DNA Damage and Repair

Systematic Screen Identifies miRNAs That Target RAD51 and RAD51D to Enhance Chemosensitivity

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Abstract

Homologous recombination mediates error-free repair of DNA double-strand breaks (DSB). RAD51 is an essential protein for catalyzing homologous recombination and its recruitment to DSBs is mediated by many factors including RAD51, its paralogs, and breast/ovarian cancer susceptibility gene products BRCA1/2. Deregluation of these factors leads to impaired DNA repair, genomic instability, and cellular sensitivity to chemotherapeutics such as cisplatin and PARP inhibitors. microRNAs (miRNA) are short, noncoding RNAs that posttranscriptionally regulate gene expression; however, the contribution of miRNAs in the regulation of homologous recombination is not well understood. To address this, a library of human miRNA mimics was systematically screened to pinpoint several miRNAs that significantly reduce RAD51 foci formation in response to ionizing radiation in human osteosarcoma cells. Subsequent study focused on two of the strongest candidates, miR-103 and miR-107, as they are frequently deregulated in cancer. Consistent with the inhibition of RAD51 foci formation, miR-103 and miR-107 reduced homology-directed repair and sensitized cells to various DNA-damaging agents, including cisplatin and a PARP inhibitor. Mechanistic analyses revealed that both miR-103 and miR-107 directly target and regulate RAD51 and RAD51D, which is critical for miR-103/107–mediated chemosensitization. Furthermore, endogenous regulation of RAD51D by miR-103/107 was observed in several tumor subtypes. Taken together, these data show that miR-103 and miR-107 overexpression promotes genomic instability and may be used therapeutically to chemo sensitize tumors.

Implications: These findings demonstrate a role for miR-103 and -107 in regulating DNA damage repair, thereby identifying new players in the progression of cancer and response to chemotherapy. Mol Cancer Res; 11(12); 1564–73. ©2013 AACR.

Introduction

Homologous recombination is an error-free pathway of DNA double-strand break (DSB) repair. DSBs occur in the genome following exposure to exogenous DNA damaging agents such as ionizing radiation or from endogenous cellular events such as replication fork stalling and collapse (1). RAD51 is essential for homologous recombination and is recruited to sites of DNA damage to mediate repair; this recruitment can be visualized immunocytochemically as the appearance of distinct nuclear foci (2). RAD51 loading at sites of DNA damage requires many factors including the breast and ovarian cancer susceptibility proteins (BRCA1, BRCA2, FANCD1, and PALB2/FANCN) and the RAD51 paralogs (RAD51B, RAD51C/FANCO, RAD51D, XRCC2, and XRCC3; refs. 3, 4). Defects in homologous recombination lead to genomic instability and mutations in some homologous recombination genes, such as BRCA1, BRCA2, PALB2, RAD51C, and RAD51D, confer cancer susceptibility (5). On the other hand, homologous recombination defects render cancer cells hypersensitive to DNA-damaging chemotherapeutics such as interstrand DNA crosslinking agents and inhibitors of PARP and topoisomerases (6). Thus, identifying and understanding novel modes of homologous recombination regulation is critical for understanding the pathobiology of cancer as well as shaping more effective treatment.

microRNAs (miRNA) are short noncoding RNAs that posttranscriptionally downregulate gene expression through translational repression and mRNA destabilization (7). There are approximately 1,000 miRNAs encoded by the human genome, which are estimated to collectively regulate approximately 60% of protein-coding transcripts (8) and thus the majority of biologic processes. Furthermore, aberrantly expressed miRNAs can initiate or drive the progression of diseases such as cancer (7).

Some miRNAs have been implicated in the regulation of factors required for DNA DSB repair (9, 10). miR-24 and the breast cancer–associated miRNAs miR-182 and...
miR-146a/b-5p target BRCA1 (11–13), whereas miR-1245 targets BRCA2 (14). miR-24 also targets the DSB-associated histone variant, H2AX, as does miR-138 (15, 16). We recently reported that miR-96 targets RAD51 (17). However, miRNAs that regulate homologous recombination have not been systematically identified. In this study, we developed a cell-based screen to identify miRNAs whose overexpression altered RAD51 nuclear foci formation following ionizing radiation. We present the results of the screen and the characterization of two of the strongest hits, the paralogous miR-103 and miR-107.

