enzymes involved in biosynthetic pathways such as ornithine decarboxylase. Also, spermidine synthase might have role to extend the longevity of Ames dwarf mouse (Bates et al. 2010). The other feature of ageing is mitochondrial dysfunction. miRNAs may contribute to ageing through interference intracellular pathways such as those involving the mitochondrial antioxidative enzymes superoxide dismutase 2 (SOD2) and thioredoxin reductase 2 (Txnrd2) that play a key role in modulating cellular senescence via detoxifying reactive oxygen species (ROS). In ageing mesangial cells miR-335 and miR-34a can inhibit the expression of SOD2 and Txnrd2 by targeting 3′-untranslated regions of these genes. Indeed, an increment in the expression of miR-335 and miR-34a has stimulated the premature ageing of young mesangial cells by suppression of SOD2 and Txnrd2 led to ROS production increasing (Bai et al. 2011). Cellular senescence can be supposed as a major tumor suppressor mechanism and a form of irreversible growth arrest. Many studies have been published in studying senescence triggered acutely through a variety of stimuli including the expression of tumor suppressor genes and suppression of key cellular proteins such as B-Myb. B-Myb oncogene is a transcription factor that regulates cell cycle progression and other genes involved in cell proliferation such as c-Myc (Joaquin and Watson 2003; Sala 2005). Interestingly, B-Myb can regulate senescence. This

Table 2 miRNAs in the pathogenesis of ageing with target genes

miRNA	Expression levels during ageing	Target tissue	Target genes	Major finding	Reference(s)
lin-4	Reduced	*C. elegans*	lin-14	Overexpressing lin-4 or reducing the activity of lin-14 extended life span it is dependent on the DAF-16 and HSF-1 transcription factors	Boehm and Slack (2005)
miR-1	Increased	Rat	IGF-1, IGF-1R	miR-1 and IGF-1 protein levels are correlated inversely in models of cardiac hypertrophy and failure	Elia et al. (2009), Yu et al. (2008)
				IGF-1 signal transduction cascade regulates miR-1 expression through the Foxo3a transcription factor	
miR-320	Increased	Rat	Flk-1, IGF-1 and IGF-1R	miR-320 impaired angiogenesis	Wang et al. (2009)
miR-206	Increased	Rat	IGF-1	miR-206 is involved in apoptotic cell death in myocardial infraction	Shan et al. (2009)
miR-145b	Reduced	Human	IGF-1R and IRS-1	down-regulation of insulin receptor substrate-1 plays a significant role in activity of miR145	La Rocca et al. (2009a), La Rocca et al. 2009b)
miR-140b	Reduced	Human	IL-1 and IGFBP-1	Transfection of chondrocytes with ds-miR-140 down-regulated IL-1beta-induced ADAMTS5 expression and rescued the IL-1beta-dependent repression of AGGRECAN gene expression	Miyaki et al. (2009), Tardif et al. (2009)
miR-100	Reduced	Human	mTOR, FRAP1	Overexpression of the mir-22 repressed the EVI1 oncogene	Nagaraja et al. (2010)
miR-217	Increased	Human	SIRT1	miR-217 leads to an impairment in angiogenesis via inhibition of SirT1 and modulation of FoxO1 and endothelial nitric oxide synthase acetylation	Menghini et al. (2009)
miR-34ab	Increased	Human	SIRT1, Notch1, Notch2, Jagged1, c-Met, and bcl2, etc	FXR activation in these mice reversed the miR-34a and SIRT1 level	Lee et al. (2010)
miR-199a	Decreased	Rat	SIRT1	Sirt1 is also a direct target of miR-199a and is responsible for downregulating prolyl hydroxylase 2, required for stabilization of Hif-1alpha,	Rane et al. (2009)
miR-132	Decreased	Human	SIRT1	Inhibitors of miR-132 decreased acetylated p65 and partially inhibited the production of IL-8 and MCP-1 induced by serum deprivation	Strum et al. (2009)
let-7b	Increased	Mouse	HMGA2	Hmga2 promotes neural stem cell self-renewal by reducing p16Ink4a and p19Arf Expression	Nishino et al. (2008)
let-7 family	Increased	*C. elegans*	hbl-1	DAF-12 and its steroidal ligand directly activate promoters of let-7	Bethke et al. (2009)
miR-145b	Increased	Human	SOX2, OCT4, and KLF4	Increased miR-145 expression inhibits hESC self-renewal, represses expression of pluripotency genes, and induces lineage-restricted differentiation	Xu et al. (2009)
miR-302–367	Decreased	Human	Cyclin-D1,	Inhibition of miR-302 causes G1 phase arrest	Card et al. (2008)

