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Noncoding RNAs in DNA Repair and Genome Integrity

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Abstract

Significance: The well-studied sequences in the human genome are those of protein-coding genes, which account for only 1%–2% of the total genome. However, with the advent of high-throughput transcriptome sequencing technology, we now know that about 90% of our genome is extensively transcribed and that the vast majority of them are transcribed into noncoding RNAs (ncRNAs). It is of great interest and importance to decipher the functions of these ncRNAs in humans. ***Recent Advances:*** In the last decade, it has become apparent that ncRNAs play a crucial role in regulating gene expression in normal development, in stress responses to internal and environmental stimuli, and in human diseases. ***Critical Issues:*** In addition to those constitutively expressed structural RNA, such as ribosomal and transfer RNAs, regulatory ncRNAs can be classified as microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), and long noncoding RNAs (lncRNAs). However, little is known about the biological features and functional roles of these ncRNAs in DNA repair and genome instability, although a number of miRNAs and lncRNAs are regulated in the DNA damage response. ***Future Directions:*** A major goal of modern biology is to identify and characterize the full profile of ncRNAs with regard to normal physiological functions and roles in human disorders. Clinically relevant ncRNAs will also be evaluated and targeted in therapeutic applications. *Antioxid. Redox Signal.* 20, 655–677.

Introduction

In all organisms, faithful propagation of genetic material and transmission into daughter cells is essential to avoid propagation of mutations that could lead to genomic instability and aberrant cell activities (4). A wide variety of DNA lesions may occur by extrinsic insults, such as ultraviolet (UV) radiation, ionizing radiation (IR), and numerous genotoxic chemicals. Meanwhile, the by-products of cellular metabolism, such as reactive oxygen species (ROS), also threaten the integrity of genomic DNA. In order to maintain genomic stability, eukaryotes have evolved a highly coordinated cellular system to recognize and repair damaged DNA. Collectively, this system is named DNA damage response (DDR), encompassing DNA damage signal transduction, DNA repair, cell-cycle checkpoints, and apoptosis. Of the many forms of DNA damage, double-stranded DNA break (DSB) is one of the most lethal to the cell if left unrepaired. The DSB is repaired by nonhomologous end joining (NHEJ) in all phases of the cell cycle and homologous recombination (HR) when a template is available in the S or G2 phase. Other types of DNA damage are processed through nucleotide excision repair (NER), base excision repair (BER), and mismatch repair (MMR) (39).

The DDR is composed of a set of tightly regulated steps: initial detection of DNA damage, recruitment of repair factors to damage sites, and the final repair of DNA lesions. Therefore, all the components in the DDR are functionally categorized into DNA damage sensors, signal transducers, and effectors. In addition to previously identified protein-coding genes, noncoding RNAs (ncRNAs) have been shown to join the DDR. Accumulating evidence suggests that various types of ncRNAs play an important role in DNA repair and safeguarding genome integrity (29, 115, 212, 225). The ncRNAs are highly abundant and functionally important although they are not translated into proteins (5, 43). Except for those housekeeping ribosomal and transfer RNAs (rRNAs and tRNAs), ncRNAs are divided into two major groups based on their size: small ncRNAs and long noncoding RNAs.

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MicroRNAs

The most well-studied group of ncRNAs are microRNAs (miRNAs), which are ~19- to 24-nucleotide (nt) small ncRNAs with post-transcriptional regulatory functions that control the translation of mRNA into protein (10). First identified in *Caenorhabditis elegans*, miRNAs are universally expressed in nearly all metazoans, plants, and even DNA viruses (70). To date, almost 2000 mature miRNAs have been annotated in the human genome that are involved in many cellular processes such as proliferation, differentiation, stress responses, apoptosis, and development (10). Classically, the biogenesis of miRNAs is a tightly regulated multistep process. In the nucleus, primary miRNAs (pri-miRNAs), which bear one or more imperfect stem-loop hairpin-like structures, are first processed by the RNaseIII enzyme Drosha and its cofactor DGCR8 (DiGeorge Syndrome Critical Region Gene 8). The processed products, which are called precursor miRNAs (pre-miRNAs), have a hairpin structure of ~70-nt and are exported to the cytoplasm by the Ran GTPase Exportin-5. In the cytoplasm, the stem loops of pre-miRNAs are cleaved off by another RNaseIII, Dicer, and its cofactor, Tar RNA-binding protein (TRBP), resulting in the production of mature ~22-nt RNA duplexes. Most often, one strand of the duplex is preferentially incorporated into a member of the Argonaute protein subfamily to form the RNA-induced silencing complex (RISC). The other strand, known as the miRNA star or passenger strand, is often degraded. RISCs loaded with mature miRNAs are subsequently guided by miRNAs to pair with target transcripts at their 3′ untranslated region (3′-UTR) and induce mRNA degradation or inhibition of translation (10). Since a single miRNA may potentially target more than 300 different mRNA transcripts, almost 60% of human protein-coding genes are predicted to be targets of miRNAs. In addition, several types of miRNAs may regulate the same pathway cooperatively by targeting the same or different targets.

Long noncoding RNAs

The other most common ncRNAs are mRNA-like long noncoding RNAs (lncRNAs), which range in length from 200 nt to ~100 kilobases and lack significant open reading frames. Similar to their protein-coding counterpart, most lncRNAs are transcribed by RNA polymerase II (RNA pol II) and polyadenylated, and their expression is tightly associated with cell and tissue specificity (51, 64). However, compared with protein-coding genes or miRNAs, lncRNAs are usually expressed at lower levels and poorly conserved between species. With the advent of RNA sequencing and computational methods for transcriptome reconstruction, thousands of lncRNAs have been identified in various cell types and tissues in mammals (22). Since the number of characterized long noncoding transcripts has increased, so has the uncertainty regarding their putative functions. How do lncRNAs exert their functions? At present, only a handful of lncRNAs have been well characterized with distinctive biological roles, such as XIST and TSIX, in X-chromosome inactivation (20, 119), H19 and AIR in genomic imprinting (18, 189), NRON in cytoplasmic-to-nuclear trafficking of NFAT transcriptional factor (224), and HOTAIR and HOTTIP in trans-acting regulation of the *HOX* gene family (173, 216). Although only a minority have been studied in detail, it is now becoming evident that lncRNAs provide important transcriptional outputs of the genome.

LncRNAs include a heterogeneous group of noncoding transcripts. These RNAs can be classified according to their proximity to protein-coding genes: sense, antisense, bidirectional, intronic, and intergenic (168). Antisense lncRNAs are transcribed from the opposite DNA strand of a protein-coding gene and overlap, in part, with sense mRNA. Both ends of protein-coding genes may be able to encode antisense transcripts. Antisense transcription is a widespread phenomenon of mammalian genomes. More than 70% of transcription units sequenced in the mouse genome are antisense transcripts, and a majority of them are lncRNAs (99). However, only a few antisense lncRNAs have been functionally validated. As an example, BACE1-AS is a conserved lncRNA that is implicated in Alzheimer's disease–associated pathophysiology. As an antisense transcript for β-secretase-1 (BACE1), a crucial enzyme in Alzheimer's disease, BACE-AS has been found to regulate the stability of BACE1 mRNA and, subsequently, BACE1 protein expression *in vitro* and *in vivo* (52).

More recently, another group of lncRNAs, termed large or long intergenic ncRNAs (lincRNAs), has been identified by searching the distinctive "K4–K36" chromatin signature, which is indicative of active transcription. These lincRNAs are exclusively intergenic and are marked by trimethylation of lysine 4 of histone H3 (H3K4me3) at the promoter region and trimethylation of lysine 36 of histone H3 (H3K36me3) along the transcribed region. By searching for K4–K36 domains that do not overlap with known protein-coding genes, the Rinn laboratory has revealed approximately 1600 regions in the mouse genome and approximately 2500 regions in the human genome that show higher evolutionary conservation across mammals in contrast to other lncRNAs (72, 103). The biological functions of most lincRNAs are poorly defined, although they are presumably involved in transcription regulation by physical association with different chromatin regulatory proteins. For instance, using loss-of-function studies, dozens of lincRNAs have been found to play key roles in the circuitry controlling embryonic stem cell state in trans. Knockdown of these lincRNAs causes either exit from the pluripotent state or up-regulation of lineage commitment programs, comparable to knockdown of well-known embryonic stem cell regulators, such as Oct4 and Nanog (73).

Targets of ncRNAs in the DDR and ROS Signaling Pathways

Genotoxic stress is a life-threatening event for humans, as it changes the content and organization of DNA. In addition to many types of exogenous DNA-damaging agents, another important determinant of genomic integrity and cellular response to DNA damage is the level of intracellular ROS, which is tightly regulated through the coordinated activities of cellular pro-oxidants and antioxidants. Intracellular ROS can act as a cellular toxicant or a signaling molecule, depending on its concentration and localization. Endogenous ROS produced by cellular metabolism account for the major oxidative lesions that induce DNA damage (149, 163). A mechanistic link between ROS and DDR pathways has not been clearly elucidated. A recent study demonstrated that ROS induction after treatment of cells with neocarzinostatin (NCS) is partly mediated by increasing histone H2AX, a

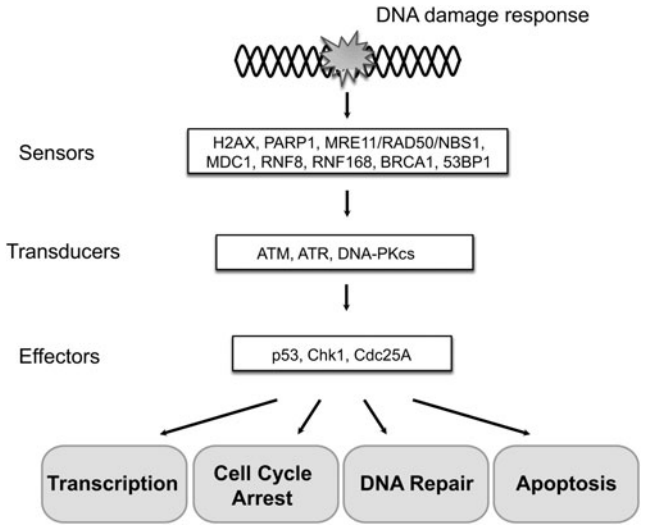

FIG. 1. The components of the canonical DNA damage response (DDR). The key proteins in the DDR pathway are summarized in the order of sensors, transducers, and effectors; while the effectors are involved in transcription activation, cell-cycle arrest, DNA repair, and apoptosis.

biomarker for the DDR (98). Therefore, ROS is not only a causative factor to generate DNA damage, but is also regulated by the DNA damage-signaling pathways.