Materials and Methods

Cell lines

U2OS, HeLa, and H1299 were purchased from the American Type Culture Collection. The PEO1 C4-2 clone has been described previously (18). MDA-MB-231 was a gift of the Paulovich laboratory (Fred Hutchinson Cancer Research Center, FHCRC, Seattle, WA). These human cancer cell lines were authenticated by short tandem repeat DNA profiling (Bio-Synthesis Inc.) and used for this study within 6 months of resuscitation. Mouse embryonic fibroblasts were a gift of the Clurman laboratory (FHCRC). RAT-1 fibroblasts were a gift of the Fausto/Campbell laboratory (University of Washington, Seattle, WA). H1299 cells were cultured in RPMI-1640, supplemented with 10% FBS and 2 mmol/L glutamine. H1299 cells were irradiated, simultaneously (21), RAD51 (#1 target sequence, 5′-AACCTACTGAGTG-GTAGCCTA-3′; #2 and #3 from ref. 22), and RAD51D (target sequence, 5′-CTGGGTGAAAATAGCTTATA-3′; Qiagen and Sigma) and negative controls [nontargeting siRNA (21) or an equimolar pool of nontargeting siRNA, siLuc (17), and siAllstars (Qiagen)] were transfected at 10 nmol/L using HiPerFect (Qiagen). Locked nucleic acid-based negative (negative control B) or a combination of miR-103- and miR-107 power inhibitors (Exiqon) were transfected at 15 to 50 nmol/L with HiPerFect (Qiagen).

Immunofluorescence microscopy

Cells were grown on coverslips, irradiated (10 Gy), and then simultaneously fixed and permeabilized as described previously (16). Cells were immunostained for RAD51 (H-92; Santa Cruz Biotechnology) and analyzed using MetaVue (Universal Imaging) and ImageJ (NIH, Bethesda, MD). At least 100 cells per experimental point were scored and cells with five or more foci were considered foci positive. Each experiment was independently replicated at least three times.

miRNA mimic library screening

U2OS cells were transfected (20 nmol/L; HiPerFect; Qiagen) with the Human miRIDIAN miRNA mimic library (v10.1; Dharmacon) in glass-bottom 96-well plates (#655892; Greiner Bio-One). Two days posttransfection, cells were irradiated, simultaneously fixed and permeabilized, and immunostained for RAD51 as described above. Images were acquired with the Cellomics Arrayscan microscope (Thermo Scientific) and processed as described previously (16). Using DAPI staining to define nuclei, the number of RAD51 foci–positive cells (containing at least 10 RAD51 subnuclear foci) was quantified using the automated counter. The Z-score was calculated on the basis of the formula \( Z = (X - \mu)/\sigma \), where \( X \) was the individual sample score, \( \mu \) was the mean of negative controls in each plate and \( \sigma \) was the SD of the whole population. Screening was independently replicated three times.

Western blot analysis

Whole-cell extracts were prepared and resolved by polyacrylamide gel electrophoresis as described (16) and transferred onto nitrocellulose membranes. Antibodies against BRCA2 (Ab-2; Calbiochem), CtIP (ab14601; Abcam), Dicer (ab14601; Abcam), PALB2 [N200; a gift of the Xia laboratory, University of Medicine and Dentistry of New Jersey

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Real-time quantitative reverse transcription PCR

Total RNA was extracted using TRIzol (Life Technologies) and reverse-transcribed using the TaqMan miRNA Reverse Transcription Kit or the TaqMan cDNA Reverse Transcription Kit (Life Technologies). The TaqMan MiRNA Assay Kit or the Gene Expression Kit (Life Technologies) was used for quantitative PCR (qPCR). The comparative $C_t$ value method was used for transcript quantification. miR-103 and miR-107 expression was normalized to RNU24 or RNU44 snoRNA. RAD51 and RAD51D expression was normalized to 18S rRNA or TBP mRNA.

