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Roles of MicroRNA in DNA Damage and Repair

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1. Introduction

DNA damage mainly results from either endogenous metabolic activity, such as oxidative stress, or environmental exposure, such as ionizing irradiation. In human cells, endogenous and exogenous genotoxic agents produce as many as 1 million molecular lesions per cell per day. If the unrepaired lesions occur in certain critical genes, they can cause mutations that can lead to tumors (Lodish H, 2004).

There are several different types of DNA damage, including DNA hydrolysis, DNA adduction, DNA crosslinking, and DNA strand breakage. DNA hydrolysis is the breaking of DNA through the addition of water. Hydrolysis of DNA bases consists of deamination, depurination, and depyrimidination. A DNA adduct is a piece of DNA covalently bonded to a chemical. DNA crosslinks are links formed within a single (intrastrand) or between strands of DNA (interstrand). There are two types of DNA strand breaks, single strand breaks and double strand breaks. DNA double strand breaks are particularly hazardous to the cells because they can lead to genome rearrangements. (Rich et al., 2000).

Cells respond to DNA damage through a variety of different mechanisms, such as apoptosis, senescence, and DNA repair. Excessive DNA damage induces apoptosis, or programmed cell death, that eliminates cells with heavily damaged DNA, thus protecting the organism from the mutations potentially induced by the damage. Unrepaired DNA damage is a driving force for senescence. Senescence serves as a functional alternative to apoptosis in cases where the physical presence of cells is required for spatial reasons. If DNA replication occurs before DNA damage is repaired, mutations can be formed in the cells. To prevent mutation formation, cells have developed DNA repair mechanisms to correct DNA.

There are several different types of DNA repair. They are direct reversal, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end-joining (NHEJ), and homologous recombination repair (HRR). Direct reversal can remove DNA damage by chemically reversing it. Since the correction only occurs in one of the four bases and not the phosphodiester backbone, this type of repair does not need any DNA template. For example, methylation of guanine bases can be directly reversed by methyl guanine methyl transferase (MGMT) that removes the methyl group. BER amends damage to single nucleotides produced by oxidation, alkylation, or hydrolysis. NER corrects ethylation products, bulky DNA adducts, helix-distorting changes, such as thymine dimers, and single-strand breaks. MMR repairs mismatched bases in double-stranded DNA (e.g., A:C or G:T). HRR is a mechanism for DNA double-strand repair that reconstitutes the

original sequence using the sister chromatid as a template. NHEJ is a relatively simple way for DNA double-strand repair and it just rejoins two broken ends without correcting any deletions or rearrangements of DNA.

2. Biogenesis of miRNA

A microRNA gene can be located in an intron of another gene, in either the sense or antisense orientation. miRNA can be coordinately expressed with its host gene, or it can have its own promoter independent of its host gene (Ozsolak et al., 2008). The biogenesis of miRNA is a complex process as shown in Figure 1. miRNA is first transcribed as a long primary miRNA (pri-miRNA) by RNA polymerase II in the nucleus (Lee et al., 2004). Pri-miRNA is structurally similar to mRNA, but contains a stable stem-loop structure (Cai et al., 2004). Recognition of the hairpin and selection of a cleavage site are mediated by DGCR8. Nuclear RNase III (Drosha) then cleaves the pri-miRNA to release the hairpin-shaped precursor miRNA (pre-miRNAs). The pre-miRNA is exported from the nucleus to the cytoplasm by Exportin 5 (Exp5). In the cytoplasm, the pre-miRNA is subsequently cut by cytoplasmic RNase III (Dicer) in complex with Argonaute2 (Ago2) and TRBP, a double-stranded RNA-binding protein. This process cleaves the pre-miRNA hairpins to remove its hairpin loop, resulting in a miRNA duplex with the appropriate length (Gregory et al., 2005; Han et al., 2004; Lee et al., 2003). Normally, one strand of the duplex is then degraded. The mature miRNA are incorporated into an RNA-induced silencing complex (RISC) (Gregory, et al., 2005; Grishok et al., 2001; Hutvagner et al., 2001; Ketting et al., 2001; Maniataki and Mourelatos, 2005). RISC recognizes target mRNAs through full or partial base-pairing interactions between the miRNA and the 3'-untranslated region (UTR) of the target mRNA. Depending on pairing interactions between miRNAs and their targets, miRNAs suppress their target gene expression by either mRNA cleavage or translational repression. If an mRNA target match perfectly or near-perfectly to the miRNA, the mRNA will be degraded; otherwise, the mRNA will be translationally suppressed (Meister and Tuschl, 2004).