The DDR is a complex signal transduction pathway that detects DNA damage signals and transduces those signals to execute proper cellular responses (39). The signals collected and transmitted by sensors, mediators, and transducers are ultimately used to make a cell fate determination: Either the cell cycle is arrested to allow repair of damaged DNA or, if the damage is beyond repair, programs are initiated that instruct the cell to undergo apoptosis (Fig. 1).

miRNA targets in the DDR

miRNAs modulate the initiation, maintenance, and activity of the DDR by targeting and modulating key genes in the pathway. These miRNAs are summarized in Table 1. The DDR is initiated at DNA damage sites by a number of sensors that recognize damaged DNA and recruit signaling proteins to the damage site. One of the most important sensors, H2AX, is extensively phosphorylated after DNA damage by two phosphatidylinositide 3-kinase-like kinases: ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR). Overexpression of miR-24, the first miRNA

Table 1. Regulatory miRNAs in the DNA Damage Response

Targets	*Function in the DDR*	*MiRNAs*	*Refs.*
ATM	Transducer	miR-18a, miR-100, miR-101, miR-181, miR-421	(86, 188, 221, 232, 242)
BAX	Apoptosis	miR-886-5p	(122)
Bcl-2	Apoptosis	miR-15a, miR-16-1, miR34a, miR-195	(15, 41, 81)
BRCA1	Mediator, DNA repair	miR-182, miR-146a, 146b-5p	(60, 150)
Cdc25A	Cell cycle checkpoint	miR-21, miR-424, miR-449a, miR-503, miR-449a/b	(26, 34, 46, 178, 217)
Cdc25B	Cell cycle checkpoint	miR-148a, miR-449a, miR-449b	(123)
Cdc25C	Cell cycle checkpoint	miR-129b	(117)
Cdc42	Cell cycle checkpoint	miR-29, miR-137, miR-185, miR-206	(36, 116, 124, 126, 127, 160)
CDK2	Cell cycle	miR-124a, miR-372, miR-376a, miR-885-5p	(1, 152, 200, 214)
CDK6	Cell cycle	miR-16, miR-22, miR-34, miR-107, miR-195, miR-124a, miR-29, miR-449a/b	(34, 53, 128, 166, 193, 228, 229)
Cyclin D	Cell cycle	miR-15, miR-16, miR-195	(16, 128, 229)
Cyclin E	Cell cycle	miR-16, miR-29c, miR-195, miR-424	(48, 154, 181, 213)
Cyclin G1	Cell cycle	miR-122	(68)
DNA-PK	DNA repair	miR-101	(232)
E2F	Transcription factor	miR-11, miR-15, miR-16, miR-17, miR-20a, miR-106b	(159, 202, 203)
H2AX	Sensor/mediator	miR-24, miR-136	(114, 220)
MDM2	Cell cycle checkpoint	miR-143, miR-145, miR-605	(227, 246)
MSH2	DNA mismatch repair	miR-21, miR-155	(205, 242)
p21	Cell cycle checkpoint	miR-17, miR-20a/b, miR-106a/b, miR-663, miR-93, miR-215, miR-192	(65, 84, 93, 239)
p27	Cell cycle	miR-221/222, miR-181	(54, 66)
p53	Cell cycle checkpoint, apoptosis	miR-125b, miR-504	(87, 117)
P57	Cell cycle	miR-221/222	(54)
p63	Transcription factor	miR-92, miR-302	(179)
PLK1	Cell cycle checkpoint	miR-100	(164)
PUMA	Apoptosis	miR-125b	(184)
RAD23B	DNA repair	miR-373	(45)
RAD52	DNA repair	miR-210, miR-373	(45)
Wee1	Cell cycle checkpoint	miR-195	(81, 172)
Wip1	Cell cycle checkpoint	miR-16	(251)

found to target H2AX, down-regulates the level of H2AX, resulting in higher sensitivity of cells to IR (114). ATM is responsible for the activation of a number of signaling pathways after DSBs, the most lethal DNA damage in the cell. It is estimated that ATM may phosphorylate as many as 700 proteins in human cells (139). Homeostatic regulation of ATM activity in the DDR is primarily mediated by the Wip1 phosphatase (135). Recently, several miRNAs, including miR-18a, miR-100, miR-101, miR-181, and miR-421, have been identified as novel regulators to control the protein level of ATM (86, 188, 221, 232, 242). BRCA1, a critical tumor suppressor, BRCA1, is also recruited to DNA damage lesions, where it facilitates DNA repair. The level of BRCA1 is regulated by miR-182, miR-146a, and 146b-5p (60, 150).

The tumor suppressor p53 has a central role in the activation of genes in multiple pathways, including cell-cycle regulation, tumor suppression, and apoptosis. miR-125b and miR-504 have been identified as negative regulators of p53 in several types of human cells (87, 117). Interestingly, miR-605 (227), and miR-143/miR-145 (246) are post-transcriptionally activated by p53 and, subsequently, target Mdm2, leading to rapid accumulation of p53. These findings reveal a miRNA/Mdm2/p53-positive feedback loop that ensures rapid activation of p53 after DNA damage (76).

miRNA targets in the ROS signaling pathways

ROS are chemically reactive molecules containing oxygen, including the superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), and nitric oxide (NO). ROS are constantly produced in the living cells and cause a significant portion of DNA damage. ROS not only are byproducts of cellular metabolic processes, but also are generated by specific plasma membrane oxidases in response to growth factors and cytokines and serve as secondary messengers in specific signaling pathways. Recently, miRNAs are found to target the central regulators of the ROS signaling pathway (Nrf2, Keap1, and TNFα) and the ROS scavenger (superoxide dismutase [SOD], catalase, and thioredoxin reductase [TXNRD]), representing a key role in the regulation of antioxidant response (Table 2).

Nuclear factor-erythroid 2-related factor 2 (Nrf2) is an important transcription factor for cell survival during oxidative stress. On oxidative stress, Nrf2 binds to the antioxidant response element and activates the expression of cellular antioxidant enzymes, such as SOD, catalase, and glutathione peroxidase (GSHPX). Recently, Sangokoya *et al.* discovered that miR-144 modulated oxidative stress tolerance in sickle cell disease through reducing Nrf2 levels and increased anemia severity in patients homozygous for sickle cell disease (177). Subsequent studies showed that Nrf2 can be regulated by other miRNAs, including miR132, miR-155, miR-153, miR-27a, miR-142-5p, and miR-28, to trigger the redox homeostasis within cells (155, 190, 210, 237). miRNAs also regulate Kelch-like ECH-associated protein 1 (Keap1) that mediate the degradation of cytoplasmic Nrf2. For example, miR-200a binds with the Keap1 3′-UTR, leading to Keap1 mRNA degradation (49). A reduction in Keap1 level was implied to be associated with Nrf2 nuclear translocation and transcriptional activation of Nrf2-dependent antioxidant enzymes.

Some miRNAs directly inhibit ROS scavengers that modulate ROS signaling. Considered the first line of defense against ROS, SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. The Chen group reported that miR-335 suppressed SOD2 expression with a concomitant increase in ROS and induced premature senescence of young mesangial cells (7). The reduction of SOD2 by miRNAs also links the antioxidant response to the epithelial-mesenchymal transition process in that it indirectly regulates matrix metalloproteinase 1 (MMP1) and transforming growth factor beta 1 (TGFβ1) (111, 131). Other crucial ROS scavengers believed to be targeted by miRNA are GSHPX and catalase. GSHPX is responsible for catalyzing the reduction of H_2O_2 and reduces lipid hydroperoxides to their corresponding alcohols and free H_2O_2 to water, whereas catalase catalyzes the conversion of H_2O_2 to water and oxygen, preventing the generation of hydroxyl radicals in cells (67). Recent studies have also suggested that miR-17 suppresses GSHPX2 *via* directly binding its 3′UTR sequence (230) and that miR-30b targets catalase and inhibits its expression at the transcript and protein levels under an oxidant environment (78). In summary, miRNA fine-tunes the ROS signaling pathway by modulating regulators and scavengers that function in the ROS signaling pathway (Fig. 2).

Mitochondrial miRNAs and their roles in DNA repair and ROS signaling pathways

miRNAs are known to be encoded by the nuclear genome and to exert their influence by modulating gene expression mainly in the cytosol. Interestingly, recent studies using microarray analysis have found that a unique set of miRNAs are enriched in the rigorously purified mitochondria (8, 9, 13, 110), Such findings are beginning to shed light on how miRNAs are

Table 2. miRNAs That Regulate the Reactive Oxygen Species Pathway

Targets	*Function in the ROS*	*MiRNAs*	*Refs.*
Catalase	Scavenger	miR-30b	(78)
GPX2	Scavenger	miR-17*	(230)
Keap1	Regulator	miR-141, miR-200a	(49, 208)
Nrf2	Regulator	miR132, miR-155, miR-144, miR-153, miR-27a, miR-142-5p, miR-28	(155, 177, 190, 210, 237)
SOD2	Scavenger	miR-222, miR-382, miR-335, miR-23a, miR-17*	(7, 111, 131, 215, 230)
SOD3	Scavenger	miR-21	(249)
TNFα	Regulator	miR-21	(249)
TXNRD2	Scavenger	miR-34a, miR-17*	(7, 230)

