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Regulation of DNA repair by non-coding miRNAs

Venkateswaran Natarajan

Diagnostic Molecular Oncology Centre, Department of Pathology, National University Hospital, Singapore

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ABSTRACT

DNA repair is an important signaling mechanism that is necessary to maintain genomic stability. Various types of DNA repair proteins are involved in the repair of different types of DNA damage. However, most of the DNA repair proteins are modified post-translation in order to activate their repair function, such as, ubiquitination, phosphorylation, acetylation, etc. Similarly, DNA repair proteins are also regulated by posttranscriptional modifications. Non-coding microRNAs (miRNAs) induced posttranscriptional regulation of mRNAs has gained attention in recent years. MiRNA-induced regulation of DNA repair proteins is of great interest, owing to its potential role in cancer therapy. In this review, we have summarized the role of different miRNAs in the regulation of various types of DNA repair proteins, which are essential for the maintenance of genomic stability.

1. Introduction

MicroRNAs (miRNAs) are non-coding RNAs that play an important role in various signaling mechanisms in the cells [1]. MiRNAs are single-stranded and short (usually 21–25 nucleotides) sequences that regulate cellular signaling by regulating post-transcriptional modification of different mRNAs [2]. Protecting genomic stability is important for normal cells in order to maintain homeostasis, which will otherwise lead to carcinogenesis [3]. Cells become genomically unstable under various conditions like DNA damage by intrinsic [4] or extrinsic sources [5], chemotherapeutic or radiation agents in cancerous as well as in normal bystander cells [6–9], oncogene-induced replication stress [10,11], etc. However, all these damages are fixed by the DNA damage response and repair network of signaling mechanisms [12], which is required for the proper maintenance of genomic stability. Various types of DNA damage are repaired by various types of DNA repair pathways. For example, DNA double strand breaks (DSB)s [13] are repaired by homologous recombination (HR) or non-homologous recombination (NHEJ), DNA crosslinks are repaired by Fanconi anemia (FA) pathway [14], bulky DNA adducts are repaired by nucleotide excision repair (NER) [15], base lesions are repaired by base excision repair (BER) [16] and mis-incorporation of DNA bases during replication is repaired by mismatch repair (MMR) [17], but sometimes these damages are bypassed by translesion synthesis (TLS) pathway [18].

Most of the DNA damage response and repair proteins or genes are activated by post-translational modifications like ubiquitination, phosphorylation, acetylation, etc or post transcriptionally by miRNAs respectively. While single miRNA can target multiple mRNAs, single mRNA can also be a target of multiple miRNAs. Especially, miRNAs bind to the mRNAs and mediate their degradation [19]. Degradation of mRNAs that are actively involved in DNA repair changes cellular homeostasis. However, down-regulation/degradation of the DNA repair miRNAs in cancer cells potentially sensitizes them to chemotherapeutic agents, which otherwise makes them chemoresistant. Similarly, cells that have deficient miRNA biosynthesis mechanism have defective cell cycle regulation and DNA repair [20]. Studies have also shown that most of the miRNAs are also altered, especially transcription of various miRNAs are altered upon DNA damage [21]. Understanding the basic mechanisms behind the miRNA-induced regulation of DNA repair network in cancer cells will help us to design better therapeutic options. In this review we have focused on different types of miRNAs that regulate DNA repair mechanisms in cancer cells and how it will improve the therapeutic efficacy of chemotherapeutic agents.

Abbreviations: DSB, double strand break; HR, homologous recombination; NHEJ, non-homologous end joining; NER, nucleotide excision repair; BER, base excision repair; TLS, translesion synthesis; FA, Fanconi anemia; MIS, micro-instability syndrome; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia mutated related.

E-mail address: vittall8@yahoo.com.

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2. MiRNA-induced regulation of DSB repair

DSBs are the most lethal as well as the most susceptible DNA damage for carcinogenesis. Approximately, a cell undergoes more than ten DSB per day. Various exogenous agents like radiation, chemotherapy and endogenous agents like oxidative metabolism, V(D)J recombination are responsible for inducing DSB [22]. Owing to its importance, DNA DSBs are repaired by two different mechanisms, either HR or NHEJ. HR is an error free repair, which requires a template DNA and occurs mostly in cells in the S/G2 phase of the cell cycle where DNA is replicated; on the other hand, NHEJ is an error prone repair, which simply rejoins the broken strands of DNA and occurs mostly in G1 phase of the cell cycle, but also has limited activity throughout the cell cycle [13].