3. Alteration of miRNA biogenesis in response to DNA damage and repair

Because miRNAs are actively involved in regulation of genes that are related to DNA damage and repair, it was not surprising to find that miRNA biogenesis changes in response to DNA damage and repair. Several studies demonstrated that both miRNA transcription and maturation process are altered in response to DNA damage and repair.

Recent studies show that transcription of miRNA can be directly affected by DNA damage. The *P53* gene plays a critical role in this regulation. For example, miR-34a can be up-regulated by the *P53* gene in response to DNA damage (Chang et al., 2007; Corney et al., 2007; He et al., 2007; Raver-Shapira et al., 2007; Welch et al., 2007). Up-regulation of miR-34a results in apoptosis, cell-cycle arrest, and DNA repair. miR-34a is a direct transcriptional target of P53 because the promoter region of miR-34a contains a canonical P53 binding site. When DNA damage activates the *P53* gene, P53 protein binds to the promoter of miR-34a and up-regulates miRNA expression. In *Caenorhabditis elegans*, miR-34a expression was enhanced by irradiation in a P53 independent manner, and knocking down of the *Cep1* gene (homolog of the *P53* gene) had no effect on the miR-34a response to irradiation (Kato et al., 2009). Up-regulation of miR-34a in response to genotoxin exposure is also observed in different biological systems (Chen et al., 2011; Li et al., 2010;

Li et al., 2011; Zenz et al., 2009). miR-34c, another member of miR-34 family, is transcriptionally up-regulated by P53 following DNA damage (Cannell et al., 2010). In addition to miR-34a, P53 can also regulate the expression of miR-192, miR-194, and miR-215. These miRNAs are considered tumor suppressor miRNAs (Braun et al., 2008; Georges et al., 2008).

miRNA biogenesis is globally induced upon DNA damage in an ATM (ataxia telangiectasia mutated) dependent manner (Zhang et al., 2011). The ATM gene encodes a DNA damage-inducible kinase. ATM controls cell growth rate by interacting with other proteins, for example BRCA1, following DNA damage. In response to strand breaks or other type of DNA damage, the ATM protein coordinates DNA repair by activating other proteins. Because of its central role in cell division and DNA repair, the ATM protein is important in carcinogenesis. More than one-fourth of miRNAs were significantly upregulated after DNA damage, while loss of ATM activity abolished their induction. Their results show that DNA damage activates the ATM kinase that directly binds to and phosphorylates KH-type splicing regulatory protein (KSRP), leading to enhanced interaction between KSRP and pri-miRNAs and increased KSRP activity in miRNA processing. The increased activity, in turn, results in more pre-miRNAs from pri-miRNAs, so that more miRNA products are produced to respond to the DNA damage.

Other studies show a different mechanism by which DNA damage signaling is linked to the miRNA maturation processes. Several miRNAs with growth suppressive function, including miR-16-1, miR-143 and miR-145, were regulated at the post transcriptional level through a P53-mediated miRNA maturation process in response to DNA damage (Suzuki et al., 2009; Toledo and Bardot, 2009). The P53 tumor suppressor protein binds to Drosha to facilitate the processing of pri-miRNAs to pre-miRNAs. Mutation in the DNA-binding domain of P53 decreases processing of pri-miRNAs by Drosha, and reduces the expression of the related miRNAs. In silico analyses, all three components of the P53 tumor suppressor, P53, P63, and P73, can regulate the major components of miRNA processing, such as Drosha-DGCR8, Dicer-TRBP2, and Agronaute proteins. Thus, when DNA damage activates the P53 gene, the activated P53 gene can modulate miRNA expression by affecting the miRNA biogenesis processes.

miR-24 regulates the DNA damage response by down-regulation of H2AX, the initial sensor protein for the DNA damage response. miR-100, miR-101 and miR-421 suppress ATM, the chief transducer of the DNA damage response, by targeting the 3'-UTR of ATM. miR-16 can up-regulate ATM activity by suppressing levels of Wip1. DNA repair pathways are regulated by a number of miRNAs involved in different types of DNA damage correction. The NER protein RAD23B was down-regulated by miR-373. MMR protein MSH2 and MSH6 were down regulated by miR-21 and MLH1/MSH2 were suppressed by miR-155. The HRR protein BRCA1 was down-regulated by miR-182 and RAD52 was suppressed by miR-210 and miR-373. The NHEJ protein DNA-PKcs was suppressed by miR-101 (Yan, Ng, 2010).

