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Review

DNA damage response regulation by microRNAs as a therapeutic target in cancer

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ABSTRACT

The inability of cancer cells in taking care of DNA damages can lead to cancer development and/or progression. Due to the essential role of DNA repair in maintaining genomic stability, tightly controlled regulatory mechanism are required for these processes. Recent studies have shown a myriad of interactions among DNA damage response (DDR) components and miRNAs. While DDR modulates miRNA expression in transcriptional and post-transcriptional levels and affects miRNA degradation, miRNAs in turn, directly modulate the expression of multiple proteins in the DDR pathways, or indirectly fine-tune the expression of such proteins. A better understanding of DDR-miRNA interactions can facilitate the development of new anticancer agents targeting miRNAs involved in the DNA repair process. In this review, we provide a brief introduction about miRNA biogenesis and functions, DDR pathways, and recent findings about DDR-microRNA interactions. Finally, the therapeutic importance of miRNAs in modulation of DDR/DNA repair mechanisms will be discussed.

1. Introduction

Structural alternations in DNA severely affect its functions including replication and transcription. The inability of cancer cells to properly repair DNA is an underlying phenomenon in tumor development [1]. In response to various DNA lesions, a complex DNA damage response (DDR) mechanism is activated by a kinase-based sig-naling network [2]. Through this molecular mechanism, cells can detect such damages and transduce signals to recruit DNA repair elements to the site of damage, and finally repair damage by effectors, or as an alternative, activate cell cycle checkpoints or apoptosis, in the case of unrepairable damages [2]. Because of the pivotal role of DDR in maintaining genomic stability and integrity, precise regulating mechanisms are required for the repair process to respond to multiple types of DNA damage in various stages of cell cycle [3]. Given the undeniable involvement of DDR in the cancer development and progression, therapies targeting DDR offer new opportunities in cancer therapy [4]. Accumulating evidence has suggested that miRNAs are emerging as novel players in DDR and DNA repair pathways. Understanding the interplay between DDR/DNA repair and miRNAs will help to increase our knowledge about cancer progression and therefore, introduce new potential targets for successful treatment of cancer [5]. In this review, we provide a brief introduction about miRNA biogenesis and functions, DDR pathways, and recent findings about DDR-microRNA interactions. Finally, the therapeutic importance of miRNAs in modulation of DDR/DNA repair mechanisms will be discussed.

1.1. The DNA damage response and repair

Exposure to various endogenous and exogenous stressors including reactive oxygen species (ROS), ionizing radiations (IR) and ultraviolet (UV) light as well as radio- and chemo-therapeutic agents can bring about DNA damage in the form of mutations, base adducts, DNA mismatch, O6 alkylguanine formation, double strand breaks (DSBs), single strand breaks (SSBs), insertions, deletions and chromosomal rearrangements upon cell division or DNA replication [6]. DDR is conserved across all organisms for maintaining genomic integrity and consists of proteins working in different levels as sensors, mediators, transducers, and effectors in the repair process [7]. DDR is mediated by phosphorylation-driven signaling events, followed by a delayed response that induce cyclin dependent kinase (CDK) inhibitors at transcriptional levels for extending the time of cell cycle arrest. Early signaling pathways activated upon DDR include three phosphoinositide 3- kinase (PI3K)-like protein kinases, namely ATR, ATM, and DNA PKcs. These protein kinases are activated by different kinds of DNA damages and act by phosphorylation of different target proteins [5,6]. ATR kinases are induced upon UV damage and detection of SSD molecules, such as stalled replication forks and DSBs. ATR kinases principally phosphorylate Chk1 kinases, and control genomic stability and cell cycle checkpoints [8]. ATM kinases also phosphorylate Chk2, p53 and BRCA1, which are involved in regulating the induction of DNA repair and cell cycle checkpoints

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[9]. Cdc25 phosphatase family are one of the most important target proteins of both Chk1 and Chk2. Cdc25 phosphatase are involved in the activation of the CDKs [10]. DNA-PKcs are induced upon detection of DSBs, and subsequently phosphorylate themselves and other substrates. PKcsplay an important role in DSB repair through non-homologous end joining [1].

DNA damages can be repaired by three main mechanisms including base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR) [11,12]. NER is mainly required for repairing of transcription blocking and helix sorting lesions such as pyrimidine dimers and intrastrand crosslinks [13]. BER functions by removing chemical modifications of DNA or single nucleotides which have been altered by oxidation, alkylation, deamination, or methylation [14]. In turn, MMR machinery corrects improperly incorporated nucleotides during DNA synthesis or replication errors in DNA repeats [12]. Non-homologous end joining (NHEJ) or homologous recombination (HR) are also two major repair mechanisms for removing the most frequently toxic and difficult-to-repair DNA damage, DSBs. NHEJ is activated during pre-replicative (G0 and G1) phases of cell cycle and directly rejoins broken DNA ends. In spite of NHEJ, HR predominates in S phase of the cell cycle and requires a homologous DNA template sequence for error-free repair [15].