Luciferase assay

U2OS cells were seeded in 24-well plates ($5 \times 10^4$well) and cotransfected with miRNA mimics (0.5 nmol/L; HiPerfect), pRL-TK (50 ng/well; Mirus TransIT-LT-1; a gift of the Fero laboratory, FHRCR), and pGL3-control vectors containing empty, wild-type or mutant RAD51 (or RAD51D) 3$'$-UTR sequences (200 ng/well). Two days posttransfection, cells were lysed and the luciferase activities assayed using the Dual-Luciferase Assay Kit (Promega). Relative luciferase activity was calculated by normalizing the ratio of Firefly/Renilla luciferase to that of miR-Neg–transfected cells.

Homologous recombination assay

U2OS DR-GFP cells (a gift from Drs. Maria Jin and Koji Nakashiba, Memorial Sloan-Kettering Cancer Center, New York, NY; ref. 23) were transfected with siRNAs or miRNA mimics and then transfected 24 hours later with pCBA5c (I-Scel expression vector) or empty vector. Two days after plasmid transfection, cells were harvested and analyzed using a FACSCalibur Analyzer to determine the percentages of GFP-positive cells.

Cell-cycle analysis

Cells were pulse-labeled with BrdU, fixed, and then stained for DNA content and BrdU incorporation as described previously (17). Flow cytometry was performed to determine the cell-cycle distribution.

Survival assay

Transfected or transduced cells were seeded into 12-well plates at $5 \times 10^3$ per well (H1299 and HeLa) or $6 \times 10^3$ per well (U2OS and PEO1 C4-2) and treated with cisplatin, etoposide, camptothecin, paclitaxel (Sigma), or AZD2281 (Axon Medchem) at indicated concentrations. After incubation for 5 to 7 days, cell survival was assessed by crystal violet staining as described previously (16). Clonogenic assays were performed as described previously (17).

Statistical analysis

The Student or paired $t$ tests were used to evaluate the significance of differences between 2 groups of data (Excel; Microsoft Inc.). All results were expressed as mean ± SD or SEM. A $P$ value of less than 0.05 was considered significant.
overexpression did not significantly alter cell-cycle distribution in either untreated or irradiated cells (Supplementary Fig. S1D–S1F and data not shown). Therefore, the reduction in RAD51 foci formation mediated by miR-103/107 overexpression is likely independent of changes in cell-cycle progression.

**miR-103/107 impair homologous recombination and promote chemosensitivity to DNA damaging agents**

Next, we examined the effect of miR-103/107 overexpression on homologous recombination–mediated DSB repair using U2OS DR-GFP cells (23). The overexpression of miR-103/107 significantly reduced homologous recombination efficiency as judged by the percentage of GFP-positive cells following induction of a DSB by I-SceI (Fig. 2A), consistent with the reduction in RAD51 foci formation.

Proficient homologous recombination is required for cellular resistance to agents that induce DNA DSBs in S-phase, such as cisplatin, topoisomerase poisons (e.g., camptothecin and etoposide), and PARP inhibitors. As expected, miR-103/107 overexpression sensitized U2OS, HeLa, and PEO1 C4-2 cells to cisplatin and a PARP inhibitor, AZD2281 (Fig. 2B; Supplementary Fig. S3A–S3C). Overexpression of miR-103/107 also sensitized U2OS cells to camptothecin and etoposide (Fig. 2C). Furthermore, chemosensitization to these DNA damaging agents was observed when miR-103/107 were overexpressed by lentiviral transduction (Supplementary Figs. S2E and S4C). In contrast, miR-103/107 overexpression did not sensitize cells to paclitaxel (Fig. 2D; Supplementary Fig. S3A and S3B), a microtubule-stabilizing agent, suggesting that chemosensitivity is specific to DNA damage.