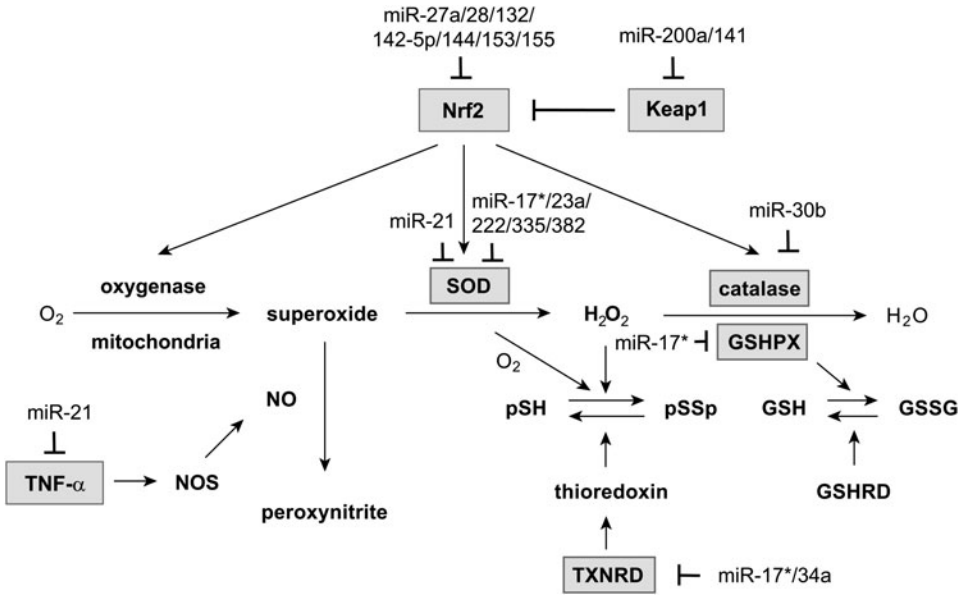

FIG. 2. miRNAs in the reactive oxygen species (ROS) signaling pathway. ROS are constantly produced as superoxides, originating as by-products of cellular metabolism, or by oxygenases from specific signaling pathways. On oxidative stress, the nulcear factor-erythroid 2-related factor 2 (Nrf2)-mediated antioxidant response is activated to maintain intracellular redox homeostasis and limit oxidative damage. miR-200a and miR-141 form the Nrf2 positive feedback loop by targeting Kelch-like ECH-associated protein 1 (Keap1), a negative regulator of Nrf2. Other miRNAs target the central regulators Nrf2, transforming growth factor (TNF)-α, and the ROS scavengers superoxide dismutatese (SOD), catalase, glutathione peroxidase (GSHPX), and thioredoxin reductase (TXNRD).

involved in the regulation of mitochondria. However, these miRNAs that are enriched in mitochondria (mitomiRs) are species specific and cell-type dependent. At least 15 nuclear-encoded miRNAs have been uniquely and reproducibly identified in mitochondria isolated from adult rat livers (110). Computational target prediction analysis (TargetScan and miRanda) for potential mRNA targets revealed that apoptosis, cell death, cell cycle/cell division, development, and neurogenesis were the most significant processes, but found no interaction with nucleus-derived transcripts expressed in the mitochondria. An examination of the 3′-UTR of mitochondria-derived mRNAs found a single potential interaction between miR-130a and mitochondria-encoded cytochrome c oxidase III (COX3) (110). A subsequent study in mice reported that 20 miRNAs were specifically and abundantly restrained in liver mitochondria with regard to the whole liver tissue, such as miR-122, miR-805, and miR-609 (13). Notably, the expression profile of mitochondria-associated miRNAs is significantly altered in mouse livers after treatment with streptozotocin, an antibiotic often used to induce experimental type 1 diabetes in mice. These results suggest that mitochondria-associated miRNAs may be correlated with mitochondria dysfunction (13).

More recently, a signature of 13 nuclear-encoded miRNAs was reproducibly enriched in mitochondria of human Hela cells, including hsa-miR-494, hsa-miR-1275, and hsa-miR-1974 (9). In comparison to cytosol-enriched miRNAs, these mature mitomiRs were smaller than 19 nt and exhibited unique thermodynamic features. A computational target analysis of the 13 mitomiRs in parallel with canonical miRNAs revealed that the former appeared to lack any preferential predicted targeting of the mitochondrial genes encoded by the nuclear genome, but 10 out of 13 mitomiRs were predicted to target 120 mtDNA sites (9). Intriguingly, three mitomiRs (hsa-miR-1974, hsa-miR-1977, and hsa-miR-1978) also showed a perfect match in the human mtDNA genome, but it remains to be ascertained whether the transcription of those three mitomiRs could also occur from the mitochondrial genome. Not only miRNAs are enriched in mitochondria, but also other components of miRNA machinery are also detectable in mitochondria. For example, it was shown that purified mitochondria contain Argonaute 2 (AGO2), a key active protein of the RISC complex, suggesting a potential function of miRNAs in mitochondria (8, 13)

Mitochondria are essential organelles in all cells, as they provide cellular energy by generating ATP *via* respiration, accounting for approximately 85%–90% of the oxygen consumed by the cell (106). Incomplete processing of oxygen or release of free electrons results in the production of ROS. The environment of the mitochondria is highly oxidative. Thus, mtDNA is believed to be more susceptible than in nuclear DNA to DNA damage caused by the oxidative effects of ROS than is nuclear DNA. Although mtDNA was originally thought to lack DNA repair activity, after four decades of research on mitochondria, it has become clear that they possess multiple mtDNA repair pathways, including BER, single-strand break repair, MMR, and, possibly, HR (102). All the mtDNA repair machinery identified so far in mammals are similar in activity to those operating in the nucleus, encoded by nuclear genes, and subsequently transported into the mitochondria (207). In the last decade, numerous studies revealed that miRNAs regulate multiple aspects of the nuclear DDR, including directly regulating the expression of diverse components of the DDR pathway and indirectly fine-tuning the expression of master regulatory proteins, such as p53, through cross-talking with other signaling pathways (132). However, the physiological and pathological roles of these

miRNAs identified in mitochondria remain elusive. Whether they function similarly to regulate DNA repair and ROS signaling pathways needs to be further studied.

LncRNA targets in the DDR

The DDR is dependent on sequentially post-transcriptional and post-translational events that occur on the protein components of the pathway. Phosphorylation is a primary event that modulates the activity and stability of proteins in the DDR. In addition, chromatin remodeling and epigenetic factors can alter transcriptional status and thereby influence the DDR (206).

Recent large-scale genomic transcriptome analyses have revealed that transcription in mammals is not restricted to protein-coding regions, but pervades throughout the genome, giving rise to a complex network of transcripts, most of which have no protein-coding capacity (14). Although the functions of this class of transcripts (ncRNAs) are largely unknown, several studies have elucidated extensive signatures of lncRNAs within cell-cycle promoters and have found that these lncRNAs can control cell cycle or apoptosis during the DDR. One such lncRNA, PANDA (p21-associated lncRNA DNA damage activated), is induced after DNA damage and regulates apoptosis (89). Global gene expression analysis demonstrated that 224 genes were induced, and 193 genes were repressed by at least two-fold after PANDA knockdown. Genes induced by PANDA knockdown were significantly enriched for those involved in apoptosis. Somewhat surprisingly, PANDA does not affect the expression of p21, even though it is antisense to the *p21* gene. PANDA is transcribed in a p53-dependent manner. Chromatin immunoprecipitation analysis showed that PANDA regulates apoptosis *via* modulation of the transcription factor NF-YA. An lncRNA from the promoter region of *CCND1* (encoding cyclin D1) is induced by IR and regulates transcription of CCND1 in *cis* by forming a ribonucleoprotein complex repressor complex (219). This lncRNA, named lncRNA-CCND1, binds to and allosterically activates the RNA-binding protein TLS (translated in liposarcoma), which inhibits histone acetyltransferases and, thus, results in repression of CCND1 transcription. The lncRNA-ANRIL (antisense ncRNA in the INK4 locus) is transcribed in an opposite direction of p15Ink4b and regulates its expression directly or by recruitment of polycomb proteins (108, 162). It is transcriptionally up-regulated by the transcription factor E2F1 in an ATM-dependent manner after DNA damage, and elevated levels of ANRIL suppress the expression of INK4a, INK4b, and ARF at the late stage of the DDR, allowing the cell to return to normal at the completion of the DNA repair. A recent study showed that ANRIL splicing variants play a role in coordinating tissue remodeling, by modulating the expression of genes involved in cell proliferation, apoptosis, and extra-cellular matrix remodeling (42).

LncRNA expression is context specific. As an example, the DDR caused by the topoisomerase inhibitor camptothecin was shown to increase the cellular levels of two antisense lncRNAs at the 5′ (5′aHIF-1α) and 3′ (3′aHIF-1α) ends of the human antisense RNA of the HIF gene in human cancer cell lines and kidney tumor specimens (12). The observed induction of lncRNAs was dependent on DNA damaging agents and cells. In HCT116 cells, camptothecin treatment induces the transcription of both 5′ and 3′ antisense RNA, whereas desferoxamine only increases the transcription of 3′ antisense RNA. However, camptothecin could not induce the transcription of 3′ antisense RNA transcription in HeLa cells. Alternatively, the two antisense transcripts might, alternatively, be involved in mRNA degradation or chromatin inactivation of the HIF-1α gene locus after DNA damage and prevent hypoxic induction of HIF-1α protein (12, 133).

Transcribed from noncoding DNA sequences between protein-coding genes, lincRNAs are also involved in regulation of the DDR. The first studied lincRNA, lincRNA-p21, runs in an antisense direction opposite to the *p21* gene. It regulates the expression of p53-repressed genes that are involved in apoptosis and cell-cycle regulation. Knockdown of either p53 or lincRNA-p21 increases the viability of cells, suggesting a direct physiological role of lincRNA-p21 in the DDR. A marked reduction in apoptosis was observed in doxorubicin-treated cells with depleted lincRNA-p21, leading to reduced levels of the proapoptotic genes *NOXA* and *PERP*. A biotin-labeled RNA pull-down experiment coupled with protein tandem mass spectroscopy analysis identified the RNA-binding protein hnRNP-K as a lincRNA-p21-associated protein, which possibly mediates the regulatory function of lincRNA-p21 in p53-dependent transcription (88).