1.2. miRNAs: biogenesis and function

Since miRNAs have broad biological and functional implications, they have received the major attention among other classes of non-coding RNAs. Classified as a conserved category of short and single-stranded RNA molecules with an average size of 22 nucleotides, miRNAs fine-tune gene expression through their interactions in the DNA, RNA and protein levels [16,17]. Two distinct biosynthesis pathways have been envisioned for small ncRNAs, which are further divided into multiple steps [18]. In the first step of canonical or Drosha/Dicer-dependent biosynthesis pathway, RNA polymerase II transcribes primary miRNA (pri-miRNA) from two target genomic loci: miRNA genes or the introns of protein-coding mRNAs [19]. The resulting pri-miRNAs, which fold into secondary structures comprised of base-paired stem loops, can subsequently be polyadenylated and regulated by transcription factors. In the second step, in the nucleus, the pri-miRNAs are cleaved into about 70-nucleotide premature-miRNAs (the so-called pre-miRNAs) containing hairpin structures by Drosha/DGCR8 complex, a RNase III type endonuclease microprocess (Fig. 1) [20].

The next step is to traverse the pre-miRNAs into cytoplasm across the nuclear membrane by Exportin-5 via a Ran-GTP-mediated mechanism. Once in the cytoplasm, the pre-miRNAs are cleaved into RNA duplexes of roughly 22 nucleotides by a complex of Dicer (a second RNase III-type enzyme) and TAR RNA-binding protein 2. The RNA duplexes bind to a 182 kDa protein constituting glycine-tryptophan repeat and argonaute proteins, AGO1-4, resulting in the formation of the miRNA-induced silencing complex (RISC) [21,22]. In the next step, the mature guide strand (20–22 nucleotides in length) remains in association with RISC. This strand is also referred to as miRNA-5p [23]. The other anti-sense strand, known as passenger miRNA (the so-called miRNA-3p, and is a complementary star-form miRNA, miRNA*) is released from RISC. It was initially believed that the antisense strand is degraded in the cytoplasm; however, a number of recent studies have shown that some might have biological importance [24].

Subsequently, the mature miRNA exerts its biological function(s) via aligning the RISC to complementary sequences in the 3′UTR of target mRNA [25,26]. The resulting association, most commonly represses the translation of target proteins and recruits some protein complexes which contribute to deadenylation and degradation of the related target mRNA and finally, leading to down-regulation in gene expression [27]. Alternatively, in the non-canonical pathway, also termed as Drosha-independent/Dicer-dependent pathway, pre-miRNAs bypasses the Drosha/DGCR8 complex and are processed by AGO2 to yield the mature guide strand. The RNA products of this pathway are very short introns often referred to as mirtrons. After translocation to the cytoplasm, mirtrons act similarly to miRNA produced from the canonical pathway [28].

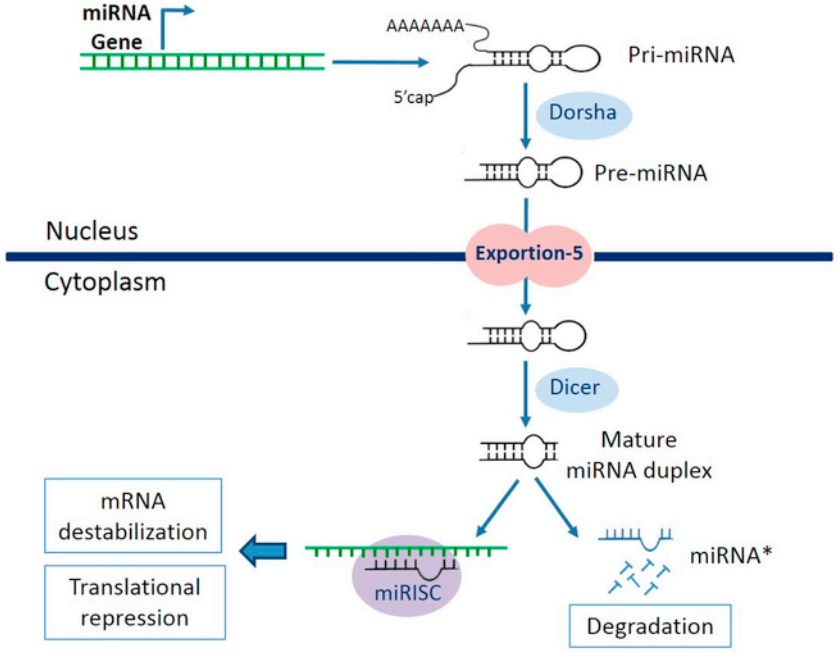

Fig. 1. An overview of mRNAs biogenesis.