Table 2 continued

miRNA	Expression levels during ageing	Target tissue	Target genes	Major finding	Reference(s)
miR-106a	Increased	Human	p21, RARG	Changes in miRNA expression might contribute to phenotypic alterations of senescent cells	Li et al. (2009)
miR-21	Increased	Human	TGF-bR2	miR-21 may play a role in ' 'inflammageing'', thus affecting the risk of major age-related diseases	Olivieri et al. (2012)
miR-146a/b	Increased	Human	IL-6 and IL-8	IL-1 receptor signaling initiates both miR-146a/b upregulation and cytokine secretion	Bhaumik et al. (2009)
miR-130a-3p	Decreased	Rat	TNF-α, IL-10	miR-130a-3p desregulation may be associated with elderly hip fracture-induced immune disturbance	Chen et al. (2018)
miR-29	Increased	Mouse	p85a, IGF-1 and B-myb,	miR-29 suppressed the proliferation and increased levels of cellular arrest proteins, recapitulating ageing-induced responses in muscle	Hu et al. (2014)
miR-18, -19	Decreased	Mouse	CTGF and TSP-1	During ageing, decreased miR-18/19 and increased CTGF and TSP-1 levels identify the failure-prone heart	van Almen et al. (2011)

transcription factor is suppressed through the interaction with Rb-E2F complexes to B-Myb promoter, thus loss of B-Myb expression can bring ageing. It has been shown that miR-29 and miR-30 can regulate the expression of B-Myb by often targeting to its 3′UTR. Indeed, these miRNAs directly play a major role in suppress of B-Myb during senescence and regulating Rb-driven cellular ageing (Martinez et al. 2011). Senescence-associated miRNAs (SA-miRNAs) can act as a barrier to cancer progression in vitro in vivo. It is reported that miR-22 as a SA-miRNAs is overexpressed in senescent fibroblasts and epithelial cells while its expression is decreased in various cancer cell lines. Indeed, the upregulation of miR-22 stimulates the growth repression and induction of a senescent phenotype in both normal and cancer human-cell. It seems that these effects are exerted through CDK6, SIRT1 and Sp1 genes associated with the ageing program in cancer cell that target miR-22 (Xu et al. 2011). On the whole, these studies have suggested that senescence-associated miRNAs can modulate cellular senescence. More interestingly, it is shown that various miRNAs play critical function in ageing through regulating some important signaling pathways such as insulin/insulin-like growth factor (IGF) pathway, target of rapamycin (TOR) pathway, Notch, PI3K, p53, and inflammatory pathways (Table 2). Therefore, with regards to the role of miRNAs in ageing a new view could be open for the therapeutic miRNA delivery in a variety of cancers and ageing-related diseases.

miRNA's therapeutic function in ageing based on its regulation of the DDR

Multiple pathways are involved in the process of ageing when DDR is one of the most important. A study by Zou et al. (2018) has found that single nucleotide polymorphisms in 3′-terminal untranslated region of XPC involved in nucleotide excision repair has significant associations with nuclear Age-related Cataract. Also, miRNAs have been regarded as targets in enhancing DNA repair in keratinocytes. A study by Joo et al. has found that the extract of *Trichosanthes kirilowii* could enhance DDR in keratinocytes undergoing UVB radiation by downregulating the expression of miRNA-142-3p and upregulating the brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1) (Joo et al. 2018). A study by Boon et al. has found that micro-RNA-34a has played an important role in age related decrease in

cardiac function. It is shown that PNUTS plays an important role in regulating DDR. Inhibiting microRNA-34a has been resulted in increased rates of recovery after ischemic attacks and decreased fibrosis (Boon et al. 2013).

Conclusion

Different miRNAs directly or indirectly affect the expression of multiple components in DDR, as well as the expression of genes involved in features of ageing. Therefore, considering the importance of miRNAs in pathogenesis of ageing and DDR, miRNAs are emerging as key targets, which can be open new views to be used by drugs to eradicate a variety of cancers and ageing-related diseases. However, extra studies are required in the cross-talks between miRNAs, ageing and DDR, providing invaluable information to the mechanism of miRNAs action in these processes.

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Compliance with ethical standards

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