4. miRNA regulation of signal transduction for DNA damage

miRNAs regulate multiple aspects of the DNA damage response pathway, including regulation of signal transduction of DNA damage, changing expression level of master regulatory proteins such as P53, modulating key protein expression in different types of DNA repair such as MMR, NER, NHEJ and HRR. Figure 2 and Table 1 summarize recently reported miRNAs associated with DNA damage and repair.

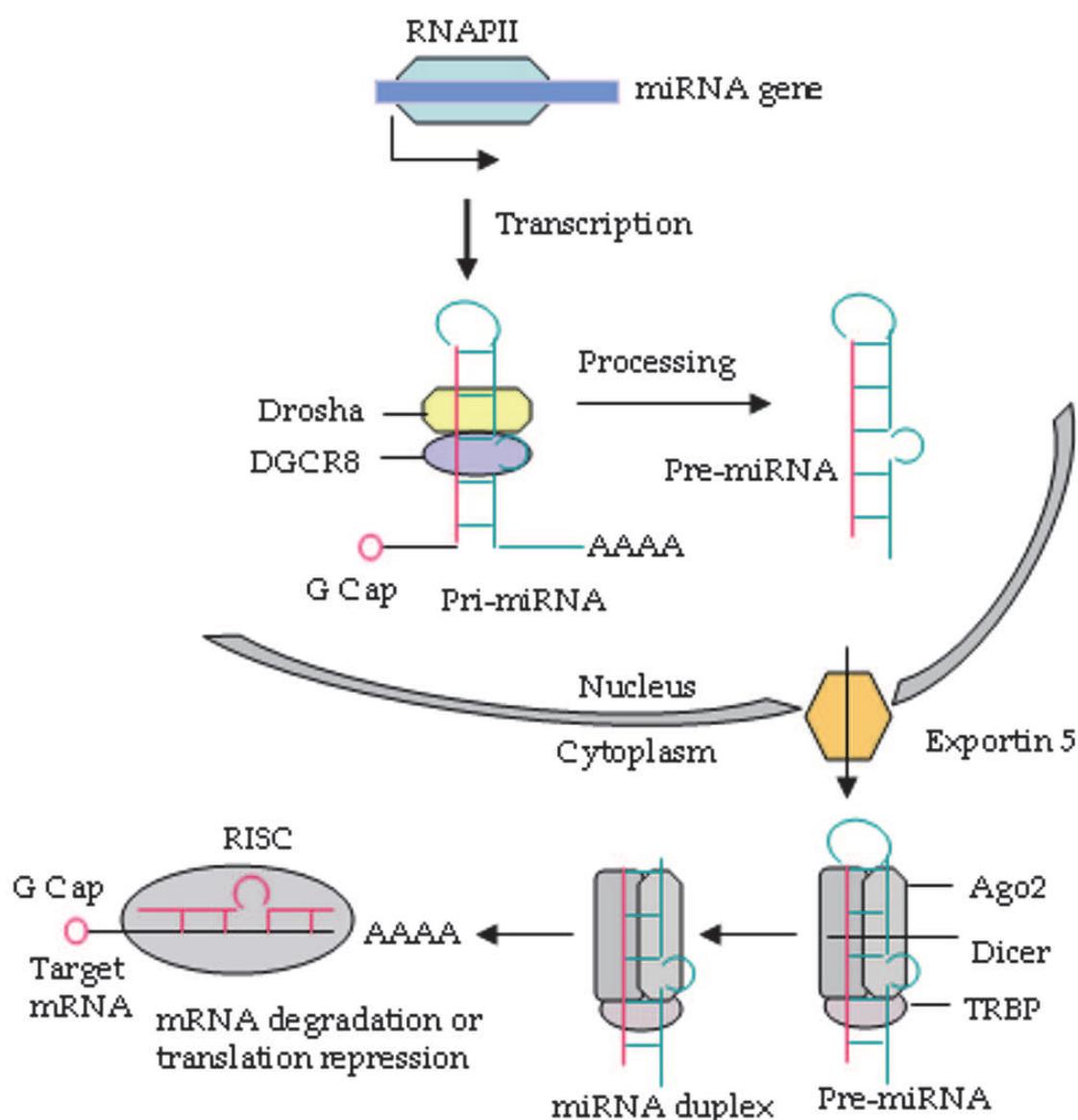


Fig. 1. MicroRNA biogenesis. A microRNA gene is transcribed by RNA polymerase II (RNAPII) to produce a pri-miRNA. The pri-miRNA is formed by RNase III family Drosha, cooperating in a complex with dsRNA-binding proteins DGCR8. The Drosha-DGCR8 complex processes the pri-miRNA into an ~70-nucleotide pre-miRNA, which is exported to the cytoplasm by exportin 5. The cytoplasm pre-miRNA is cleaved by Dicer, assisted by TRBP and AGO2, and yields an ~20-bp miRNA/miRNA* duplex. One strand of the miRNA/miRNA* duplex is preferentially incorporated into a miRNA-induced silencing complex (RISC), whereas the other strand is degraded (not shown). RISC recognizes target mRNAs and lets the miRNA binds to its target mRNA to suppress gene expression, either by mRNA cleavage or translational repression.

DNA damage activates the signal transduction process that leads to cell cycle arrest, which can lead to apoptosis or DNA repair. This DNA-damage response is mainly regulated at the transcriptional and posttranslational levels. Recent evidence suggests that miRNAs offer another degree of regulation at the posttranscriptional level in response to DNA damage. The DNA damage response to UV light was severely attenuated after the key components of