miRNAs plays certain roles in the control of multiple processes, including differentiation, proliferation, development and apoptosis [29,30]. A number of mechanisms have been explained for miRNAs in controlling gene expression, which include but may not be limited to mRNA cleavage, cap-40S initiation blockage, inhibition of 60S ribosomal unit association and elongation, ribosome premature termination, co-translational protein degradation and decomposition in P-bodies, as well as mRNA destabilization and gene silencing [31,32].

mRNA cleavage or translational repression are the two main post-transcriptional mechanisms by which the miRNAs-RISC complex can reduce gene expression. If the miRNA in combination with cytoplasmic RISC has adequate complementarity to the mRNA (usually to 3′ UTR), it will determine the cleavage process [33–35]. On the other hand, in case the mRNA is not complementary to be degraded mRNA, but does have an appropriate constellation of miRNA complementary sites, it will inhibit productive translation [36]. Moreover, after this process, the miRNA remains intact and can therefore assist in the recognition and degradation of other targets. Another possible mechanism is that a recently synthesized polypeptide is specifically deconstructed after translation [37,38]. Finally, although a large number of studies have been dedicated to miRNA mode of action, further biochemical and molecular investigation will be required to describe miRNA-mediate gene regulation.

2. miRNAs in DNA damage response

2.1. DDR modulates miRNAs expression in transcription level

In transcription level, DNA damage can directly regulate miRNA expression by numerous transcription factors such as TP53, TP63, E2F, NF-κB, c-jun, and MYC, because the promoter characteristics of many miRNA are similar to those of normal protein-coding genes [39,40]. It is quite well known that regulation of miRNAs expression by transcription factors is mediated by two mechanisms; regulation by directly binding to miRNA promoters, and modification of the expression of miRNA processing machinery components [9]. The tumor suppressor p53 is a transcription factor induced in DNA damage, known to regulate the expression of a subset of miRNAs in transcription level [41]. To identify the contribution of miRNAs in TP53-mediated transcriptional pathways, miRNA expression profiling of wild-type and TP53-deficient cells as well as genome-wide miRNA screening for TP53-dependent regulation upon DNA damage have been performed [40]. The miR-34 family was the first identified link between transactivation of miRNAs by p53. The expression of this family is induced by p53 following DNA damage and oncogenic stress. The main mechanism behind the p53-mediated transcriptional activation of miR-34 family is the direct binding of p53 to their promoters. On the other hand, miRNA-34 family members have been reported to inhibit the transcription of multiple genes regulating cell proliferation, cell survival, and cell cycle progression, including CCND1 CCNE2, BCL2, CDK4, MYC, CDK6, and SIRT1 [40]. In other words, ectopic expression of miR-34 family results in cell cycle arrest at G1 and decrease in the expression of a group of genes promoting cell cycle progression, which suggest their tumor suppressive potentials [40]. Transactivation of miR-34a was shown to inhibit cell proliferation through the induction p53-mediated apoptosis, cell cycle arrest or senescence [40]. As another member of the miR-34 family, MiR-34c is transcriptionally induced by p53 upon DNA damage [42]. However, in the absence of p53, miR-34c induction is mediated by an alternative pathway that probably involved signaling through p38 MAPK to MK2 [42].

MiR-192, miR-194, and miR-215 cluster are other examples of miRNAs which are upregulated transcriptionally by p53 upon treatment with genotoxic agents [40]. The genomic region surrounding the miRNA-194 and miRNA-215 cluster contains a putative TP53-binding element, indicating that these miRNAs are transcriptionally activated by p53 [40]. Ectopic expression of miR-192/215 leads to cell-cycle arrest by targeting several transcripts that modulate G1/S and G2/M checkpoints [43]. In addition, miRNA-192 has been shown to enhance the level of P21 in TP53+/+ colorectal carcinoma cell line, but not in TP53-/- cells, suggesting the existence of a positive feedback loop for the modulation of p53 activity [43]. Moreover, downregulation of miRNA-192 and miRNA-215 was reported in many colon cancer samples, indicating tumor suppressor potential of miRNAs [43]. In contrast to the above mentioned miRNAs, which are upregulated by p53 upon DNA damage, miR-17-92 cluster is repressed by p53 under hypoxic conditions, subsequently resulting in sensitization to hypoxia-induced apoptosis. The p53-mediated transcriptional suppression of miR-17-92 works by preventing the TATA binding protein (TBP) from binding to a TATA box that overlaps with the p53-binding site within the miRNA-17-92 promoter [44]. More importantly, the expression of pri-miR-17-92 is inversely related to p53 status in colorectal cancer, suggesting the tumor-promoting role of this miRNA in cancers.