2.1. MiRNA-induced regulation of DNA repair

Upon DNA damage, various repair members get activated and act as sensors (H2AX), transducers (ATM/ATR), mediators (MDC1) and effectors. Phosphorylation of H2AX at serine 139 is an important process to recruit all DNA repair associated proteins and also considered as a reliable marker for DNA DSB [23]. 3'UTR region of H2AX is found to have a conserved region for the binding of miR-24 [24]. Expression of miR-24 was found to be high in terminally differentiated cells and correlated well with decreased expression of H2AX. This study reveals the basic mechanism behind the reduced efficiency of DSB repair in terminally differentiated cells.

ATM (Ataxia-telangiectasia mutated) is an important serine/threonine kinase that is required for the repair of DSB [25]. It was found that miR-421 binds to 3'UTR region of ATM mRNA and facilitates its degradation [26]. Inhibition of ATM mRNA by miR-421 sensitized cancer cells to IR, which mimics the phenotype of AT patients. Further analysis revealed that oncogene and transcription factor N-Myc induces the expression of miR-421 in neuroblastoma. This further confirms the role of miRNA mediated suppression of DNA repair and genomic instability, which ultimately leads to carcinogenesis. Another important DSB transducer that works similar to ATM is ATR, a serine/threonine kinase [27]. Recent research found that ATR mRNA is a direct target of miR-185 and regulates it post-transcriptionally. Further analysis showed that irradiation of cancer cells downregulates the expression of miR-185, which in turn upregulates ATR mRNA and results in active repair of radiation induced DNA damage. However, downregulation of ATR mRNA by transfection with pre miR-185 results in sensitization of cancer cells to irradiation [28].

Mediator of DNA damage checkpoint protein (MDC)1 is an important member of DSB repair that is regulated by miRNAs [29]. Mice or human cells lacking MDC1 are sensitive to radiation induced DNA damages. A recent study revealed that miR-22 binds to MDC1 mRNA and regulates it post-transcriptionally. Inhibition of MDC1 during neoplasm associated replication stress might result in accumulation of DNA damage and genomic instability.

2.2. MiRNA-induced regulation of HR repair

BRCA1 is an important member of HR repair and is often mutated in breast and ovarian cancer [30]. MiR-182 downregulates BRCA1 mRNA expression by binding to its (BRCA1) 3'UTR in a non-canonical manner. Inhibition of BRCA1 by ectopically over-expressing miR-182 results in sensitization of breast cancer cells to ionizing radiation and PARP1 inhibitor [31]. The results of this study highlighted the potential impact of miRNAs in anticancer therapy. Similarly, miR-1255b, miR-193b, and miR-148b were found to regulate important HR proteins like BRCA1, BRCA2 and RAD51 [32]. Further analysis revealed that all the three miRNAs binds to BRCA1, BRCA2 and RAD51 mRNA in a non-canonical manner and regulates the HR genes post-transcriptionally. Similarly, hypoxia induced expression of miR-210 was found to regulate the expression of RAD52, an important member of HR [33]. Rad51 mRNA was also found to be regulated by miR-96 and increased expression of miR-96 sensitized cancer cells to cisplatin and PARP inhibitors [34].

FA is another chromosomal instability disorder resulting from mutations in 19 complimentary genes that are important for DNA repair [35]. FA patients are often characterized by bone-marrow failure and susceptibility to acute myelogenous leukemia, squamous cell carcinoma of head and neck, hepatocellular carcinoma, congenital abnormalities and infertility. FA proteins is required mostly to fix inter-strand cross links and also required during DNA replication to maintain genomic stability [35].