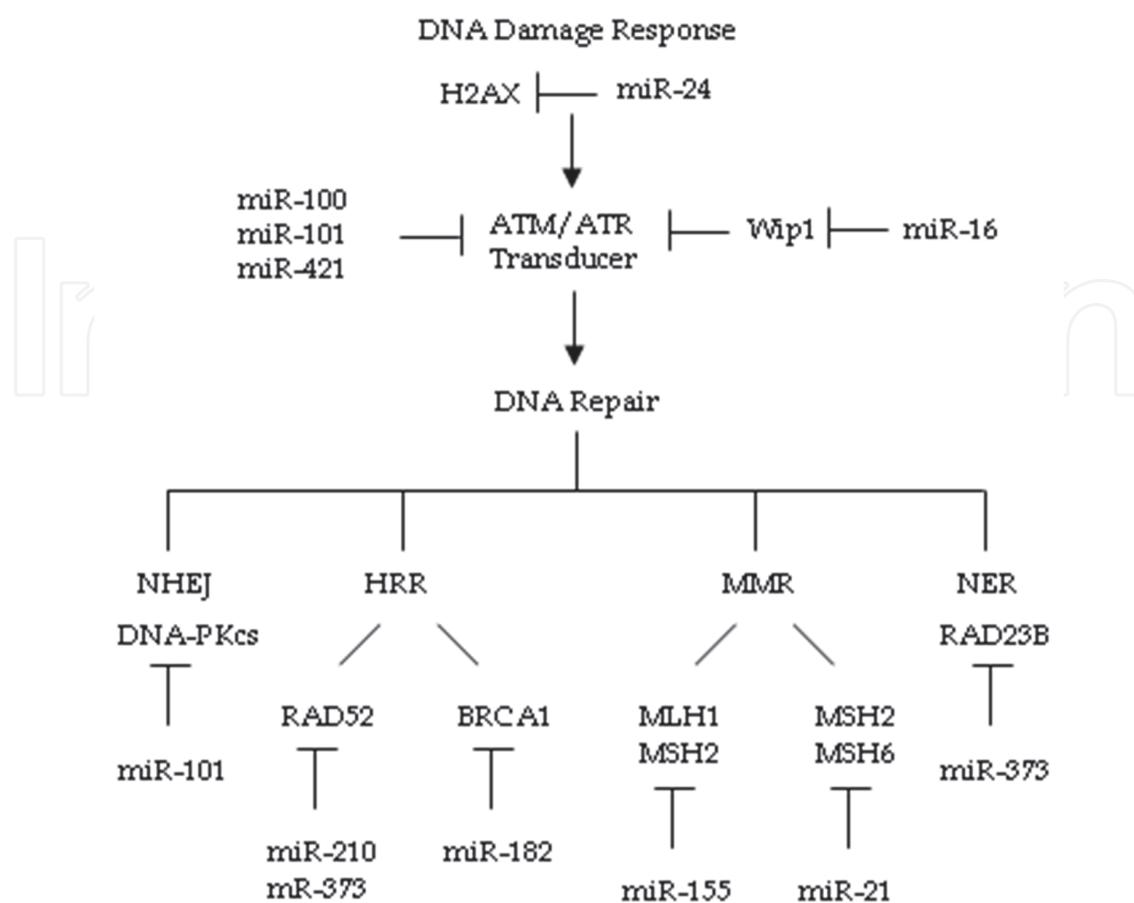


Fig. 2. miRNAs directly regulate DNA repair

the miRNA-processing pathway (Dicer and Ago2) were knocked down. miRNA mediated gene regulation operates earlier than most other transcriptional responses following genotoxic stress (Pothof et al., 2009).

H2AX, a histone variant, is an initial sensor protein for the DNA damage response. The function of H2AX is associated with DNA double strand break repair. miR-24 expression is up-regulated during hematopoietic cell differentiation into multiple lineages. miR-24 regulates H2AX expression through binding to its 3'-UTR. Both H2AX mRNA and protein levels are dramatically reduced by high levels of miR-24 in terminally differentiated human blood cells. miR-24 mediated suppression of H2AX in terminally differentiated blood cells renders them hypersensitive to gamma-irradiation, deficient in DSB repair, and susceptible to chromosomal instability (Lal et al., 2009).

Wild-type p53-induced phosphatase 1 (Wip1) is an oncogene with critical function in the ATM/ATR-p53 DNA damage signaling pathway. Wip1 reverses DNA damage-induced cell cycle checkpoints by dephosphorylating several key DNA damage responsive proteins. Recently, miRNAs are found to play an important role in suppressing Wip1 activity. Knockdown of miR-15a and miR-16 promotes survival, proliferation and invasiveness of untransformed prostate cells, and tumor formation in immunodeficient NOD-SCID mice. Conversely, reconstitution of miR-15a and miR-16 expression results in marked regression of prostate tumor xenografts. The function of miR-15a and miR-16 is considered through their regulation of Wip1 expression. miR-16 can down-regulate the expression level of Wip1

by targeting the 3' UTR of Wip1. As a result, the Wip1 protein level is significantly decreased, which prevents a premature inactivation of ATM/ATR signaling and allows a functional completion of the early DNA damage response (Zhang et al., 2010).