p53 also transcriptionally activates miR-29, miR-145, miR-107, miR-15a/16 and miR-605, and suppresses the expression of miR-520g [45–50]. In addition to p53, E2F and c-Myc are two other transcription factors that have important regulatory function in DNA damage-induced cell cycle checkpoints and activate the expression of several miRNAs. Both transcription factors induce the transcription of miR-17-92 cluster that, in turn, suppresses E2F expression, generating an auto-regulatory feedback loop [51]. MiR-12-92 is yet another example, the expression of which is regulated by E2F and c-Myc [52,53]. miR-203 is regulated by E2F1 [54]. miR-203 expression was elevated upon activation of ectopic E2F1. Moreover, it was demonstrated that E2F1 transactivates miR-203 through direct binding to its gene promoter [54]. c-Myc alone enhances the expression of miR-20a, miR-221, and miR-222 in transcription level [55].

Moreover, TAp63, an important transcript of the p63 gene, has a substantial role in suppression of tumorigenesis and metastasis. Similar to p53, TAp63 is activated by DNA damage and other cellular stresses. It has been shown that the upregulation of Dicer and miR-130b significantly affected the metastatic potential of TAp63-deficient cells [56]. Further studies demonstrated that activation of miR-130b and Dicer transcription by TAp63 is mediated by direct binding of TAp63 to their promoter region.

NF-kB and c-jun also induce gene transcription of miR-221 and miR-222 [57,58]. Additionally, NF-kB alone regulates miR-21 expression in the transcription level [59]. Moreover, the transcription factor STAT3 −which is dependent on NF-κB-mediated IL-6 induction for activation, upregulates miR-181a after genotoxic treatments in breast cancer cell line [60]. In line with the above, high miR-181a levels are linked to poor survival and prognosis after treatment in breast cancer patients. Interestingly, activated STAT3 has been shown to directly bind to MIR181A1 promoter to drive transcription and to also facilitate the recruitment of MSK1 to the same region. MSK1 subsequently phosphorylating histone H3, this promoting a local active chromatin state.

2.2. DDR modulates miRNAs processing and maturation post-transcriptionally

Not only DDR affects miRNA gene transcription, it also modulates the post-transcriptional processing of miRNAs, which is achieved by regulating the essential steps in the miRNA processing and maturation [61]. The underlying evidence for this suggestion is the increase in the levels of some pre-miRNAs and mature miRNAs without alternation in the levels of their primary transcripts under DNA damage stress.

Similar to its role in transcriptional control of miRNA expression, p53 also plays an active role in the post-transcriptional regulation upon DDR. This is manifested by the fact that the regulation of miRNA maturation by DDR is p53 dependent. Upregulation of some miRNAs such as miR-16-1, miR-143 and miR-145, has been shown to be post-transcriptionally induced in a p53- and p68/p72-dependent manner upon genotoxic stress [62,63]. DEAD box RNA helicases p68 (DDX5) and p72 (DDX17) act as subunits of the Drosha complex and are essential for recognition and processing of a group of primary miRNAs. p53 interaction with the Drosha processing complex is facilitated by binding to p68/p72 and, in turn, this interaction mediates the processing of pri-miRNAs to their pre-miRNAs. However, transcriptionally inactive p53 mutants disrupt the assembly between the p68 and Drosha complex, resulting in inhibition of miRNA processing activity. More importantly, p53 mutations are frequently observed in malignancies and most of them are located in a domain that is required for both miRNA processing function and transcriptional activity [64]. Thus, loss of p53 functions in miRNA processing might be involved in the cancer progression. Since the promoter regions of the main components of the miRNA processing machinery such as Dicer and P2P-R contain p53-responsive elements, it has been suggested that these components are targeted by p53 and its homologs p63 and p73. Previous genome analyses have shown that the guardians of genome, p53, p63, and p73 can regulate the miRNA processing components, either in a positive or negative manner. These miRNAs include let-7, miRNA-16, miRNA-21, miR-26, miR-29, miR-34, miRNA-107, miRNA-134, miRNA-143, miR-145, miR-146a, miRNA-449a, miRNA- 200c and miRNA-503 [65,66]. A recent study showed that p53 directly binds to AGO2, leading to an induction or reduction in loading of a subset of miRNAs – including lethal 7 (let-7) miRNA family members- onto AGO2, in response to DNA damage [67]. Mutant p53 suppresses miRNA production at post transcriptional level by interfering with the microprocessor complex. Garibaldi et al. [68]. have reported that endogenous mutant p53 binds to microprocessor complex, sequestering RNA helicases p72/82 and interfering with Drosha-pri-miRNAs association. In agreement with this finding, p72 overexpression enhances mature miRNAs levels. Moreover, mutant p53-dependent miRNAs such as miR-517a, −519a, −218, −105 possess oncosuppressive roles, as shown by functional experiments [68].