**miR-103/107 regulate RAD51 expression**

We observed a reduction in the overall intensity of RAD51 immunostaining upon miR-103/107 overexpression (Fig. 1D; Supplementary Fig. S1A and S1B). Consistently, miR-103/107 overexpression was found to reduce RAD51 protein as well as mRNA expression in several cancer cell lines (Fig. 3A and B; Supplementary Figs. S2C and S2D, S4A and S4B). The downregulation of Dicer (29) served as a control for miR-103/107 mimic transfection (Fig. 3A). Using the TargetScan algorithm (34), we noted that human RAD51 is a predicted target of miR-103/107 and their putative binding site in the 3’UTR of RAD51 is conserved in rats but not mice (Fig. 3C and Supplementary Fig. S5A). Consistent with this observation, miR-103/107 downregulated RAD51 protein expression in RAT-1 rat-derived...
fibroblasts but not in mouse embryonic fibroblasts (Supplementary Fig. S5B).

To determine whether RAD51 is a direct target of miR-103/107, we generated a luciferase reporter construct containing the human RAD51 3′UTR. miR-103/107 significantly reduced the activity of this construct relative to miR-Neg (Fig. 3D and Supplementary S5C). Point mutations introduced in the putative miR-103/107–binding site of the construct relieved this repression (Fig. 3C and D and Supplementary Fig. S5C), suggesting that miR-103/107 directly target the 3′UTR of RAD51D, a predicted target of miR-103/107 by TargetScan (Fig. 3C).

miR-103 and miR-107 directly regulate RAD51D

To identify other homologous recombination–relevant miR-103/107 targets, we analyzed the expression of several factors that regulate RAD51 foci formation (Fig. 3A). We found consistent downregulation of RAD51D protein and mRNA expression when miR-103/107 are overexpressed in several cell lines (Fig. 3A and B, S2D and S5D). RAD51D is a predicted target of miR-103/107 by TargetScan (Fig. 3C). Using luciferase reporter constructs containing the RAD51D wild-type or mutant 3′UTRs, we determined that miR-103/107 directly target the 3′UTR of RAD51D (Fig. 3D and Supplementary Fig. S5E).

The overexpression of ectopic RAD51D partially rescued ionizing radiation–induced RAD51 foci formation in miR-107–overexpressing PEO1 C4-2 cells (Fig. 4A and B). Chemoresistance to cisplatin and AZD2281 were also partially complemented by RAD51D expression (Supplementary Fig. S8). Interestingly, the coexpression of RAD51 and RAD51D largely reversed miR-107–mediated inhibition of HR repair efficiency and chemoresistance to cisplatin and AZD2281 (Supplementary Fig. S7A–S7C). These results demonstrate that RAD51 is one of the crucial targets of miR-103/107 in the regulation of homologous recombination.
RAD51 foci formation and chemosensitivity to cisplatin and AZD2281 (Fig. 4C). Our results indicate that RAD51 and RAD51D are the major targets through which miR-107 regulate RAD51 foci formation and chemoresistance.

Endogenous miR-103/107 regulate RAD51D expression

To determine whether endogenous miR-103/107 regulate RAD51 and RAD51D expression, we inhibited endogenous miR-103/107 in H1299 (non–small cell lung carcinoma cell line) and MDA-MB-231 (breast cancer cell line), which abundantly express these miRNAs (29, 35, 36). Anti-sense oligonucleotides (PI-103 and PI-107) effectively inhibited miR-103/107 (Fig. 3E and S9A-C). Upon inhibition of miR-103/107, we observed a modest upregulation of RAD51D protein and mRNA in these cell lines and no appreciable change in RAD51 expression (Fig. 3E and F and S9D). This suggests that endogenous miR-103/107 have a significant role in regulating the expression of RAD51D, but not RAD51, in these cell lines.