Chromatin remodeling at the site of DNA breaks prepares for the consequent gene transcription, which is a key step in the DDR. Although exact details have not yet been worked out, several lncRNAs appear to modulate the chromatin state directly or through modifications of proteins involved in the DDR. A recent model delineated that lncRNAs provide a scaffold for the binding of polycomb protein complex PRC1/2 and direct it in a sequence-specific manner to regulate the expression of genes required during several physiological processes, including stress response. In agreement with their potential importance in gene regulation, many lncRNAs have been shown to be altered in human cancer (64). Along with their functional identification, it is expected that more lncRNAs will be identified in the DDR.

Potential roles of other small ncRNAs in the DDR

Although miRNAs and the recently identified lncRNAs are the most studied ncRNAs, other ncRNAs have been identified with deep sequencing technologies followed by extensive bioinformatics-based characterization of genomic locations and predictions of RNA secondary structures. These ncRNAs are also implicated in the DDR, including ncRNAs that regulate gene expression (such as small nucleolar RNAs [snoRNAs] and transfer RNAs) (6) and genes that mediate gene silencing (such as Piwi-interacting RNAs [piRNAs] and endogenous small interfering RNAs) (63).

DDRNAs. Most recently, a group of Dicer- and Drosha-dependent small RNAs ($\sim$21 nt) were found to be induced by DSBs and involved in HR-mediated DSB repair. RNA deep sequencing revealed that these small RNAs arise from the sequences in the vicinity of DSB sites. These RNAs have been referred to as DDRNAs. Wei *et al.* proposed that DDRNAs function as guide molecules to direct either chromatin modifications or the recruitment of protein complexes to DSB sites to facilitate repair (222). Moreover, Francia *et al.* reported that DDR foci formation was sensitive to RNase A treatment and

that DDRNAs, either chemically synthesized or generated *in vitro* by Dicer cleavage, were sufficient to restore DDR in the RNase A-treated cells (55).

SnoRNAs. SnoRNAs are a class of small RNA molecules that primarily mediate modifications of rRNAs, tRNAs, and small nuclear RNAs. Several snoRNAs have been suggested to be involved in the DDR. Through their analyses of snoRNA TIF-IA conditional knockout mice, Yuan *et al.* showed that TIF-IA plays a key role in cell-cycle arrest, up-regulation of p53, and induction of apoptosis (243). TIF-IA mediates growth-dependent regulation of ribosomal RNA synthesis, and its depletion may increase binding of ribosomal proteins, such as L11, to MDM2 and decrease the interaction of MDM2 with p53 and p19ARF. In another study, Michel *et al.* reported that loss of three box C/D snoRNAs in the L13a(rpL13a) locus was sufficient to render cells resistant to lipotoxic and oxidative stress *in vitro* and prevented the propagation of oxidative stress *in vivo* (148). Cells with disruption of one rpL13a allele have intact cell death pathways but are resistant to apoptosis induced by lipotoxic conditions.

tRNAs. Before fulfilling their functions, all tRNA transcripts should be extensively processed in multiple steps, including the removal of the 5′ leader by RNase P, removal of the 3′ trailer sequence by endonucleases and exonucleases, addition of CCA, splicing of introns, and modifications at multiple residues (85). Trm9 catalyzes conversion of cm5U to mcm5U at position 34 of substrate tRNAs (97). Lack of the mcm5U moiety of tRNAs can affect apoptosis, as shown in a study in which silencing of human Trm9 homolog ABH8 led to apoptosis of urothelial carcinoma lines and down-regulation of NOX-1-dependent ROS, as well as suppression of angiogenesis and invasion (185). Both mitochondrial and cytosolic tRNAs bind to cytochrome c. This binding prevents cytochrome c interaction with Apaf-1, thereby blocking Apaf-1 oligomerization and caspase activation. tRNA hydrolysis in cells enhances apoptosis and caspase activation, whereas introducing tRNA into living cells blocks apoptosis. These findings suggest that in addition to its well-established role in gene expression, tRNA may determine cellular responsiveness to apoptotic stimuli (142).

pi-RNAs. piRNAs are the largest class of small ncRNA molecules that are expressed in animal cells. They are distinct from miRNAs in that they are larger (26–31 nt rather than 21–24 nt), lack sequence conservation, and are more complex. Loss of Piwi proteins leads to germline-specific apoptosis, which may be triggered by DNA damage. In the miwi2 (piwi homologue in mouse) mutant mouse, the level of phosphorylated histone H2AX (γ-H2AX), a biomarker for the DDR, is significantly increased in zygotene-stage spermatocytes compared with wild-type cells (27). Failure to repair DSBs and/or defective synapses prevents germ cells from entering the pachytene stage of spermatogenesis and leads to apoptosis. Increased levels of apoptosis have also been observed in the testes of ziwi (piwi homologue in zebrafish) mutant zebrafish, (30). These findings suggest that piRNA biogenesis is involved in the maintenance of genome integrity. By sequencing small RNAs (RNA-seq) in primary marrow cells of patients with low- and high-grade myelodysplastic syndromes, Beck *et al.* found that piRNAs were enriched in only the small RNAome in low-grade myelodysplastic syndromes and potentially protected DNA from the accumulation of mutations (11).

qiRNAs. RNA interference pathways use small RNAs such as small interfering RNAs (siRNA) to mediate gene silencing in eukaryotes. It was recently reported that in the filamentous fungus, Neurospora DNA damage induces expression of the Argonaute protein QDE-2 and a novel class of small RNAs termed qiRNAs because of their association with QDE-2 (118). qiRNA biogenesis also requires DNA-damage-induced presiRNAs as precursors. Neurospora RNA interference mutants show increased sensitivity to DNA damage, suggesting a role for qiRNAs in the DDR by inhibiting protein translation.

Other ncRNAs. Despite recent progress in our understanding of ncRNAs, the findings to date represent only the tip of the iceberg. The transcription landscape in higher eukaryotes has turned out to be more complex than expected, suggesting that the RNA transcripts are not restricted to well-defined functional features. More recently, scientists have identified various chromatin-associated ncRNAs such as transcription initiation RNAs (180), 5′ capped promoter-associated small and large RNAs (2), and splice-site RNAs (196). However, the roles of these ncRNAs in the DDR need to be clarified.

Transcriptional Regulation of ncRNA Expression in the DDR

The first step for ncRNA expression is RNA polymerase-mediated transcription, which also involves transcription factors or cofactors and their interaction with the RNA polymerase complex and regulatory DNA elements in the ncRNA genes. Increasing evidence has shown that the DDR markedly alters the expression of ncRNAs and, thus, post-transcriptionally modulates DDR proteins such as sensors, mediators, transducers, and effectors to orchestrate a number of distinct actions in detecting DNA damage, arresting the cell cycle, mediating DNA repair, and inducing apoptosis (212). Here, we focus on the role of the DDR in the biogenesis of two major classes of ncRNAs, miRNAs and lncRNAs.

Transcriptional regulation of miRNAs after DNA damage

Various DNA damage stresses alter miRNA expression profiles. Pothof *et al.* first identified the differential expression of miRNAs in cell-cycle checkpoints and DNA repair in UV-treated cells (170). miRNA expression profiles were later analyzed in cells treated with other DNA damaging agents, including cisplatin, doxorubicin, IR, and NCS (59, 176, 195, 250). Different doses of DNA damage appear to activate unique as well as common sets of miRNAs, suggesting that miRNAs regulate the DDR by a mechanism based on the nature and intensity of the DNA damage.

Similar to regular protein-coding genes, miRNA genes are transcribed to pri-miRNAs. For some miRNAs, this transcription process is regulated in the DDR. The tumor suppressor p53 is a well-known transcription factor that is induced after DNA damage, which itself induces cell growth arrest, promotes apoptosis, blocks angiogenesis, and mediates DNA repair on DNA damage signals (141). Global miRNA expression analyses revealed that a cohort of miRNAs are up-regulated in a p53-dependent manner after DNA damage

and identified the miRNA components of p53 transcriptional pathways. The miR-34 family (miR-34a and miR-34b/c) was the first identified transcriptional target of p53. When ectopically expressed, the miR-34 family causes a cell-cycle arrest in the G1 phase and inhibits cell-cycle progression by targeting numerous cell cycle regulators, suggesting their tumor-suppressing potential. For example, the miR-34 family directly targets and down-regulates cyclin-dependent kinase 4 (CDK4), CDK6, E2F3, Myc, and NMYC (33, 82). In addition to the miR-34 family, p53 directly transactivates miR-15a/16-1, miR-29, miR-107, miR-145, miR-192, miR-194, miR-215, and miR-605 (Fig. 3). These p53-induced miRNAs contribute to cell-cycle arrest by inhibiting the transcripts of several genes that regulate cell-cycle checkpoints or metabolism (19, 62, 83, 107, 126, 192). miR-16 and miR-29 target and repress Wip1 phosphatase, a master inhibitor in the DDR that inhibits the activation and stabilization of p53, leading to p53 induction (204, 251). Ectopic expression of miR-192/215 induces cell-cycle arrest through targeting a number of transcripts that regulate G1/S and G2/M checkpoints (21). miR-145 directly targets the oncogene c-Myc, suggesting that p53 represses c-Myc functions through regulation of miRNA expression (175, 192). Interestingly, p53-induced miRNAs regulate p53 activity in a positive feedback loop (76, 83). miR-34 inhibition of SIRT1 results in increased p53 acetylation and activation (231). miR-192, miR-194, miR-215, and MiR-605 directly inhibit Mdm2 expression, and miR-29 inhibits Wip1, leading to an increased p53 level and activity (19, 165, 227).

The p53 protein also functions as a transcriptional repressor by binding to miRNA promoters and preventing the recruitment of transcriptional activators. As an example, p53 suppresses the transcription of the miR-17-92 cluster gene by preventing recruitment of the TATA-binding protein to the TAATA site in the promoter (Fig. 3). The miR-17-92 cluster is repressed under hypoxic conditions *via* a p53-dependent mechanism, leading to sensitization to hypoxia-induced apoptosis (233). Thus, fine-tuning between the p53 signaling pathway and the miRNA network enables cells to amplify the p53 signal, which enhances cell sensitivity to external signals.