miRNA	Pathway Involved	Target Protein	Net Effect	Reference
miR-24	DDR	H2AX	-	Lal, Pan. 2009
miR-16	DDR	Wip1	+	Zhang, Wan. 2010
miR-100	DDR	ATM	-	Ng, WL. 2010
miR-101	DDR	ATM	-	Yan, Ng. 2010
miR-421	DDR	ATM	-	Hu, Du. 2010)
miR-373	NER	RAD23B	-	Crosby, Kulshreshtha. 2009
miR-21	MMR	MSH2, MSH6	-	Valeri, Gasparini. 2010)
miR-155	MMR	MLH1, MSH2	-	Volinia, Calin. 2006
miR-182	HRR	BRCA1	-	Moskwa, Buffa. 2011
miR-210	HRR	RAD52	-	Crosby, Kulshreshtha. 2009
miR-373	HRR	RAD52	-	Crosby, Kulshreshtha. 2009
miR-101	NHEJ	DNA-PKcs	-	Yan, Ng. 2010
miR-29	P53	P85a, CDC42	+	Park, Lee. 2009
miR-34a	P53	SIRT1	+	Yamakuchi, Ferlito. 2008)
miR122	P53	Cyclin G1	+	Fornari, Gramantieri. 2009
miR-125b	P53	P53	-	Le, Teh. 2009
miR-504	P53	P53	-	Hu, Chan. 2010

Table 1. miRNAs involved in DNA repair (notes: - means inhibit and + means stimulate)

ATM is a serine/threonine kinase that transfers the DNA damage signals to downstream events, such as cell cycle arrest, apoptosis and DNA repair (Lavin, 2008; Shiloh, 2003). ATM plays a critical role in the maintenance of genomic stability by activating cell cycle checkpoints and promoting DNA double-strand breaks repair. M059J is a human malignant glioma cell line with high sensitivity to ionizing radiation due to low-expression of ATM. The low-expression of ATM is related to miR-100 (Ng et al., 2010). Both computational analysis and luciferase reporter gene assay indicate that miR-100 can target the 3'-UTR of ATM. miR-100 was found to be highly-expressed in M059J cells by RNase protection assay and qRT-PCR. Up-regulation of miR-100 in M059K cells reduces ATM expression and renders them hypersensitive to ionizing radiation, while Knock-down of miR-100 promotes ATM expression in M059J cells. These results indicate that the low-expression of ATM in M059J cells is mainly due to the high expression of miR-100.