Next, we looked for inverse relationships between the expression of miR-103/107 and RAD51 and RAD51D in the NCI-60 panel of cancer cell lines (37). Using CellMiner (37), we found no significant inverse correlation between miR-103/107 and RAD51, RAD51D or several other target mRNAs in the NCI-60 panel (Supplementary Table S2). As the NCI-60 panel is heterogenous with respect to tissue origin (37), we additionally analyzed expression datasets from the majority of tumor subtypes in The Cancer Genome Atlas (http://cancergenome.nih.gov/) to identify tissue-specific correlations between miR-103/107 and RAD51 and RAD51D in clinical tumor samples (see Supplementary Methods; Supplementary Table S3). Although no significant inverse correlations between miR-103/107 and RAD51D mRNA were found in any of the tumor subtypes analyzed,
RAD51D mRNA expression was found to be inversely correlated with miR-103/107 levels in lung adenocarcinomas (Pearson \( r = -0.2266 \) and \(-0.2756 \) for miR-103 and miR-107, respectively; \( P < 0.05 \)) and uterine corpus endometrial carcinomas (Pearson \( r = -0.1193 \) and \(-0.1387 \) for miR-103 and miR-107, respectively; \( P < 0.05 \)) and with miR-103 levels in stomach adenocarcinomas (Pearson \( r = -0.2246 \), \( P < 0.05 \); Supplementary Fig. S10 and Supplementary Table S3).

**Discussion**

We conducted an unbiased screen of a miRNA library to systematically identify miRNAs that regulate homologous recombination. Overexpression of the paralogous miR-103 and miR-107, the two strongest hits from our screen, inhibited ionizing radiation–induced RAD51 foci formation, impaired homologous recombination, and conferred chemosensitivity to DNA damaging agents. Downregulation of RAD51 and RAD51D as a consequence of direct targeting was critical to the regulation of homologous recombination by miR-103/107 (Fig. 4D). To date, several miRNAs have been implicated in the regulation of repair of DNA DSBs (9, 10). The deregulation of some of these miRNAs has been suggested to contribute to genomic instability and chemosensitivity in cancer. It is therefore plausible that cancer-associated deregulation of miR-103 and miR-107 (24–28) potentially contributes to genomic instability and chemosensitivity of tumors.

In this and our previous work, we have characterized several miRNAs (miR-103, miR-107, and miR-96) that posttranscriptionally downregulate RAD51 expression. RAD51 has long been suspected of being a tumor suppressor in cancer. It plays an essential role in homologous
recombination and the deregulation of several RAD51 mediators such as BRCA1, BRCA2, and some RAD51 paralogs confer cancer susceptibility. RAD51 expression is downregulated in some cancers (38, 39), but cancer-associated alleles of RAD51 are rare (40). Alternatives to RAD51 dysfunction may therefore exist. One potential mechanism is the regulation of its expression by cancer-associated miRNAs such as miR-103, miR-107, and miR-96. In addition, several other hits from our screen are also predicted to target RAD51 (e.g., miR-221/222, miR-124a/506, miR-494, and others) and may collectively contribute to the overall regulation of homologous recombination (Supplementary Table S1).

In addition to RAD51, we found that miR-103/107 can target RAD51D, which was also relevant to miR-103/107–mediated regulation of homologous recombination (Fig. 4A and S8). Although ectopically expressing RAD51 and RAD51D largely restored miR-103/107–mediated impairment of RAD51 foci formation and chemoresistance (Fig. 4A and C), we cannot exclude the possibility that other targets may be involved. We found that two RAD51 paralogs, XRCC2 and XRCC3, were also consistently downregulated in miR-103/107–overexpressing cells (Supplementary Fig. S5D). Decreased XRCC2 levels are possibly due to RAD51D downregulation (4), but the mechanism of XRCC3 downregulation is unknown. Though a predicted target, our luciferase assays indicated that miR-103/107 do not target the XRCC3 3’UTR (data not shown). The role of XRCC3 in RAD51 foci formation is unclear (4, 41), but it has additional roles in the late stages of homologous recombination and in checkpoint signaling (3). Therefore, its repression by miR-103/107 may contribute to some of the phenotypes observed.

miR-103/107 also target Dicer and TRBP2, which are both components in the miRNA biogenesis pathway (Fig. 3A; refs. 29, 42). Both of these factors have been implicated in promoting chemoresistance to cisplatin (43). Furthermore, Dicer has been implicated in DNA damage response signaling (44) and homologous recombination (45). In addition to RAD51 and RAD51D, these and other targets may be relevant to miR-103/107–mediated regulation of homologous recombination and chemosensitivity.