DNA damage-responsive transcription factors other than p53, such as NF-κB, E2F, and Myc, are also involved in the transcriptional control of miRNA expression. Both E2F and Myc activate the transcription of the miR-17-92 cluster, which, in turn, inhibits E2F and Myc expression, forming an auto-regulatory negative feedback loop (3). In addition, Myc-induced miRNAs influence Myc-mediated cell proliferation and cell fate (104). For example, Myc-induced miR-20a targets cdkn1a, a gene encoding a negative regulator of cell-cycle progression, and Myc-induced miR-221 and miR-222 target the CDKN1b and CDKN1c genes, which initiate cell-cycle arrest. Owing to a lack of basic information regarding miRNA gene structure, not much is currently known about how miRNA gene expression is transcriptionally regulated. Global prediction and verification of promoter regions of miRNA genes would allow us to further explore the functional interaction of transcriptional machinery and epigenetic miRNA regulation.

Transcriptional regulation of lncRNAs after DNA damage

LncRNAs are an important class of pervasive genes that are involved in a variety of biological functions (74). They act to integrate contextual and environmental cues such as DNA damage stress. The majority of lncRNAs are transcribed by RNA polymerase II, as evidenced by Pol II occupancy, 5′ caps, histone modifications associated with Pol II transcriptional

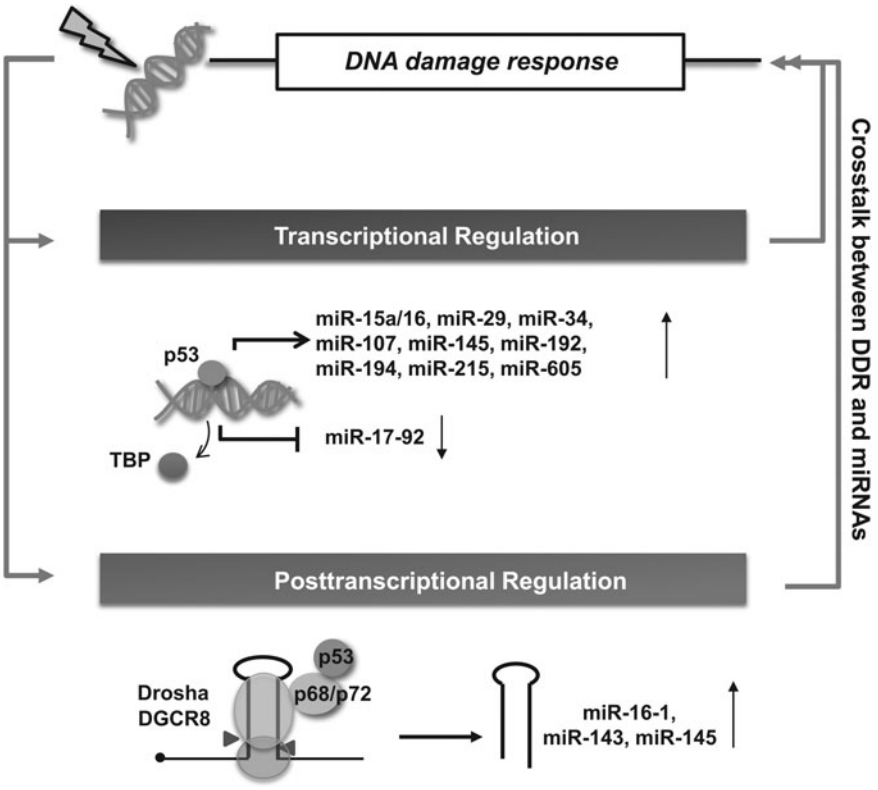

FIG. 3. Transcriptional and post-transcriptional regulation of p53 in miRNA biogenesis. p53 modulates miRNA maturation at not only the transcription step but also the processing step of primary miRNA transcripts and results in production of crosstalk between the p53 network and the miRNA biogenesis machinery in the DDR. Many miRNAs regulated by p53 modulate the DDR by targeting proteins in the DDR, such as cell-cycle progression and apoptosis.

elongation, and polyadenylation (72). LncRNAs show cell type-specific expression and respond to diverse stimuli, suggesting that their expression is under considerable transcriptional control. However, only a small number of functional lncRNAs have been well characterized, and little is known about how lncRNA expression is controlled in different contexts.

The tumor suppressor protein p53 coordinates the cellular response to DNA damage through regulation of gene expression. In order to identify specific lncRNAs that operate within the p53 pathway, several research groups have designed tiling microarrays to detect their expression in mouse cell lines engineered with controllable expression of p53 or in various human samples treated with doxorubicin (89, 103). Hung *et al.* used an ultrahigh-density array that tiles the promoters of 56 cell-cycle genes to interrogate 108 samples representing diverse perturbations. They observed that DNA damage induced five lncRNAs from the *CDKN1A* promoter, one of which was PANDA, which is induced in a p53-dependent manner (89). PANDA was found to interact with transcription factor NF-YA and to prevent its binding to chromatin, leading to the repression of pro-apoptotic genes and thus facilitating cell-cycle arrest. In a subsequent study, Huarte *et al.* showed that one of the direct p53 targets in response to DNA damage, lincRNA-p21, which is located upstream of the p21 gene, acted as a transcriptional repressor mediating p53-induced apoptosis (88). p53 regulates lincRNA-p21 by directly activating its expression, through direct binding to the lincRNA-p21 promoter. Another p53-regulated lncRNA in the DDR is TUG1. TUG1 was originally identified as a lncRNA that is up-regulated by taurine in developing retinal cells and was found to repress the p53-dependent cell-cycle regulation (103). Recently, Yang *et al.* showed that TUG1 served as a scaffold RNA that binds with methylated Pc2 in Polycomb bodies, which are an important antimitogenic signal and, under certain stimuli, a stress-induced modification mark required for growth-control gene repression and senescence (236). Other than p53, transcription factor E2F1 regulates the expression of lncRNAs in the DDR. Our group found that ANRIL is induced by E2F1 after DNA damage in an ATM-dependent manner. Elevated ANRIL regulates cell proliferation and cellular senescence (211). Notably, ANRIL has been shown to interact with PRC2 and PRC1 complex to repress the expression of INK4B–ARF–INK4A locus (108). These findings showed that lncRNAs can play key regulatory roles in the p53 or E2F1 transcriptional response after DNA damage (Fig. 4).

While lincRNA-p21, PANDA, and several other lncRNAs may function in an important p53-dependent pathway in the DDR, it is tempting to speculate that other lncRNAs also play key roles in numerous other tumor suppressor and oncogenic pathways, representing a hitherto unknown paradigm in tumorigenesis.

Nuclear-cytoplasmic distribution and nuclear export/import of miRNAs in the DDR

Post-transcriptional processing has been shown to play a key role in the regulation of miRNA levels in the DDR (76, 212). While the processing of pri-miRNAs into pre-miRNAs is increased by the Drosha-p68/p72/p53 complex or the Drosha-KSRP complex in the nucleus, accumulated pre-miRNAs should be exported from the nucleus to the cytoplasm for further processing by the Dicer complex. Thus, XPO5-mediated nuclear export of pre-miRNAs represents a rate-limiting step for miRNA maturation (240). Previous studies have shown that depletion of *Xpo5* resulted in a global reduction of miRNAs (138). Recently, Melo *et al.* identified a genetic defect on the *Xpo5* gene in a subset of colorectal cancers with microsatellite instability, which traps pre-miRNAs in the nucleus, thereby reducing miRNA processing (143). They further found that haploinsufficient XPO5 failed to sustain the mature miRNA levels required to control cell differentiation and proliferation, and promoted tumorigenesis. Our group demonstrated that XPO5-mediated pre-miRNA nuclear export is promoted in an ATM-dependent manner after DNA damage (data unpublished). On DNA damage, we observed enhanced interaction between the nucleopore and XPO5 complex. This interaction accelerated the nuclear export of pre-miRNAs, thus facilitating more production of mature miRNAs in response to DNA damage. It is noted that some mature miRNAs are required to function in the nucleus. Therefore, import of these mature miRNAs to the nucleus is necessary in the DDR. CRM1 (or XPO1) was recently shown to interact with the Argonaute complex and to mediate nuclear-cytoplasmic shuttling of mature miRNAs (28). Inhibition of CRM1 resulted in an increased accumulation of miRNA guide sequences in the nucleus. It would be of great interest to investigate the modulation of CRM1-mediated miRNA transport after DNA damage.

Post-Transcriptional Regulation of ncRNA Expression in the DDR

miRNA genes are initially transcribed to yield a primary, long transcript that is sequentially processed in both the nucleus and cytoplasm. Nuclear processing is mediated by the RNase III enzyme Drosha–DGCR8 microprocessor complex to generate pre-miRNAs of ~70-nt in length. Pre-miRNAs are subsequently transported to the cytoplasm by export 5-Ran-GTP, where they are cleaved by the RNase III enzyme Dicer to generate mature miRNAs (105). Accumulating evidence shows that post-transcriptional processing may play a major role in the regulation of miRNA levels. Recent studies have shown that DNA damage leads to increased levels of some pre-miRNAs and mature miRNAs without producing significant changes in their primary transcripts (195, 250). These findings suggest that the DDR is involved in this post-transcriptional processing of miRNAs by modulating the activity or stability of the processing machines and that there are functional connections between the DDR and miRNA maturation (76, 132, 212).