Cumulative studies have reported that as many as one fourth of all miRNAs are significantly induced following DDR in an ATM-dependent manner. A group of these miRNAs are associated with KSRP (KH-type splicing regulatory protein), which is an AU-rich single-strand RNA-binding protein that regulates RNA decay, and at the same time, is a key component of both the Drosha and Dicer complexes [69]. KSRP interacts with the terminal loop of pre-miRNA precursors with high affinity. As such, KSRP positively regulates the maturation of miRNA precursors, such as pri-miRNA-1, pri-miRNA-15, pri-miRNA- 21 and pri-let-7 [70]. Upon ATM-dependent phosphorylation, KSRP significantly contributes to the recruitment of pri-miRNAs to the Drosha complex and boosts their processing. These results strongly indicate that ATM is a key regulator of KSRP in miRNA processing, and that the biogenesis of a subset of miRNAs is promoted via KSRP. Finally, ATM also activates DNp63a, which upregulates Dicer to promote miRNA maturation after treatment with the DNA damage-inducing agents [69].

In addition to initiating PI3K- like protein kinases such as ATM, DDR also activates many downstream kinases which might regulate miRNA processing. The mitogen-activated protein kinase (MAPK) Erk- dependent phosphorylation of TRBP, stabilizes the Dicer-TRBP complex and enhances mature miRNA production [71]. A group of miRNAs including miR-17, miR-20a and miR-92a (with growth promoting effects) are upregulated by phosphorylation of TRBP. However, opposite effects have been observed on let-7 family (with tumor suppressor effects). These finding suggest that phosphorylation of TRBP results in a mitogenic miRNA expression profile, including upregulation of pro-growth miRNAs and downregulation of anti-growth miRNAs [72]. c-Myc is also involved in the promotion of miRNA processing by upregulating the Drosha expression level [73].

MMR pathways are yet among the other alternative mechanisms which mediate the miRNA processing and maturation in response to DNA damages. The MLH1-PMS2 heterodimer was reported to positively regulate the processing of numerous miRNAs such as miRNA-422a, by interaction with pri-miRNAs, binding to the Drosha/Pasha complex, and activating the Drosha/Pasha-mediated processing of pri-miRNAs to pre-miRNAs [74]. Additionally, the tumor suppressor BRCA which is also an important part of the DSBs response, has been recently shown to increase the expression of both precursor and mature forms of let-7a-1, miRNA-16-1, miRNA-34a and miRNA- 145 by direct interaction with p68 RNA helicase and Drosha. Drosha has also been shown to interact with DGCR8 to form a complex called microprocessor, which plays a key role in modulating the homeostasis of miRNA expression [75]. A previous study reported that oxidative stress-responsive heme oxygenase-1 modulates miRNA expression by downregulating DGCR8. Moreover, DDR stimulates the processing of miR-34 family by tyrosine kinase ABL-dependent tyrosine phosphorylation of DGCR8 [76].

2.3. DDR regulates miRNA degradation

In addition to the major function of DDR in the regulation of transcriptional and post transcriptional expression of miRNAs, a recent study has suggested that one of the main causes of miRNA downregulation is increase in the degradation of miRNAs following DNA damage. Two exoribonuclease are responsible for the degradation of the single-stranded miRNA, the 50′–30′ exoribonuclease XRN2 or 30′–50′ exoribonuclease human polynucleotide phosphorylase [77,78]. Previous studies have reported that pre-miRNA degradation can be facilitated by binding to protein components such as MCPIP1. A recent study showed that the nucleotidyl transferase PAP associated domain containing 5 (PAPD5) and the poly (A)- specific ribonuclease PARN can work in concert to mediate 30′ adenylation and subsequent degradation of miR-21 [79]. However, further research is required to elucidate the detailed mechanisms by which DNA damage can induce miRNA turnover and degradation.