Upon DNA damage, FANCD2 gets monoubiquitinated and localizes into the nucleus, where it forms a complex with BRCA1, BRCA2 and RAD51, and facilitates homology mediated repair [36]. Recent research found that upregulation of miR-302 reduces the monoubiquitination/foci formation of FANCD2 upon DNA damage [37]. Cells with miR-302 overexpression and simultaneous treatment with MMC showed increased chromosomal damage, a hallmark of deficient FANCD2. Another member of FA pathway that has been found to be regulated by miRNA is FANCG. Bioinformatic analysis revealed that miR-23a binds to FANCG mRNA and regulates it negatively [38]. It has been found that areca nut extracts (ANE) or arecoline (ARE) induces DNA DSB by upregulating miR-23a, which in turn downregulates FANCG expression. This observation is important because ANE or ARE nut-chewing habits often results in the development of oral cancer.

2.3. MiRNA-induced regulation of NHEJ repair

DNA-dependent protein kinase (DNA-PKcs) is an important member of NHEJ playing an active role in V(D)J recombination, which is required for maturation of B and T cells [27]. miR-101 was found to bind to the 3'UTR region of DNA-PKcs and facilitate its degradation. Interestingly, miR-101 has also been found to regulate ATM mRNA in a similar way [39]. Downregulation of DNA-PKcs and ATM mRNAs by miR-101 transfection and simultaneous treatment with radiation sensitized the cancer cells by inhibiting DSB repair.

Similarly, 53BP1 which is necessary for NHEJ was also found to be regulated by miR-34a. Inhibition of 53BP1 in glioblastoma cells post-irradiation showed increased DNA damage associated with mitotic catastrophe. Further analysis revealed that these cells do not undergo G2/M arrest which usually happens after irradiation [40]. Most chemotherapeutic agents that are now in use for cancer therapy kill cancer cells by inducing DSB either directly or indirectly. Therefore, it is important to study the role of miRNAs that regulate DSB repair in detail, so as to improve therapeutic efficacy of cancer treatments.

3. MiRNA-induced regulation of nucleotide excision repair

NER is a specialized repair mechanism that is required for the active repair of DNA adducts formed by UV and chemicals [41]. More than 25,000 bases per human genome per cell undergoes DNA adducts induced damage every day. Various types of NER is available for the repair of DNA adducts based on whether DNA damage occurred in the transcribed region or in the un-transcribed region. For example, GG-NER (global genome repair) takes place in the total genomic DNA and TC-NER (transcription coupled repair) is restricted to removing lesions preferentially from the transcribed DNA strand of active genes.

ERCC3 otherwise called as XPB (xeroderma pigmentosum type B) is a DNA helicase necessary for NER [42]. ERCC4 is another

important helicase necessary for NER and it is also called as DNA repair endonuclease XPF [43]. Functionally disabling mutations in these two genes results in Xeroderma pigmentosum, Cockayne's syndrome, and Trichothiodystrophy. It has been found that miR-192 is able to bind and inhibit the mRNAs of ERCC3 and ERCC4 in HepG2.2.15 cells that are stably transfected with HBV. It is interesting to note that the control HepG2 cells not transfected with HBV showed no reduction in ERCC3 and ERCC4 expression. This confirms that HBV induces the expression of miR-192, which in turn represses NER by inhibiting ERCC3 and ERCC4. This study also supports the fact that viral infection induced downregulation of important DNA repair might be an important mechanism for viral induced carcinogenesis [44]. Similarly, hypoxia induced expression of miR-373 suppresses the expression of RAD23b mRNA, a protein involved in NER [33].

4. MiRNA-induced regulation of mismatch repair

Six billion bases are replicated in each cell during replication. Even though highly specific and reliable replication machinery works to avoid any errors, there are always some errors that occur during replication. Mis-match repair is specific for fixing the errors that take place during replication [45]. It mostly involves deletion, insertion and mis-incorporation of bases. The nucleotide adenine always base pairs with thymidine and guanine always base pairs with cytosine. Mis-base paring is the most common error that happens during replication [45]. Mutations in proteins that are involved in MMR results in genomic instability syndrome called microsatellite instability (MIS). Mutations in MMR are also associated with most of the cancers [46].

Similar to other types of DNA repair mechanisms, MSH2, MSH6 and MLH1, the important components of MMR mechanism are also regulated by miRNAs. A study has shown that expression of miR-155 significantly downregulates the expression of MSH2, MSH6 and MLH1 mRNA [47]. Mutations in these genes are generally associated with MIS or Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC). Analysis of MIS tumor samples revealed at least two-fold increase in miR-155 expression compared to samples from adjacent controls. However, association between miR-155 expression and the stages of tumors are not significant. This observation potentially confirms the role of miR-155 in MSI tumors by downregulating MMR mRNA. The authors have concluded that MSI tumors with unknown MMR defects may result from miR-155 overexpression.