Major components in the Dicer and Drosha complexes and their regulation in the DDR

Drosha and Dicer plays a central role in miRNA biogenesis, and their expression levels directly influence the clinical outcomes of malignant cancer (147). Drosha interacts with DGCR8, a double-stranded RNA-binding domain protein, to form a complex called the microprocessor. They regulate each other post-transcriptionally. The Drosha–DGCR8 complex destabilizes DGCR8 mRNA by cleaving its hairpin structure. DGCR8, in turn, stabilizes Drosha through protein–protein interaction (77). This mutual regulation between Drosha and DGCR8 may contribute to the homeostatic control of miRNA

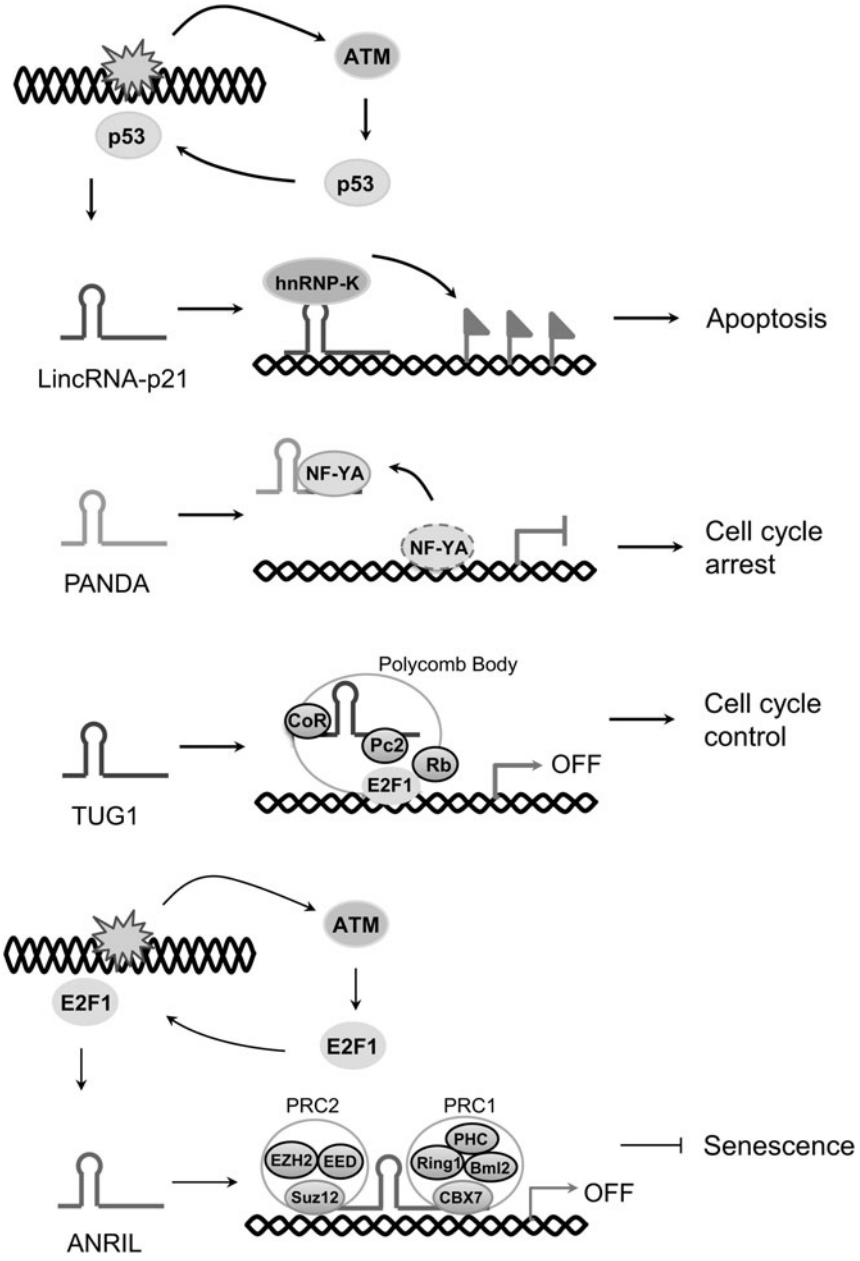

FIG. 4. Regulation of lncRNA expression in the DDR. On DNA damage, ATM-induced transcription factors p53 and E2F1 transcriptionally activate the expression of, lincRNA-p21, PANDA, TUG1, and ANRIL. Up-regulated lincRNA-p21 functions as a guide to the hnRNP-K repressor complex, leading to p53-mediated apoptosis. Up-regulated PANDA acts as a decoy to interact with NF-YA, resulting in cell-cycle arrest. Induced TUG1 functions as a scaffold in the Polycomb body, repressing E2F1 target genes in cell-cycle control. Up-regulated ANRIL interacts with PRC1 and PRC2 complexes and represses the INK4b-ARF-INK4a locus, inhibiting cellular senescence.

biogenesis. Other major components in the miRNA maturation machinery are also under control in the cell. A recent study reported that oxidative stress-responsive heme oxygenase-1 (HMOX1) can modulate miRNA processing by down-regulating DGCR8 protein levels (109). Pothof *et al.* observed that UV damage triggered a cell cycle-dependent relocalization of Ago2 into stress granules and promoted miRNA expression in a partially ATM/ATR-independent manner (170). The p38 mitogen-activated protein kinase (MAPK) pathway and MAPK/Erk signaling regulate the stability of Ago2 and the Dicer-TRBP complex, respectively (161, 244). Phosphorylated TRBP stabilizes the Dicer-TRBP complex and increases mature miRNA production. Remarkably, Erk and MAPKs are phosphorylated and activated after DNA damage (47), which suggests a connection between the DDR and Dicer complex activity. TAp63, the transactivation isoform of p63, binds to the promoter of Dicer and transactivates its expression (191), revealing a direct regulation of Dicer expression.

Regulatory factors in the Dicer and Drosha complexes and their regulation in the DDR

In addition to the major components Drosha and DGCR8, the microprocessor contains a variety of cofactors in this large

complex around RNA. These cofactors have been suggested to promote the fidelity, specificity, and activity of the Drosha-mediated cleavage of pri-miRNAs (187). In particular, many of these accessory factors are also involved in the DDR. DEAD box RNA helicases p68 (DDX5) and p72 (DDX17) were identified in the Drosha complex and found to contribute to the efficient processing of a subset of pri-miRNAs into the corresponding mature miRNAs such as miR-16-1, miR-143, and miR-145 (56, 69). In addition to regulating transcription, p53 regulates the processing of miRNAs by binding to Drosha. A direct interaction between p53 and p68/p72 facilitates p53's promotion of miRNA processing under conditions of DNA damage (195) (Fig. 5). Recent studies from our group provide direct evidence that as many as a quarter of miRNAs are significantly induced on DNA damage in an ATM-dependent manner (250). Among these induced miRNAs, a cohort of miRNAs associated with KH-type splicing regulatory protein (KSRP), a key component of both the Drosha and Dicer complexes, was identified (201). Trabucchi *et al.* presented compelling evidence that KSRP promotes maturation of this selected group of miRNA precursors (201). KSRP binds with a high affinity to the terminal loop of these miRNAs and interacts with both Drosha and Dicer. As a key kinase for the initiation of the DNA damage signaling cascade, ATM directly binds to and phosphorylates KSRP, leading to enhanced interaction between KSRP and pri-miRNAs and increased KSRP activity in miRNA processing (250). These findings strongly support the hypotheses that ATM functions as a major switch for the activity of KSRP in miRNA biogenesis, and that KSRP acts as a molecular gatekeeper which accelerates the production of a subset of miRNAs that regulate cell activities in response to DNA damage.

Other regulatory molecules that respond to DNA damage signals have recently been identified in the post-transcriptional regulation of miRNA expression. RNA-binding-motif protein 38 (RBM38), which is regulated by p53, may affect miRNA target gene selection by competing with miRNAs for binding to 3′-UTRs of target mRNAs. RBM38 is required for optimal induction of G1 cell-cycle arrest after DNA damage by protecting the 3′-UTR of the p53 target, p21, from binding by miRNAs. This study suggested that RBM38 decreases miRNA accessibility in a number of p53-induced transcripts, allowing an optimal target gene induction and cell-cycle control (121). BRCA1, a human tumor suppressor protein, interacts with the Drosha microprocessor complex and Smad3/p53/DHX9 and accelerates the processing of primary miRNA transcripts such as let-7a-1, miR-16-1, miR-145, and miR-34a (101). TAR DNA-binding protein 43 (TDP-43) facilitates the processing of a subset of pri-miRNAs and pre-miRNAs through its interaction with Drosha and Dicer complexes and the relevant miRNAs (100). Interestingly, TRP-43 also regulates Cdk6 messenger RNA level by interacting with a DNA damage-induced lncRNA, gadd7. Interaction of gadd7 with TRP-43 blocks the interaction of TDP-43 with Cdk6 mRNA at the post-transcriptional stage (129). This study demonstrated a unique type of regulation: TDP-43 modulates the DDR through miRNA biogenesis and DNA damage-induced lncRNA.

Although we now know that miRNA expression is regulated transcriptionally and post-transcriptionally in the DDR,

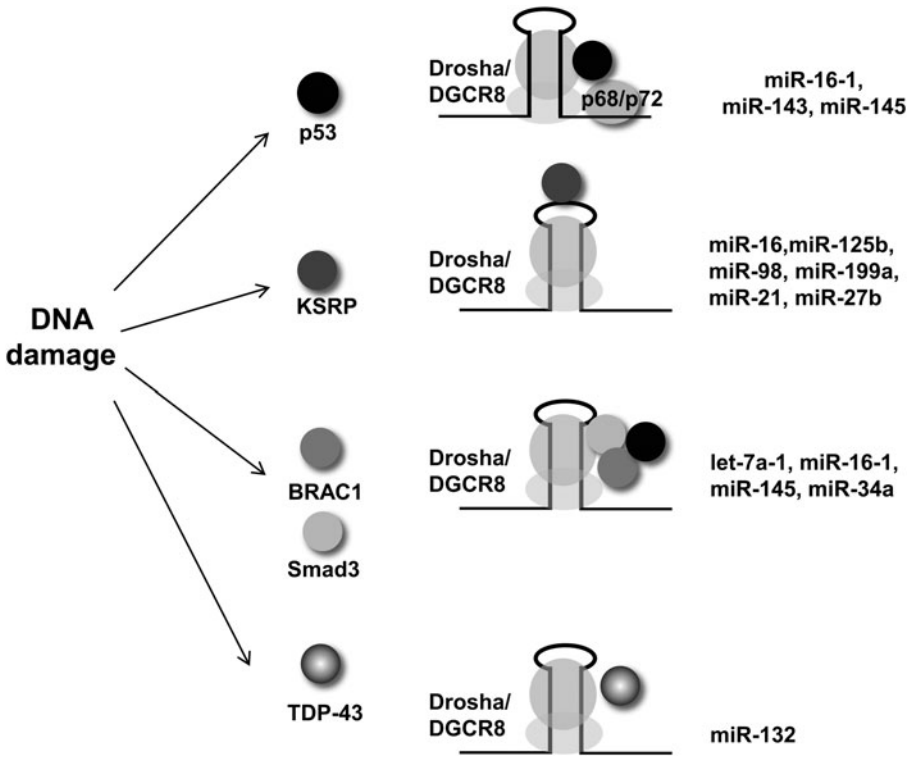

FIG. 5. Components in the DDR regulate the function of the Drosha complex in miRNA biogenesis. Many cofactors in the Drosha microprocessor promote its processing activity. DNA damage activates/induces these regulatory proteins that translate DNA damage signal to miRNA expression.