3. Role of miRNAs in regulation of DDR

Since most of the miRNA-related processes such as expression, transcription maturation and degradation are regulated by DDR, it is not surprising that bidirectional regulatory pathways exists between miRNAs and DDR. One of the first studies implicating miRNAs in

the regulation of DNA damage is that the knockdown of the primarily components of miRNA-processing systems such as Ago2 and Dicer, causes a significant reduction in altered checkpoint response and cell survival after exposure to DNA damaging agents such as UV and cisplatin [80]. It was well-known that miRNAs are involved in the control of gene expression in a post-transcriptional manner. For that purpose, miRNAs bind to complementary sequences in target mRNAs, and degrade or inhibit the translation of targets. It is becoming more and more elaborate that sensors, transducers and effectors in DDR are directly and indirectly regulated by miRNAs [41].

miRNAs directly regulate DDR by modulating the expression of multiple components of the DDR pathway. Alternatively, they indirectly fine-tune the expression of key regulatory proteins such as p53 by interacting with other signaling pathways [81]. Table 1 provides a comprehensive up-to-date list of miRNAs which regulate the different components of DDR.

In this line, it has been reported that almost all principal components of the DDR signaling pathways contain conserved miRNA target sites. Initial sensor proteins for the DDR including H2AX, MSH2 and MLH1 are subject to regulation by different miRNAs. Accumulating findings indicate that miRNAs can also act as signal transducers by directly targeting protein kinases involved in DDR. For example, following DSB DNA damage, the transducer ATM, is activated by autophosphorylation on serine residues and this activity is regulated by the WIP1 phosphatase in DDR. In response to DDR transducers, a wide array of proteins known as DDR effectors work together in a coordinated manner to determine cell fate after DNA damage including those proteins functioning in cell cycle arrest, DNA repair, and apoptosis [82]. miRNAs can also directly target DDR effectors. As shown in Table 1, miRNAs can control cell cycle progression after DNA damage by targeting BRCA1, BRCA2, RAD23B, RAD51, RAD52, RAD18, RPA1, RBSP3, Ku70, CtIP, REV1, REV3L, FANCG, MDC1, and PRKDC.

Finally, miRNAs also act by indirectly fine-tuning the expression of essential components of the DNA repair pathways, such as p53, p53, p21, p27, CHK1 and other effectors which have major functions in the regulation of cell cycle checkpoints and apoptosis. This fine-tuning takes place by down-regulation of upstream regulators of mentioned proteins (Table 2).

4. miRNAs as therapeutic target in cancer: DNA damaging agents

Compounds targeting DDR and DNA repair machinery are very promising for cancer therapy and overcoming cancer chemoresistance. Particularly, the undeniable interaction of miRNAs and DDR can provide a promising target for increasing the efficacy of conventional cancer therapy with DNA damaging agents [39]. This is brought about by the active role of miRNAs in modulating DDR by targeting DDR components to subsequently regulate cellular response to DNA damaging agents. Therefore, miRNAs may improve the outcome of chemotherapy, particularly through the regulation of the DDR. A long list of miRNAs have so far been implicated in affecting chemotherapy sensitivity, either by suppressing DNA repair or enhancing DNA damage tolerance in different cancer types (Table 3).

Furthermore, miR-24 or miR-138 promote cellular sensitivity to IR through inhibition of H2AX expression [83,84]. Several other examples of IR-responsive miRNAs include miR-521, miR-127, let-7g, miR-125a, miR-189, and microRNA-1323 which regulate radio-sensitivity by targeting DDR genes [99,162,163].

As mentioned earlier, a number of miRNAs can target various essential genes involved in DDR; therefore, modulating endogenous miRNA expression may be a promising strategy to reverse chemo-resistance in cancer therapy. Ectopic expression of mature miRNAs or their precursors can result in miRNA upregulation. On the other hand, using anti-miR oligonucleotides or miRNA sponges, which ex-

Table 1
miRNAs involved in the regulation of DDR.