Our data suggest that the physiologic significance of miRNA-mediated regulation of homologous recombination may be cell type- or tissue specific. Our miRNA knockdown studies demonstrated a role for endogenous miR-103/107 in regulating RAD51D expression in some cell lines (Fig. 3F and SupplementaryFig. S9D). Consistently, miR-103/107 expression is inversely correlated with RAD51D mRNA expression in several tumor subtypes (Supplementary Fig. S10). Collectively, these findings raise the possibility that endogenous miR-103/107 target RAD51D to regulate RAD51-mediated homologous recombination and chemosensitivity in certain tissues or cell types. We were unable to find evidence that RAD51 is a target of endogenous miR-103/107 (Fig. 3F; Supplementary Fig. S9D and Supplementary Tables S2 and S3). As the overall regulation of gene expression is complex and miRNAs are generally considered “fine-tuners” of protein expression, it is perhaps not surprising that neither significant derepression of RAD51 expression upon miR-103/107 inhibition (Fig. 3F) or significant inverse correlation between miR-103/107 and RAD51 (and some other targets of miR-103/107) was observed (Supplementary Tables S2 and S3). Importantly, our findings do not exclude the possibility that endogenous miR-103/107 may target RAD51 and/or RAD51D in more specific cellular contexts.

One possibility is that these miRNAs suppress homologous recombination in cellular states in which DSB repair would be risky or not economical, such as during cellular differentiation (15). Consistent with this, miR-24 and miR-182, which respectively repress H2AX and BRCA1, are upregulated in differentiating leukemia cell lines (13, 15). Intriguingly, miR-103 and miR-107 are upregulated during retinoic acid–induced differentiation of cultured neuroblastoma and leukemia cells, respectively (46, 47). With additional targets in cell-cycle regulation such as CDK6 (26, 31), cyclin E, and CDK2 (48), miR-103/107 potentially couple the regulation of DNA repair and proliferation during cellular differentiation.

Another possibility is that these miRNAs regulate DNA repair in response to DNA damage thereby modulating cellular outcome (17). miR-103/107 are upregulated in response to doxorubicin treatment through p53-dependent transcriptional and posttranscriptional mechanisms (30–32). On the basis of our findings, this upregulation could potentially inhibit DNA repair and sensitize cells to DNA damage. Although it may be counterintuitive for a cell to suppress DNA repair in response to cellular stress, this suppression may serve to push a damaged cell toward apoptosis (15). Alternatively, restricting or limiting homologous recombination may prevent illegitimate recombination thereby promoting genomic stability.

Targeting homologous recombination in cancer has garnered increasing interest because of the resultant hypersensitivity to agents that promote DSB formation in S-phase (e.g., cisplatin, PARP inhibitors; ref. 6). miR-103/107 overexpression in combination with cisplatin or other DNA damaging agents may therefore have therapeutic utility in the chemosensitization of tumors. Interestingly, the use of miR-107 as a therapeutic agent in cancer treatment has been proposed (49). It is tempting to ask whether combining a DNA damaging agent with nanoparticle-delivered miR-107 will chemosensitize tumors (49).

In summary, we identified the paralogous miR-103/107 as inhibitors of homologous recombination and chemoresistance to DNA damaging agents. These miRNAs as well as others from our screen help provide a more complete picture of the cellular regulation of DNA repair and may also be therapeutically useful.

During the preparation of this article, miR-107 was identified in a screen for miRNAs that confer PARP inhibitor sensitivity (50), consistent with our findings. Our independent studies both identified RAD51 as a critical target of miR-103/107 in the regulation of homologous recombination and chemosensitivity. In contrast, our
study also demonstrated that the targeting of RAD51D by miR-103/107 contributes to their regulation of DNA repair. Furthermore, we demonstrate that endogenous miR-103/107 may have a more significant role in regulating RAD51 compared to RAD51D.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
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