many important questions remain to be addressed. In particular, it remains largely unknown how miRNA biogenesis responds to DNA damage for p53- or KSRP-independent miRNAs. There could be other mechanisms that account for the induction of those miRNAs. Further studies will provide insights into the molecular mechanisms by which DNA damage signaling is linked to miRNA biogenesis.

miRNA-lncRNA interaction in the DDR

Recent evidence suggests that some lncRNAs might potentially interact with other classes of ncRNAs, including miRNAs, and modulate their regulatory role. LncRNAs may regulate gene expression post-transcriptionally by directly binding to miRNAs, acting as a "sponge" to prevent specific miRNAs from binding to their target mRNAs (31, 96). These findings have revealed a novel layer of regulation in that distinct classes of ncRNAs interplay with each other and cooperate to regulate gene expression. A transcriptome scale analysis on miRNA-lncRNA interactions was recently conducted to study the role of lncRNA as a layer of regulatory interactions with miRNAs (94). However, extensive and accumulated data will be needed to identify crosstalk between miRNAs and lncRNAs in the DDR signaling pathway.

ncRNAs in Genome Instability and Human Cancers

miRNA and lncRNA gene variation in human cancers

Cancer is a disease involving multistep changes in the genome. Increasing evidence shows that expression of miRNAs and lncRNAs is deregulated in human cancer (51, 91). The first direct evidence for an involvement of miRNAs in human cancer derived from studies on chronic lymphocytic leukemia (CLL), in an attempt to identify tumor suppressor genes at chromosome 13q14, which was frequently deleted in about 60% of the cases. By examining this recurring deletion, Dr. Croce's group found that two miRNAs, miR-15a and miR-16-1, other than protein-coding genes, were located within the smallest minimal common region of deletion. Thus, this result provided the evidence that deletion of miRNAs could be involved in the pathogenesis of human cancers. Following these initial observations, several groups reported that many miRNAs in regions of chromosomal instability (amplification, translocation, or deletion) or nearby chromosomal breakpoints are prone to deletions or amplifications (24, 247). These cancer-associated miRNA variations include amplification of the miR-17-92 cluster in lymphoma (197), translocation of miR-17-92 in T-cell acute lymphoblastic leukaemia (T-ALL) (140), and amplification of miR-26a in glioblastoma (90). Overall, about half of miRNA genes are located in cancer-associated genomic regions or in fragile sites (24). In addition, recent studies suggest that epigenetic modifications of miRNA genes cause their dysregulation in human cancers (248). Finally, several key proteins in the miRNA biogenesis pathway, such as Dicer and Ago2, may be dysfunctional or dysregulated in cancer, which may promote tumorigenesis (247). Therefore, variations in DNA copy numbers and epigenetic markers or defects in the miRNA biogenesis machinery might contribute to miRNA dysregulation in human cancer.

Somatic mutation of lncRNAs in cancer is not well explored either. Several initial studies showed that lncRNAs may be a target for genomic amplification/deletion, somatic point mutations, or other targeted aberrations in cancer. For example, the co-amplification of *MYC* and the lncRNA gene *PVT1* in the chromosome region of 8q24 contributes to serous ovarian adenocarcinoma and breast cancer pathophysiology. This amplification has also been associated with reduced survival. However, inhibition of PVT1, but not MYC, induces an amplification/overexpression-specific apoptotic response, suggesting that PVT1 exerts its pathophysiologic influence independently as an ncRNA (71). In addition, a GAS5-BCL6 gene fusion, resulting from a chromosomal translocation and retaining the full coding sequence of BCL6, has been reported in a patient with B-cell lymphoma (153). As another example, Poliseno and colleagues reported that the *PTEN* pseudogene, *PTENP1*, is selectively lost in prostate and colon cancers, which leads to dysregulated expression levels of these genes (167).

Roles of the DDR-associated ncRNAs in tumorigenesis

The importance of miRNAs in cancer is underscored by the observation that around half of miRNA genes are located in cancer-associated genomic regions or fragile sites (24, 182), which are frequently amplified or deleted, mutated, or epigenetically silenced in tumorigenesis. Global repression of miRNA processing machinery (Drosha, DGCR8, Exportin-5, Dicer1, and Ago2) promotes cellular transformation, and miRNA processing-impaired cells formed tumors with accelerated kinetics in a mouse model, suggesting a role for mature miRNAs in cancer-associated processes (113, 143, 144). Large-scale miRNA expression profiling of human cancers has revealed that miRNA dysregulation is associated with many types of cancer, including those originating from the blood, brain, thyroid, breast, lung, tongue, nose and pharynx, liver, gastro-intestinal system (esophageal, gastric, pancreatic, and colorectal cancers), and genitourinary system (cervical, ovarian, and prostate cancers) (44, 50, 75, 158). Aberrations in miRNA expression are closely linked to tumorigenesis. A single miRNA can target a variety of mRNAs and can play either an anti-apoptotic or a pro-apoptotic role depending on the cancer type. These characteristics make functional assessment of individual miRNAs difficult. Interestingly, those aforementioned DDR-associated miRNAs show a considerable overlap with frequently dysregulated miRNAs in human solid tumors, suggesting that DNA damage-responsive miRNAs play a role in cancer etiology. Some examples of DDR-associated ncRNAs involved in cancer are summarized in Table 3.

DDR-associated miRNAs have been characterized as tumor suppressors (such as miR-15/16, miR-29, miR-34, and the let-7 family) or oncogenes (such as, miR-155, miR-21, miR-221, and the miR-17-92 cluster) (Table 3 and Fig. 6). The miR-15/16 cluster induces apoptosis by targeting the important anti-apoptotic factor BCL2 at the post-transcriptional level (41). This miRNA cluster is frequently deleted in B-cell CLL, resulting in its down-regulation in the majority of cases of CLL (23). The miR-15-16 cluster has also been reported to be down-regulated in pituitary adenoma (17) and prostate carcinoma (169). Therefore, in these cancers, miR-15/16 expression is preferentially down-regulated to promote tumor progression by inhibiting apoptosis. The oncogenic miR-21 is the most consistently up-regulated miRNA across many cancer types

TABLE 3. DNA DAMAGE RESPONSE-ASSOCIATED ncRNAs AND THEIR TARGETS IN HUMAN CANCER

Name	*Function*	*Target/interactor*	*Cancer phenotype*	*Cancer type*	*Refs.*
let-7	TS	H-RAS, HMGA2	Induces apoptosis	Lung, breast	(198, 241)
miR-15/16	TS	Bcl-2, Wt-1	Induces apoptosis and decreases tumorigenicity	Chronic lymphocytic leukemia, pituitary adenoma	(17, 23, 41)
miR-155	OG	c-maf	Induces lymph proliferation	Chronic lymphocytic leukemia, lung, breast	(61, 92, 235)
miR-17 ~ 92	OG	E2F1, Bim, PTEN	Co-operates with c-myc to induce lymphoma in mice, promotes lymph proliferative disorder, and enhances cell proliferation	Lymphoma, lung	(80, 145, 226)
miR-21	OG	PTEN, PDCD4, TPM1	Induces apoptosis and decreases tumorigenicity	Breast, cholangiocarcinoma, chronic lymphocytic leukemia, lung	(57, 146, 186, 252)
miR-221	OG	P27, p57	Promotes aggressive growth and cell proliferation	Hepatocellular carcinoma, glioblastoma	(38, 54, 66)
miR-29	TS	TCL-1, MCL1, DNMT3s	Induces apoptosis and decreases tumorigenicity	Non-small cell lung cancer, cholangiocarcinoma, lung	(151, 235)
miR-34	TS	E2F, CDK4, CDK6, cyclin E2	Induces apoptosis	Gastric, pancreatic, lung, neuroblastoma	(33, 95, 223)
miR-372/373	OG	LATS2	Promotes tumorigenesis in co-operation with RAS	Testicular tumors	(209)
ANRIL	OG	PRC1, PRC2	Suppresses senescence *via* INK4A	Prostate, leukemia	(108, 162, 238)
LincRNA-p21	TS	hnRNP-k	Mediates p53 signaling, induces apoptosis	Mouse models of lung, sarcoma, lymphoma	(88)

FIG. 6. miRNA-based therapeutic strategies against cancer. One strategy is to inhibit the function of oncomirs by the use of antigomirs, miRNA sponges, anti-miRNA oligonucleotides, or locked nucleic acids. Another strategy is to restore the activity of tumor suppressor miRNAs through miRNA mimic, virus-based gene delivery, or treatment with DN-demethylating agents and histone deacetylase inhibitors.