Another miRNA miR-421 is also involved in ATM regulation. miR-421 suppresses the expression of ATM by targeting the 3' UTR of ATM. Ectopic expression of miR-421 lead to a deficient cell cycle checkpoint in S-phase and increased sensitivity to ionizing radiation (Hu et al., 2010a). Blocking the interaction between miR-421 and ATM with chemically synthesized oligonucleotides rescued the defective phenotype caused by miR-421 over expression, suggesting that ATM mediates the effect of miR-421 on cell-cycle checkpoints followed by radiation.

5. miRNA regulation of core components of DNA damage response

miRNAs are involved in DNA repair by regulating critical components of the DNA repair pathways, such as P53. As a transcription factor, the tumor suppressor P53 is a powerful regulator of diverse cellular processes including cell-cycle arrest, DNA repair, apoptosis and cellular senescence. P53 and its signaling pathway, play a pivotal role in maintaining genomic stability and tumor suppression (Levine et al., 2004; Levine et al., 2006). Recently, P53 activity was found to be widely regulated by a number of miRNAs. These miRNAs either directly target the 3' UTR of P53 or indirectly regulate P53 activity by modulating proteins associated with P53 (Figure 3). Among these miRNAs, miR-504 negatively regulate p53 expression through binding to two DNA *cis* element located in the P53 3' UTR. Ectopic expression of miR-504 reduces the protein level of P53 and impairs P53-mediated apoptosis and cell cycle arrest (Hu et al., 2010b). miR-125b is another negative regulator of P53 in both zebrafish and humans (Le et al., 2009). Knocking down of miR-125b increased the expression level of P53; and over-expression of miR-125b suppressed the expression of P53. Interestingly, miR-125b was down-regulated when the Zebrafish embryo was exposed to gamma irradiation, corresponding to the up-regulation of P53 protein induced by the irradiation exposure.

In addition to the direct binding to P53, several miRNA including miR-34a, miR-29 and miR-122 can indirectly modify P53 activity (Fornari et al., 2009; Park et al., 2009; Yamakuchi et al., 2008). miR-34a is a direct transcriptional target of P53 (Chang, et al., 2007; Corney, et al., 2007; Raver-Shapira, et al., 2007). P53 can up-regulate miR-34a expression by binding to a palindromic sequence located in miR-34a promoter region. miR-34a can positively regulate P53-dependent apoptosis through another intermediate protein, SIRT1 (Yamakuchi, et al., 2008). miR-34 inhibition of SIRT1 leads to an increase in acetylated P53. As a result, miR-34 suppression of SIRT1 ultimately leads to P53 mediated apoptosis in human colon cancer cells. miR-29 family members directly suppress P85a and CDC42, both of which negatively regulate P53. As a result, miR-29 positively up-regulates P53 level and induces apoptosis and DNA repair in a P53-dependent manner (Park, et al., 2009). miR-122 is a liver-specific miRNA accounting for 70% of the total miRNA population. miR-122 can down-regulate the expression of cyclin G1, which has the potential to inhibit P53 activity and promote cancer development. From a therapeutic perspective, miR-122 has potential to become a miRNA based therapy for hepatocellular carcinoma (HCC) patients (Fornari, et al., 2009).

6. Functions of miRNAs in mismatch repair (MMR)

MMR corrects erroneous deletion, insertion, or mis-incorporation of bases resulting from DNA replication, DNA recombination, or DNA damage. Human mutS homolog 2 (hMSH2) and mutL homolog 1 (hMLH1) function as core proteins in MMR. They form heterodimers with protein homologs hMSH3 or hMSH6 (Fishel, 2001). The over-expression of miR-21 is linked to progression of human colorectal cancer (Link et al., 2010; Ng et al., 2009). It was reported recently that miR-21 directly targeted the 3' UTRs of both the hMSH2 and hMSH6 mRNAs (Valeri et al., 2010a). Protein levels of hMSH2 and hMSH6 in the cells transfected with a locked nucleic acid (LNA) against miR-21 were significantly increased over the control cells. In addition, the over-expression of miR-21 was inversely correlated with the down regulation of hMSH2 in colorectal cancer tumors. Because the hMSH2-hMSH6 heterodimer is the key initiation component of MMR, the down regulation of hMSH2 is likely to suppress MMR, and ultimately enhance tumor progression.

miR-155 also plays a critical role in MMR. Over-expression of miR-155 reduced the levels of the human mismatch repair genes MLH1, MSH2 and MSH6 in a colorectal cancer cell line.