DDR gene	Function in DDR	miRNA	Ref.
DDR sensors			
H2AX	Histone H2A variant, Following DNA damage, extensively phosphorylated by ATM and ATR	miR-24, miR-138, miR-542-2p	[83–85]
MSH2	dimerizes with MSH6 to form the MutSα complex, which is involved in base mismatch repair and short insertion/deletion loops	miR-155, miR-21	[86,87]
MLH1	One component of a system of seven DNA mismatch repair (MMR) proteins	miR-155	[86]
DDR transducers			
ATM	Is activated by autophosphorylation on serine residues upon DNA damage and phosphorylates several target proteins	miR-421, −18a, −26a, −101, −181, −100, −27a, −223, −181a, 185, −214	[11,88–98]
DNA-PK	Is induced upon detection of DSBs, phosphorylates itself and other substrates	miR-101, miR-1323	[90,99]
DDR effectors			
BRCA1	Is part of a complex that repairs DSBs in DNA and interacts with the DNA mismatch repair protein MSH2	miR-182, −NA146a, −146-5p, −1, −99, −146a, −9	[100–104]
BRCA2	binds to the single strand DNA and directly interacts with the recombinase RAD51	miR-1245, −210, −373	[105,106]
RAD23B	Is involved in nucleotide excision repair (NER)	mi*R*-373	[107]
RAD51	Plays a major role in homologous recombination of DNA during double strand break repair	miR- 96, −99a, −100	[102,108]
RAD52	Is important for DNA double-strand break repair and homologous recombination, interacts with RAD51	miR-210	[107]
RAD18	Is a ubiquitin-conjugating enzyme required for post-replication repair of damaged DNA.	miR-145	[109]
RPA1	Binds and stabilizes single-stranded DNA intermediates	CU1276	[110]
RBSP3	A gene family of small C-terminal domain phosphatases that may control the RNA polymerase II transcription machinery	miR-100	[111]
Ku70	Binds to DNA double-strand break ends and is required for the non-homologous end joining (NHEJ) pathway of DNA repair	miR-124	[112]
CtIP	modulates the functions ascribed to BRCA1 in transcriptional regulation and DNA repair	mi*R*-335	[113]
REV1	Functions as a scaffold that recruits DNA polymerases involved in translesion synthesis (TLS) of damaged DNA	miR-96	[108]
REV3L	Interacts with Rev7 to form Pol ζ, a B family polymerase.	miR-25, −32	[114]
FANCG	DNA repair protein that may operate in a post-replication repair or a cell cycle checkpoint function. May be implicated in interstrand DNA cross-link repair and in the maintenance of normal chromosome stability	miR-23a	[115]
MDC1	Is a regulator of the Intra-S phase and the G2/M cell cycle checkpoints and recruits repair proteins to the site of DNA damage	miR-22	[116]

Table 2
miRNAs involved in the regulation of cell cycle checkpoints and apoptosis.

DDR gene	Function in DDR	miRNA	Ref.
P53	The guardian of the genome, because of its role in conserving stability by preventing genome mutation.	miR-125a, −125b, −504, −25, −30d, −33, −380-5p, −1285, −375, −605, −15b/16-2, −155, −34a	[117–126]
CDC25A	Is required for progression from G1 to the S phase of the cell cycle, but also plays roles in later cell cycle events	miR-16, −21, −322, −424, −503, −449a/b	[80,127–129]
WEE1	Is a key regulator of cell cycle progression. It influences cell size by inhibiting the entry into mitosis, through inhibiting Cdk1.	miR-128a, −155, −516-3p, −195, −15	[61,130–133]
Wip1	Involved in cell cycle checkpoint	miR-16	[134]
CHK-1	Chk1 is a central component of genome surveillance pathways and is a key regulator of cell cycle and cell survival	Let-7, miR-15, −424	[135] [131,136]
P21	Is a potent cyclin-dependent kinase inhibitor	miR-17, −106a/b	[137,138]
c-Myc	Is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation	miR-145, −130a, Let-7	[139–141]
P27	Prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controls the cell cycle progression at G1	miR-221, −222	[142]
E2F	promotes and help carry out the cell cycle	miR-17–92, −20a, −34a, Let-7b, miR-449a, miR −203	[54,143,144]
PLK1	is an early trigger for G2/M transition	miR-100	[145]
Cyclin D	Is required for progression through the G1 phase of the cell cycle	mi*R*-34c	[146]
Cyclin D3	is required for cell cycle G1/S transition	miR-138	[147]
CDK2	promotes interphase nuclear pore complex formation	mi*R*-302, −372, −885-5p,	[148–150]
HOXC9	Involved in cell cycle checkpoint	miR-193a-3p	[151]
CDK4/6	Is important for the G1 phase progression and G1/S transition of the cell cycle	miR-506	[152]
ChK2	Following DSBs prevent entry of cells into mitosis through inhibition of the CDC25 phosphatases	miR-191	[153]
PUMA, Bcl2, BAX	Involved in apoptosis	mi*R*-365, −1915, −1271, −511	[154–157]
SIRT4	Involved in apoptosis	miR-15b, −34a	[126,158]
Birk2 and Bak1	Involved in apoptosis	miR-29c	[159]
ING5	Interacts with TP53, inhibits cell growth, and induces apoptosis	miR-193a-3p	[160]
PEBP4	Involved in apoptosis	miR-15b	[161]

press a transgene-containing multiple tandem binding sites for endogenous miRNA, can suppress the expression of endogenous miRNAs. Protection of particular miRNAs targets can be achieved by miRNA-masking antisense oligonucleotides [164,165]. Multiple novel technologies have been developed for systemic delivery of miRNA mimics or anti-miRs. They consist of adenoviral or lentiviral-based delivery, nanoparticle-based delivery, and application of chemically modified oligonucleotides [166–170]. Accumulating studies provide solid evidence for the application of miRNAs as therapeutic tools or agents in cancer treatment, but the side effects of miRNA therapy must be also considered. This is important for several reasons. First, each miRNA may target multiple transcripts and might have unintended effects. Second, the high expression levels of miRNA mimics may interfere with the endogenous miRNAs or siRNAs by binding and saturating the RISC complex. As a result, the safety of miRNA formulations needs to be extensively investigated in disease models.