(44, 50, 75, 158). miR-21 was first implicated as an anti-apoptotic factor because of the finding that knockdown of miR-21 increased apoptotic cell death in human glioblastoma cells (32) and in a mouse model of breast cancer (186). miR-21 directly targets the tumor suppressor PTEN, which inhibits apoptosis in cancer cells (32). miR-21 was also reported to target PDCD4 (137), a pro-apoptotic gene frequently down-regulated in hepatocellular carcinoma (245), and other important tumor suppressor genes, including tropomyosin 1 (252) and serine peptidase inhibitor, clade B (ovalbumin), and member 5 (SERPINB5) (253). These observations suggested that miR-21 may also play a role in tumor invasion and metastasis. Hypoxia-regulated miRNAs, such as miR-210, are induced in response to low oxygen levels and play a role in cell survival by decreasing the activation of caspases, the central components of apoptotic signaling (112). Since hypoxia is an important feature of the cancer microenvironment, it is interesting that miR-210 is also overexpressed in many cancer types, indicating that hypoxia contributes to miRNA dysregulation in certain cancers. A recent study demonstrated that miR-210 is a good prognostic biomarker for breast cancer (25). In light of the roles of miRNA in apoptosis and cancer, miRNAs in tumorigenesis may not be merely either pro-apoptotic or anti-apoptotic. Rather, the coordination and perhaps synergism between several deregulated miRNAs and their protein-coding counterparts likely facilitate a favorable environment for cancer formation. Further studies that provide a detailed characterization of miRNA target and function will be necessary to improve our understanding of the role of miRNAs in tumorigenesis and to facilitate the design of appropriate therapies targeting this novel group of molecules.

DDR-associated lncRNAs function as tumor suppressors and are deregulated in cancer. For example, lincRNA-p21 and MEG3 were found to mediate p53 signaling in the DDR and to

induce apoptosis, thus inhibiting cell proliferation in a spectrum of tumors, including lung tumors, sarcoma, lymphoma, meningioma, hepatocellular tumors, leukemia, and pituitary tumors (171). Aberrant expression of the oncogenic lncRNAs uc.73a and PCGEM1 was found to inhibit apoptosis and to promote cell proliferation in leukemia and prostate cancer, respectively (171). An lncRNA suppressed in breast cancer, GAS5, was able to induce apoptosis and growth arrest, and to prevent GR-induced gene expression (171). ANRIL predisposes patients for hereditary cutaneous malignant melanoma (162). Altered ANRIL activity might result in dysregulated silencing of the INK4b/ARF/INK4a locus, thereby contributing to cancer initiation.

piRNA-pathway mutations often lead to a significant overexpression of retrotransposons and a high level of DNA damage. piRNAs and piRNA-like transcripts are involved in tumorigenesis in testicular tissue and a variety of other cancers (40, 136, 234), although their specific functions in tumorigenesis are unknown. Recent studies have implicated Piwi proteins in tumor development. For example, PIWIL1 and PIWIL2 are overexpressed in various cancer types (125, 194, 199). PIWIL1 overexpression is closely related to cell-cycle arrest (130), whereas PIWIL2 overexpression is related to anti-apoptotic signaling and cell proliferation (120). Furthermore, PIWI proteins are associated with stem cell self-renewal (183) and are restored in precancerous stem cells that have the potential for malignant differentiation (35). For some cancers, PIWIL2 overexpression may lead to cisplatin resistance, which might arise due to increasing chromatin condensation that prevents the normal process of DNA repair (218). piRNAs were also found to be aberrantly expressed in human cancer cells (37), implying that the Piwi pathway has a more important function outside germline cells than was originally thought.

Application of ncRNAs as diagnostic biomarkers and therapeutic targets

Oncogenic stress often activates the DDR in premalignant or early-stage tumors. While a large number of ncRNAs are induced or suppressed in the DDR, it is of great interest to identify the roles of these ncRNAs in tumorigenesis. The growing body of literature shows that ncRNAs play fundamental roles in development, differentiation, and malignancy, suggesting that this class of molecules contains potential diagnostic markers and novel targets for therapies. So far, most work in this field has been in the context of the roles of miRNAs in cancer, but there is also considerable interest in applying similar approaches to other ncRNAs.

Recent identification of stable miRNAs in serum, plasma, and other body fluids has paved the way for their use as a promising class of blood-based biomarkers for diagnosing human cancer. In addition to their stability in various body fluids, miRNAs possess several features that make them attractive diagnostic biomarkers. The expression patterns of miRNAs are frequently dysregulated in a variety of diseases, including cancers and appear to be tissue specific, showing signatures related to tumor classification, diagnosis, and progression. For example, a systematic expression analysis by Lu *et al.* of 217 mammalian miRNAs in various human cancers clearly reflected the developmental lineage and differentiation state of the tumors, and a general down-regulation of miRNAs was observed in tumors compared with normal tissues (134). In addition, Aharonov and coworkers applied the miRNA expression profiles to trace the tissue of origin of cancers of unknown primary origin (174). These findings highlight the potential of miRNA profiling in cancer diagnosis. Another advantage of using secretory miRNAs as biomarkers is that the level of miRNAs can be easily detected and quantified with next-generation sequencing technologies. A number of methods are currently available for the detection and quantification of miRNAs, such as Northern blot analysis, microarray analysis, quantitative real-time polymerase chain reaction, and *in situ* hybridization.

An important feature of almost all human tumors is the genome instability, which is a condition exacerbated by defects in the DDR. In general, we may exploit this inherent weakness to attack cancer cells, potentially without causing excessive damage to the surrounding normal cells. However, development of drug resistance is a persistent problem in cancer therapies using DNA damaging agents. Given the active roles of ncRNAs in the DDR and their ability to target components of DNA repair, ncRNAs are promising agents to improve efficacy of conventional cancer therapy. Indeed, several studies have shown that aberrant expression of ncRNAs, especially miRNAs, is associated with drug responsiveness, and that manipulation of endogenous ncRNAs expression may overcome chemoresistance in anticancer treatment. For example, restoration of the expression of miR-34a, a direct downstream target of p53, in human gastric cancer cells, restored p53-induced functions and increased chemotherapeutic sensitivity (95). Moreover, miRNA-mediated inhibition of the key sensors and transducers in the DDR, (for examples, ATM is inhibited by miR-101, miR-100 and miR-421 and DNA-PKcs is inhibited by miR-101) sensitized tumor cells to IR *in vitro* and *in vivo* (86, 157, 232). Using a mimetic miRNA screening approach, Ashworth and coworkers identified that several miRNAs, including miR-107 and miR-222, regulate the DDR and sensitize tumor cells to PARP inhibitor olaparib by repressing expression of RAD51, thus impairing DSB repair by HR. In addition, elevated expression of miR-107 has been observed in a subset of ovarian clear cell carcinomas, which correlates with PARP inhibitor sensitivity and reduced RAD51 expression, raising the possibility to use these miRNAs as biomarkers to identify patients who may benefit from treatment with PARP inhibitors (156).

A number of approaches have been developed to achieve systematic depletion or restoration of miRNA functions. Suppression of endogenous miRNAs can be reached with multiple strategies, such as locked nucleic acids, anti-miRNA oligonucleotides (AMOs), "miRNA sponges," and antagomirs (58, 79). In contrast, the restoration of miRNAs can be achieved by ectopic expression of mature miRNAs or their precursors, such as chemically modified miRNA mimic, adenoviral- or lentiviral-based overexpression and nanopartical-based delivery. Given the fact that multiple DNA damage-responsive miRNAs and miRNAs which regulate DDR genes play a role in the development of neoplasia, modulation of the expression of these miRNAs will be a useful therapeutic tool to overcome chemoresistance when treated with DNA damaging agents.

Concluding Remarks

Taken together, we have shown that expression of ncRNAs is regulated transcriptionally and post-transcriptionally in the

DDR. These altered ncRNAs, in turn, contribute to the maintenance and modulation of the DDR. However, biological functions of these ncRNAs are often understudied due to the lack of well-controlled cellular systems and genetically engineered animal models. In particular, as the largest group of ncRNAs, lncRNAs have yet to be fully identified as a whole. There are still many important questions to be addressed in the field of ncRNAs. Further studies on the following aspects might help delineate the mechanisms by which DNA damage signaling is linked to ncRNA expression and functions: (i) the interaction between ncRNA gene promoters and their transcriptional complexes; (ii) tissue and cell specificity of ncRNAs in animals; (iii) differential regulation of ncRNA expression in response to various types of DNA damage; (iv) post-transcriptional modifications of ncRNAs and their roles in regulating ncRNA functions; and (v) biological functions of ncRNA in animal development and diseases. Since many questions remain, it is essential that we continue to identify the molecular and cellular mechanisms involved in ncRNA expression and function. Such research will not only lead to a better understanding on the functional roles of DDR but will also provide new insights into many human diseases with DNA damage-processing defects.

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Abbreviations Used

AGO2 = argonaute 2
AMOs = anti-miRNA oligonucleotides
ATM = ataxia telangiectasia mutated
ATR = ataxia telangiectasia and Rad3 related
BACE1 = antisense transcript for β-secretase-1
BER = base excision repair
CLL = chronic lymphocytic leukemia
COX3 = cytochrome c oxidase III
CRM1 = exportin 1
DDR = DNA damage response
DDRNAs = Dicer- and Drosha-dependent small RNAs
DDX17 = DEAD box RNA helicase p72
DDX5 = DEAD box RNA helicase p68
DGCR8 = DiGeorge Syndrome Critical Region Gene 8
DSB = double-stranded DNA break
GSHPX = glutathione peroxidase
HMOX = heme oxygenase-1
HR = homologous recombination
IR = ionizing radiation
Keap1 = Kelch-like ECH-associated protein 1
KSRP = KH-type splicing regulatory protein
lincRNAs = large or long intergenic ncRNAs
LNAs = locked nucleic acids
lncRNAs = long noncoding RNAs
MAPK = mitogen-activated protein kinase
miRNAs = microRNAs
MMP1 = matrix metalloproteinase 1
MMR = mismatch repair
ncRNAs = noncoding RNAs
NCS = neocarzinostatin
NER = nucleotide excision repair
NHEJ = nonhomologous end joining
Nrf2 = nulcear factor-erythroid 2-related factor 2
piRNAs = Piwi-interacting RNAs
pre-miRNAs = precursor miRNAs
pri-miRNAs = primary miRNAs
RISC = RNA-induced silencing complex
ROS = reactive oxygen species
rRNAs = ribosomal RNAs
siRNAs = small interfering RNAs
snoRNAs = small nucleolar RNAs
SOD = superoxide dismutatese
T-ALL = T cell acute lymphoblastic leukaemia
TGFb1 = transforming growth factor beta 1
TRBP = Tar RNA-binding protein
tRNAs = transfer RNAs
TXNRD = thioredoxin reductase
UTR = untranslated region
UV = ultraviolet
XPO5 = exportin 5