Apart from MSI tumors, miR-155 induced regulation of MMR mRNA has been observed in pancreatic cancer. A recent study has shown that MLH1, an important member of MMR is downregulated in the event of miR-155 overexpression [48]. Immunohistochemical analysis of pancreatic cancer samples showed decreased expression of MLH1 compared to para-tumor samples of pancreatic cancer.

miR-21 was also found to overexpress and regulate MSH2, MSH6 mRNAs, especially in colorectal cancer [49]. In contrast to other miRNAs discussed in this review, overexpression of miR-21 in colorectal cancer reduces the therapeutic efficacy of 5-FU. The authors have described that the observed result is due to a defective MMR mechanism. While overexpression of miR-21 in colorectal cancer cells may not potentially sensitize the cells to chemotherapeutic agents, it can be a good biomarker to evaluate 5-FU therapeutic efficacy. It is important to note that different miRNAs regulate the same mRNAs in different ways in different cancers. It may be the result of a complex heterogeneity that happens in cancer cells. Unraveling the basic mechanism behind this signaling network is important for more focused and targeted cancer therapy.

5. MiRNA-induced regulation of BER repair

Single base modifications like oxidation, methylation, uracil, alkylation, and deamination results in improper formation of DNA double helix. The BER mechanism specifically recognizes these modifications and protects the DNA from genomic instability. Mutations in genes that are involved in BER are often associated with cancer. For example, somatic mutation of Pol β is found in 30% of cancers and mutations in *DNA glycosylase MYH* increases the risk of colon cancer [50].

Uracil, a demethylated form of thymidine nucleotide is misincorporated in DNA and is regularly removed by BER mechanism. Human nuclear uracil-DNA glycosylase (UNG2) is a member of BER mechanism that is necessary to remove uracil from DNA. Previous reports have shown that UNG2 proteins are downregulated during G2/M phase of cell cycle. Even though they found that both mRNA and proteins of UNG2 is going down, they did not uncover the mechanism behind this. A recent study revealed that 3'UTR region of UNG2 mRNAs is a direct target of miR-16, miR-34c, and miR-199a [51]. However, authors did conduct further studies to sensitize cancer cells.

Human DNA polymerase β (DNA polymerase β, polβ) is a protein required for BER mechanism. A recent study found that miR-499 regulates DNA polymerase β in esophageal carcinoma cell lines [52]. Further analysis found that miR-499 binds to the 3'UTR region of DNA polymerase β mRNA and facilitates its degradation. The authors observed that miR-499 overexpressed esophageal carcinoma cell lines increased sensitivity towards cisplatin treatment compared to esophageal carcinoma cell lines without miR-499 overexpression.

6. MiRNA-induced regulation of TLS

Most of the base damages or bulky adducts will be actively repaired by BER or NER respectively. However, sometimes these damages remain unrepaired and may stall replication fork progression. Stalling of replication fork will result in genomic instability or cell death. At the same time, cells have another repair mechanism to overcome or bypass the damages by DNA damage tolerance pathway or TLS pathway [53]. Basically, TLS pathway members such as E3 ligase Rad18 and DNA polymerase η will modify PCNA and facilitate the PCNA to bypass the damage during replication, and allow the damage to be repaired later. Rad18 also forms a complex with FA/BRCA repair proteins like FANCD2, BRCA1 and RAD51 and facilitates the camptothecin induced DSB repair [36]. Among the different types of TLS proteins, Rad18 is an E3 ubiquitin ligase important for DNA damage tolerance pathway. Like other important DNA repair proteins, we discussed before, Rad18 is also found to be regulated by miRNAs. A Recent study shows that the tumor suppressor miR-145 regulates Rad18 mRNA [54]. Overexpression of miR-145 negatively correlates with Rad18 expression in colorectal cancer patients, suggesting a direct link between them. The results from this study also shows that RAD18 is overexpressed in cancer cells that are resistant to 5-FU. This may be because Rad18 might help 5-FU induced DNA damage to get bypassed, thus protecting cancer cells from DNA damage induced cell death. The chemoresistance induced by Rad18 makes it as a potential therapeutic target. As expected, expression of miR-145 in cancer cells and simultaneous treatment with 5-FU sensitized the cancer cells by reversing chemoresistance. Apart from normal regulation, DNA damage induced upregulation of miRNA-630 was found to regulate Rad18 mRNA in HepG2 cells [55]. This is an interesting observation of how DNA damage regulates DNA repair proteins via miRNAs.