In addition, high expression of miR-155 was inversely correlated with the low expression of MLH1 and MSH2 protein in human colorectal cancer. More importantly, human tumors with unexplained MMR inactivation showed miR-155 over expression (Valeri et al., 2010b; Volinia et al., 2006). These results indicate that increased expression of miR-155 down-regulates MMR genes and results in an increase in genomic instability.

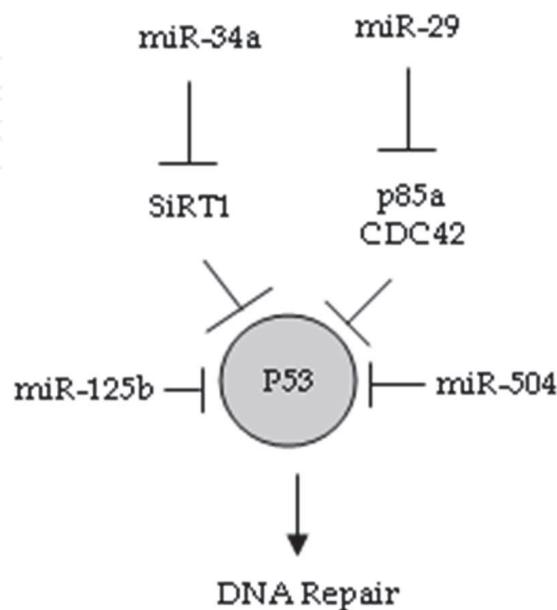


Fig. 3. miRNA indirectly regulates DNA repair through P53

miR-504 and miR-125b directly bind to the P53 3'-UTR and down-regulate P53 activity. miR-34a positively up-regulates P53 through SIRT1 inhibition, a negative regulator of P53. miR-29 down-regulates the P85a regulatory subunit of PI3K, which enhances P53 activity through the negative feedback loop between PI3K-AKT-MDM2 and P53.

7. Functions of miRNAs in nucleotide excision repair (NER)

NER recognizes bulky, helix distorting defects, such as cross-linking thymine dimers. NER is particularly important for removing the vast majority of UV-induced DNA damage. Currently, only one miRNA is reported to be related with NER (Crosby et al., 2009). miR-373 suppresses the expression of a NER protein called RAD23B. RAD23B is a key component of the XPC/RAD23B complex that mediates damage recognition in the NER pathway (Batty et al., 2000). NER activity is functionally reduced in hypoxic cells (Yuan et al., 2000). A possible mechanism for the hypoxia-induced down-regulation of RAD23B is that hypoxia can up-regulate miR-373 expression, and the up-regulated miR-373 then suppresses RAD23B expression. This mechanism was supported by the fact that pre-treating cells with anti-miR-373 reversed the hypoxia-mediated down-regulation of RAD23B in hypoxic cells (Crosby, et al., 2009).

8. Functions of miRNAs in non-homologous end-joining (NHEJ)

NHEJ is a relatively simple but error prone DNA double strand break repair. It ligates broken ends, without the need for a homologous template. DNA protein kinase (DNA-PK)

is a core component of mammalian NHEJ and involves a catalytic subunit (DNA-PKcs) that can act as a regulatory element. DNA-PKcs is a molecular sensor for DNA damage that enhances the signal via phosphorylation of many downstream targets. Therefore, DNA-PKcs is an essential factor for NHEJ. Yan et al. found that miR-101 could efficiently target DNA-PKcs and ATM via binding to their 3'-UTRs. Up-regulating miR-101 efficiently reduced the protein levels of DNA-PKcs and ATM in tumor cells, and most importantly, sensitized the tumor cells to radiation *in vitro* and *in vivo* (Yan et al., 2010). Radiotherapy kills tumor-cells by inducing DNA double strand breaks (DSBs). However, the efficient repair of double strand breaks in tumors frequently prevents successful treatment. Therefore, miR-101 could be used to target DNA DSB repair genes, in order to sensitize tumors to radiation and improve tumor radiotherapy.