5. Conclusions and perspectives

We have reviewed the current knowledge about the interactions of miRNAs with the DDR system, discussing that DDR can affect miRNA biogenesis in the expression, transcription, maturation or degradation levels. On the other hand, different miRNAs have been shown to directly or indirectly change the expression of different components in DDR. As such, considering the importance of DNA damage repair in cancer, miRNAs are emerging as important targets which can be manipulated by drugs to eradicate cancer by damaging cancer cell DNA. Further understanding of the molecular cross-talks between DDR and miRNAs will provide an invaluable input to the drug discovery campaigns around the world, hopefully in the coming years.

Conflicts of interest

None.

Table 3
MicroRNAs and their DDR targets involved in response to chemotherapeutic agents.

miRNA	Targets	Cancer	Chemotherapeutic agents	Effect	Ref.
miRNA-138	ERCC1, H2AX	NSCLC cells, osteosarcoma cells	Platinum agents, camptothecin	Chemo-sensitivity	[83,171]
miRNA-182	BRCA1, CHEK2	Embryonic kidney cells, breast cancer cells cervix adenocarcinoma cells	PARP inhibitors	Chemo-sensitivity	[11]
miRNA-181a/b	BRCA1, ATM, BCL2	Breast cancer cells, CLL	PARP inhibitors, platinum agents, fludarabine	Chemo-sensitivity	[172,173]
miRNA-181a	BAX	Breast cancer cells	genotoxic	Chemo-resistance	[60]
miRNA-155	WEE1, RAD51	Epidermoid carcinoma cells, triple-negative breast cancer, CLL	Platinum agents, taxanes, anthracyclines	Chemo-resistance Chemo-sensitivity	[130,174–176]
miRNA-15	CHEK1, WEE1	Epidermoid carcinoma cells	Platinum agents	Chemo-resistance	[130]
miRNA-96	RAD51, REV1	Breast cancer cells, osteosarcoma cells, ovarian cancer cells and tissue, cervix adenocarcinoma cells	Platinum agents, PARP inhibitors	Chemo-sensitivity	[108]
miRNA-107	RAD51	Breast cancer cells	PARP inhibitors	Chemo-sensitivity	[177]
miRNA-221/222	RAD51	Breast cancer cells, CLL	PARP inhibitors, fludarabine	Chemo-sensitivity Chemo-resistance	[177,178]
miRNA-25/32	REV3L	Burkitt's lymphoma cell, lung cancer cells	Etoposide, camptothecin, PARP inhibitors	Chemo-sensitivity	[179]
miRNA-125b	TP53, BAK1	Breast cancer cells	Taxanes	Chemo-resistance	[180]
miRNA-34a	SIRT1, BCL2	Prostate cancer cells, breast cancer cells	Taxanes	Chemo-resistance	[181,182]
miRNA-21	MSH2, MSH6	Colon cancer cells, glioblastoma cells, breast cancer cells, lung adenocarcinoma cells, pancreatic adenocarcinoma, CLL	5-FU, anthracyclines, taxanes, platinum agents, gemcitabine, fludarabine, cyclophosphamide, rituximab	Chemo-sensitivity Chemo-resistance	[87,183–187]
miRNA-451	BRCA1	Breast cancer cells	Anthracyclines	Chemo-resistance	[188]
miRNA-146	BRCA1	Breast cancer cells	Platinum agents	Chemo-resistance	[178]
miRNA-203	ATM	Colorectal cancer cell lines and tissues	Platinum agents	Chemo-resistance	[189]
miRNA-29b	Mcl-1	Ovarian cancer	Paclitaxel	Chemo-sensitivity	[190]
miRNA-27a	RKIP	Lung adenocarcinoma cells	Cisplatin	chemoressitance	[191]
miR-145	RAD18	colorectal cancer	5-FU	Chemo-sensitivity	[109]
miR-193a-3p	HOXC9 PSEN1	Bladder cancer	Pirarubicin Adriamycin Epirubicin Hydrochloride, Cisplatin	Chemo-resistance Chemo-sensitivity	[151,192]
mi*R*-320	FOXM1	Human colon cancer cells	5-FU and Oxaliplatin	Chemo-sensitivity	[193]
mi*R*-31	KCNMA1	Ovarian cancer	Cisplatin	Chemo-resistance	[194]

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