Apart from Rad18, DNA polymerase Rev1 involved in TLS was

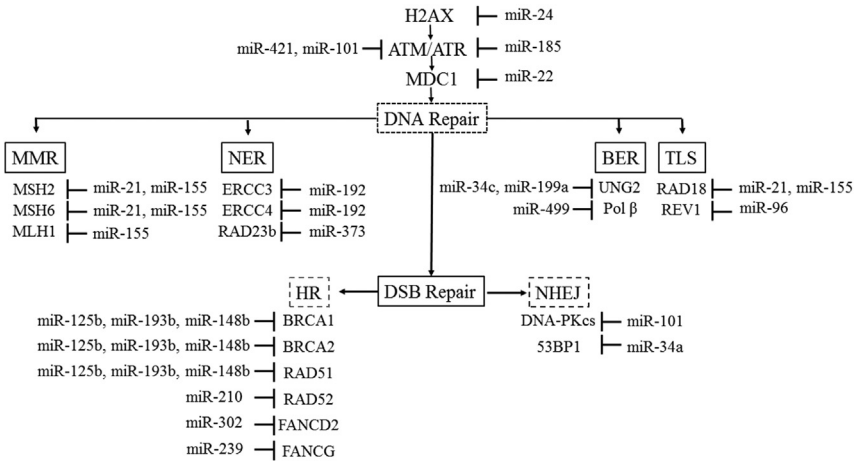

Fig. 1. Various DNA repair pathways that are regulated by miRNAs.

found to be regulated by miR-96 [34]. Inhibition of Rev1 by miR-96 increased the sensitivity of cancer cells to PARP inhibitors and cisplatin treatment. Like Rad18, Rev1 also works with FANCD2 to protect nascent DNA strands in response to replication stress [56]. While it is interesting to note that all DNA repair members are interconnected and still exciting to note that they are differentially regulated at different phase of cell cycle by specific miRNAs.

7. Conclusion

DNA repair is an important signaling network critical for the maintenance of genomic stability. The genes involved in DNA repair are mostly regulated by post-transcriptional/translational modifications, of which miRNA induced post-transcriptional regulation is an important phenomenon leading to the downregulation of both the mRNAs and protein. One of the main advantages of using miRNAs for cancer therapy is that miRNAs have the ability to sensitize cancer cells to chemotherapeutic agents by down-regulating different DNA repair genes (Fig. 1). However, when one type of DNA repair mechanism becomes defective, the cells adapt to survive by activating another type of repair mechanism [57]. To overcome the conundrum, future studies have to focus on targeting miRNAs that can regulate more than one DNA repair gene. Another important signaling pathway that functions closely in association with the DNA repair pathway is the cell cycle pathway. Down-regulation of DNA repair genes will induce DNA damage, and if the cell cycle checkpoints are in place, it will allow more time for the cells to repair [58]. For an effective cancer treatment, genes involved in both DNA repair and cell cycle checkpoints have to be downregulated simultaneously. Identifying miRNAs that can potentially bind to mRNAs of both DNA repair and associated cell cycle genes will be a beneficial tool. Various types of novel therapeutic options are now available for cancer treatments, for example stimulating apoptosis [59–61], use of bacterial toxins [62–64], DNA repair inhibitors [65]. Combination of these approaches with miRNA will also be an interesting method in the future.

In conclusion, cell specificity for miRNAs that regulate DNA repair protein coding genes has to be validated further. Down-regulation of DNA repair genes under normal conditions would result in increased genomic instability, leading to carcinogenesis. Identifying the basic mechanism of miRNA-induced regulation in normal versus cancer cells will provide useful information to increase the therapeutic efficacy of cancer treatment using miRNAs.

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