9. Functions of miRNAs in homologous recombination repair (HRR)

HRR is the most widely used repair mechanism which can accurately repair DNA double strand breaks. HRR reconstitutes the genetic information using the sister chromatid as a template. Several proteins are involved in the HRR process. Rad 52 protein recognizes double-strand breaks and adheres to the free ends of the break while the Rad51 protein, together with tumor-suppressor protein BRCA1, searches the undamaged sister chromatid for homologous pairing (Haber, 2000; Orelli and Bishop, 2001).

Both miR-210 and miR-373 were up-regulated in hypoxic cells. Up-regulation of miR-210 significantly suppressed the expression level of RAD51, while up-regulation of miR-373 inhibited the expression of RAD52. The modulation of miR-210 to RAD51 and miR-373 to RAD52 were verified by microarray analysis and luciferase reporter gene assay. Both of the miRNAs can bind to the binding sites in the 3' UTRs of their respective target mRNAs (Crosby, et al., 2009). Thus, hypoxia-inducible miR-210 and miR-373 regulate HRR via targeting RAD51 and RAD52.

BRCA1 is a constituent of several different protein complexes and is a key protein for HRR. Expression of BRCA1 is commonly decreased in sporadic breast tumors, and this correlates with poor prognosis of breast cancer patients (Mueller and Roskelley, 2003). It was recently reported that miR-182 down-regulated BRCA1 expression. As a result, the HRR efficiency for DNA double strand break repair was impaired (Moskwa et al., 2011; Yao and Ventura, 2011). Antagonizing miR-182 enhanced BRCA1 protein level, which, in turn, protected cells from irradiation exposure. Over-expressing of miR-182 reduced BRCA1 protein level, which impaired HRR efficiency and rendered cells hypersensitive to irradiation. The impaired HRR phenotype due to miR-182 over-expression was able to be fully rescued by over-expressing of BRCA1. Thus, these data demonstrate miR-182-mediated down-regulation of BRCA1 suppresses HRR.

10. Conclusion

miRNAs appear to be involved in DNA damage and repair in many ways. miRNA biogenesis, including miRNA gene transcription and miRNA maturation processes, is readily altered in response to DNA damage. miRNAs regulate the ATM and P53 that are the regulators of the global induction of miRNA biogenesis upon DNA damage. miRNAs are also involved in signal transduction processes that leads to cell cycle arrest, apoptosis or DNA repair upon DNA damage. miR-100 and miR-421 can regulate expression of ATM, a

critical protein in DNA damage signalling. miR-24 suppresses gene expression of H2AX, an initial sensor protein for DNA damage response. miR-16 down-regulates the expression level of Wip1, an inhibitor of ATM/ATR-p53 DNA damage signalling pathway. miRNAs can mediate the activity of P53, a core component of the DNA damage response. miR-504 and miR-125b negatively regulate p53 expression. miR-34a, miR-29 and miR-122 can indirectly modify P53 activity by regulating the P53-related factors. miRNAs play important roles in different types of DNA repair. miR-21 down-regulates MMR proteins, MSH2 and MSH6, while miR-155 reduced the expression of the MMS genes MLH1, MSH2 and MSH6. miR-373 suppresses expression of RAD23B, a key component of the NER. miR-101 down-regulates the protein level of DNA-PKcs, an essential factor for NHEJ. miR-210, miR-373 and miR-182 down-regulate the expression of RAD51, RAD52 and BRCA1, respectively. RAD51, RAD52 and BRCA1 are all key components of HRR. With increased studies of miRNAs' roles in DNA damage and repair, more miRNAs will be discovered to involve in the DNA damage and repair pathways.

11. Acknowledgements

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12. References

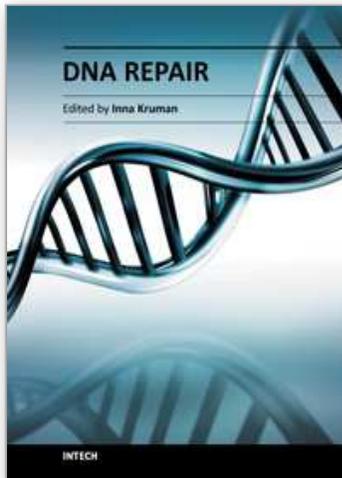
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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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